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TITLE: A Phase II Study of Nivolumab in Combination with Carboplatin and Pemetrexed, with or without Bevacizumab, in Patients with Advanced, *EGFR*-mutant or *ALK*-rearranged, Non-Small Cell Lung Cancer

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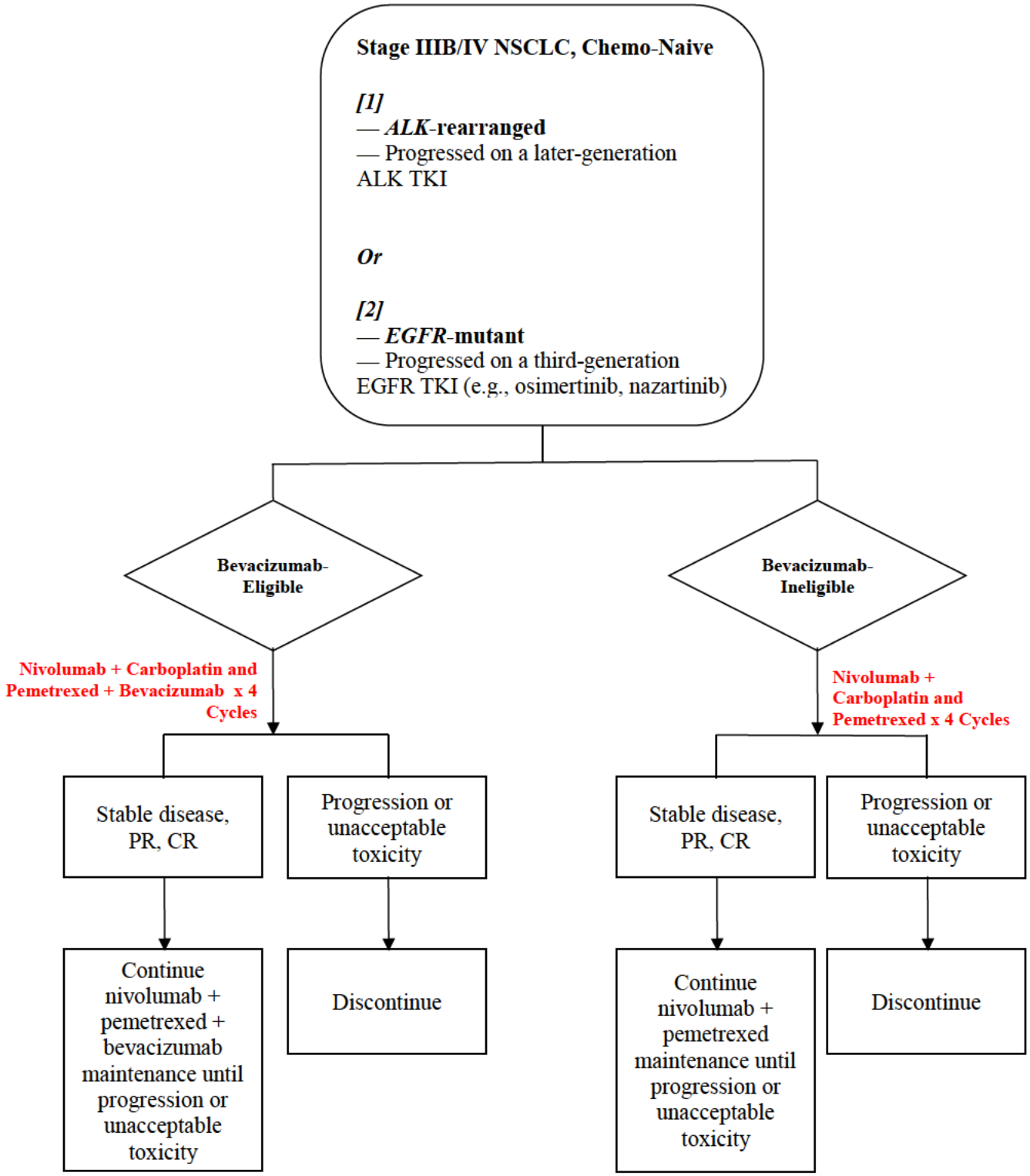
SCHEMA


Stage IIIB/IV NSCLC, Chemo-Naive
[1]
— ALK-rearranged
— Progressed on a later-generation ALK TKI
Or
[2]
— EGFR-mutant
— Progressed on a third-generation EGFR TKI (e.g., osimertinib, nazartinib)
Bevacizumab-Eligible
Bevacizumab-Ineligible
Nivolumab + Carboplatin and Pemetrexed + Bevacizumab x 4 Cycles
Nivolumab + Carboplatin and Pemetrexed x 4 Cycles
Stable disease, PR, CR
Progression or unacceptable toxicity
Stable disease, PR, CR
Progression or unacceptable toxicity
Continue nivolumab + pemetrexed + bevacizumab maintenance until progression or unacceptable toxicity
Discontinue
Continue nivolumab + pemetrexed maintenance until progression or unacceptable toxicity
Discontinue

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1. OBJECTIVES

Genotype-directed therapy is currently the standard of care for patients with advanced non-small-cell lung cancer (NSCLC) harboring targetable driver gene mutations. Epidermal growth factor receptor (*EGFR*) activating mutations and anaplastic lymphoma kinase (*ALK*) rearrangements define the two best characterized molecular subsets of NSCLC, with remarkable sensitivity to tyrosine kinase inhibitors (TKIs) targeting EGFR and ALK, respectively (1-14). However, most patients relapse on TKI therapy within 1-2 years due to acquired resistance. The underlying mechanism of resistance at the time of progression can guide the choice of next-line therapy. For example, 50-60% of *EGFR*-mutant NSCLC patients who relapse on a first- or second-generation EGFR inhibitor (i.e., erlotinib, gefitinib, or afatinib) carry the *EGFR* T790M gatekeeper mutation, and these patients can be effectively treated with a third-generation T790M-selective EGFR TKI such as osimertinib (8). Similarly, *ALK*-positive NSCLC patients who relapse on the first-generation ALK TKI crizotinib may then be treated with one of several next-generation ALK TKIs (e.g., ceritinib, alectinib, with others in development including brigatinib and lorlatinib) (12-14).

Once the available TKI options are exhausted, however, chemotherapy becomes the standard of care. In randomized trials assessing the efficacy of first-line platinum-based chemotherapy as the control arm in *EGFR*- or *ALK*-positive NSCLC (i.e., LUX-Lung 3 or PROFILE 1014), responses were seen in ~45% of patients with median progression-free survival (PFS) limited to ~7 months (6, 11). These trials, however, were performed in treatment-naïve patients. The efficacy of cytotoxic chemotherapy in patients previously treated with multiple TKIs may be significantly lower, closer to 20-30% (2, 15, 16). Patients with *EGFR*- or *ALK*-positive NSCLC who exhaust TKIs and also progress on platinum-based chemotherapy have even more limited therapeutic options. In a preliminary report of a phase III study in patients with *ALK*-rearranged NSCLC who failed crizotinib and prior chemotherapy, docetaxel or pemetrexed led to responses in less than 7% of patients (17), and median PFS was only 1.6 months. Therefore, there is an urgent unmet need for better therapeutic strategies in TKI-resistant patients.

Nivolumab is a monoclonal antibody directed against programmed death receptor 1 (PD-1), approved in the U.S. to treat advanced NSCLC after progression on platinum-based chemotherapy. This approval was based on randomized studies demonstrating improved overall survival in patients treated with second-line nivolumab compared to chemotherapy, and a favorable safety profile (18, 19). Combining nivolumab with chemotherapy, or other immunotherapeutic agents with a different mechanism of action, may enable a synergistic response. In an early-phase study of first-line nivolumab plus platinum-based chemotherapy in advanced NSCLC, there were no dose-limiting toxicities, and responses were seen in 33-47% of patients (20). The majority of patients in these studies had *EGFR*- and *ALK*-wild-type tumors. Thus, the effectiveness of nivolumab combination regimens in *EGFR*-mutant and *ALK*-rearranged patients remains unknown. In the IMpower150 study, the combination of pembrolizumab (another PD-1 inhibitor) with chemotherapy and bevacizumab demonstrated clinical benefit compared to chemotherapy and bevacizumab in patients with advanced NSCLC including those with *EGFR*-mutant and *ALK*-rearranged NSCLC (21). It is plausible that the addition of bevacizumab, an anti-angiogenesis agent, may enhance the anti-tumor activity of the combination of immunotherapy and chemotherapy.

We hypothesize that the combination of nivolumab and platinum-doublet chemotherapy may improve tumor responses in patients with TKI-pre-treated, chemotherapy-naïve *EGFR*- or *ALK*-positive NSCLC. For patients who are eligibile for treatment with bevacizumab, the combination of nivolumab and platinum-double chemotherapy plus bevacizumab may further improve tumor responses.

1.1 Study Design

This is a phase II, multi-cohort trial evaluating the efficacy and safety of nivolumab administered in combination with platinum-doublet, with or without bevacizumab, in TKI-pre-treated patients who are chemotherapy-naïve. Patients with advanced *EGFR*-mutant or *ALK*-rearranged NSCLC will be eligible. The patients must have advanced *EGFR*-mutant NSCLC that progressed on a third-generation EGFR TKI, or advanced *ALK*-rearranged NSCLC which progressed on at least one next-generation ALK TKI. Patients must be chemotherapy-naïve.

- Eligible patients who are bevacizumab-eligible will receive nivolumab plus carboplatin and pemetrexed plus bevacizumab for 4 cycles, followed by nivolumab, pemetrexed and bevacizumab maintenance therapy at the pre-specified doses.

- Eligible patients who are bevacizumab-ineligible will receive nivolumab plus carboplatin and pemetrexed for 4 cycles, followed by nivolumab and pemetrexed maintenance therapy at the pre-specified doses.

Therefore, in total, this study will consist of 4 cohorts:

<u>Nivolumab Plus Carboplatin and Pemetrexed Plus Bevacizumab (Cohorts E and F)</u>:

- **Cohort E**: *EGFR*-mutant advanced NSCLC, previously treated with at least one third-generation EGFR TKI and are chemotherapy-naïve and bevacizumab-eligible.

- **Cohort F**: *ALK*-rearranged advanced NSCLC, previously treated with at least one next-generation ALK TKI and are chemotherapy-naïve and bevacizumab-eligible.

<u>Nivolumab Plus Carboplatin and Pemetrexed (Cohorts G and H)</u>:

- **Cohort G:** *EGFR*-mutant advanced NSCLC, previously treated with at least one third-generation EGFR TKI and are chemotherapy-naïve and bevacizumab-ineligible.

- **Cohort H :** *ALK*-rearranged advanced NSCLC, previously treated with at least one next-generation ALK TKI and are chemotherapy-naïve and bevacizumab-ineligible.

Our primary objective will be to evaluate the efficacy of these combinations using objective response rate (ORR) in the treated subjects. Secondary endpoints will include the disease control rate (DCR), duration of response (DOR), duration on treatment, progression-free survival (PFS)

(including PFS rates at 6 months and at 12 months), and overall survival (OS) (including OS rates at 1 year and at 2 years). Safety and tolerability of the combination regimen will be assessed. As an exploratory analysis, efficacy endpoints will be calculated in subjects with PD-L1-expressing tumors (defined as PD-L1 expression in ≥1% of tumor cells) versus subjects with PD-L1-non-expressing tumors. Exploratory endpoints will also include molecular profiling of baseline tumor biopsy tissues to evaluate for biomarkers of response or resistance to the combination therapy (e.g., expression of immunoregulatory molecules such as PD-L1, PD-L2 cytokines, T-cell subsets).

Efficacy assessments (CT chest/abdomen) will be performed every 6 weeks for the first 6 months, after which assessments will be performed every 12 weeks. Treatment will continue until disease progression, unacceptable toxicity, patient withdrawal, death or discontinuation from the study for any other reason. Subjects may be allowed to continue study therapy after investigator-assessed progression defined by Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST 1.1), if, in the opinion of the treating investigator, they are deriving clinical benefit and tolerating the study drugs.

1.2 Primary Objectives

- To evaluate the objective response rate (ORR) of nivolumab administered in combination with carboplatin and pemetrexed, with or without bevacizumab, to patients with advanced *EGFR*-mutant NSCLC, who have been previously treated with a third-generation EGFR-TKI but are chemotherapy-naive.

- To evaluate ORR of nivolumab administered in combination with carboplatin and pemetrexed, with or without bevacizumab, to patients with advanced *ALK*-positive NSCLC, who have been previously treated with one or more next-generation ALK-TKIs but are chemotherapy-naive.

1.3 Secondary Objectives

- Disease control rate (DCR), based on RECIST 1.1

- Duration of response (DOR), based on RECIST 1.1

- Duration on therapy

- Progression-free survival (PFS), including PFS rate at 6 months, and at 12 months, based on RECIST 1.1

- Overall survival (OS), including OS rate at 1 year, and at 2 years

- Safety profile and tolerability of the combination regimen, based on reporting of adverse events and laboratory abnormalities

1.4 Exploratory Objectives

- To assess the ORR, DCR, DOR, duration on therapy, PFS (including PFS rates at 6 months and 12 months), and OS (including OS rates at 1 year and 2 years) in PD-L1(+) and in PD-L1(-) treated subjects. PD-L1(+) will be defined as subjects with tumors that express PD-L1 in ≥1% of tumor cells.

- To assess the abundance of immunoregulatory proteins (e.g., PD-L1) in tumor tissue samples prior to treatment.

- To investigate the presence of immune cytokines and/or genetic mutations in baseline tumor tissue or peripheral blood samples as biomarkers of response to nivolumab combination regimens (optional).

2. BACKGROUND

2.1 Advanced NSCLC

Lung cancer has been one of the most common cancers in the United States and in the world for decades. It is the leading cause of cancer-related deaths, accounting for over 25% of cases in the United States (22). NSCLC comprises approximately 85% of all lung cancers. The majority of NSCLC patients present with advanced or metastatic disease at the time of diagnosis. For these patients, five-year survival rate remains less than 5% (22). The current standard of care first-line therapy for advanced NSCLC without a molecular driver consists of platinum-based combination chemotherapy. First-line platinum doublet chemotherapy regimens generate an ORR of approximately 20-35% in advanced NSCLC, with median PFS ranging 4-6 months and overall survival (OS) ranging 8-11 months (23-25). The discovery of subsets of NSCLC harboring targetable driver oncogene mutations, such as *EGFR* mutations or *ALK* rearrangements, has led to a paradigm shift in the diagnostic and therapeutic approach to NSCLC. The presence of these molecular driver alterations in NSCLC guides patient treatment, and molecular testing of NSCLC at the time of diagnosis is thus recommended.

2.1.1 *EGFR*-Mutant NSCLC

Activating somatic mutations in *EGFR* were first reported in NSCLC in 2004, and are identified in 10-20% of NSCLC patients in the West and 30-40% in Asia (27). Clinically, oncogenic *EGFR* mutations are associated with adenocarcinoma histology, never or light smoking history, and female gender. The most common activating *EGFR* mutations—exon 19 deletions and the L858R point mutation in exon 21—account for approximately 90% of *EGFR*-mutant NSCLC cases. *In vitro*, these mutations lead to constitutively active EGFR and activation of multiple downstream signaling pathways that promote survival, proliferation, and angiogenesis (27, 28).

Numerous randomized trials have demonstrated the superior efficacy of EGFR TKI(s) over chemotherapy in patients with advanced *EGFR*-mutant NSCLC. Selective inhibition of EGFR in this patient population using a first-generation EGFR TKI (i.e., erlotinib and gefitinib) leads to

responses in 60-80% of patients (versus 20-30% in the chemotherapy control arms), with median PFS of 8-14 months (versus 4-6 months in the chemotherapy control arms) (1-8). The median OS of patients with advanced *EGFR*-mutant NSCLC treated with EGFR-directed therapy now exceeds 2 years (29, 30).

Despite the remarkable initial efficacy, the duration of response to EGFR TKIs is invariably limited because the tumor cells acquire resistance. While numerous resistance mechanisms have been described, the predominant mechanism is acquisition of the gatekeeper mutation in *EGFR*, T790M. This mutation is identified in 50-60% of patients after relapse on a first- or second-generation EGFR TKI, and leads to increased ATP-binding affinity of the EGFR kinase (26). Third-generation, irreversible EGFR TKIs such as osimertinib, rociletinib, and EGF816 spare the wild-type *EGFR*, but inhibit the sensitizing *EGFR* mutants L858R and exon 19 deletion and the resistant *EGFR* mutant T790M with similar potencies. In *EGFR* T790M-positive patients who have progressed after prior EGFR TKIs, osimertinib is associated with an ORR of 61% (8). Osimertinib has been approved in the U.S. for use in this patient population. Furthermore, based on the phase III FLAURA trial which compared osimertinib to a first-generation EGFR TKI in untreated *EGFR*-mutant advanced NSCLC, osimertinib is now considered the standard first-line therapy in these patients (31).

However, acquired resistance to third-generation EGFR TKIs also emerges, limiting the duration of clinical benefit (8). Studies investigating resistance mechanisms to osimertinib and/or rociletinib have identified a novel *EGFR* C797S mutation in 20-30% of resistant cases, and copy number gains in *MET*, *ERBB2*, and *EGFR* (32, 33). Once patients progress on a third-generation EGFR TKI, the standard treatment becomes platinum-based combination chemotherapy (or clinical trials of targeted therapies, if an actionable resistance mechanism is discovered in an individual patient). Platinum-doublet chemotherapy following progression on a prior EGFR TKI generally leads to responses in 20-30% with a PFS of 3-6 months (2, 15, 16). If patients subsequently progress on the platinum-based chemotherapy or cannot tolerate this regimen, then the options become further narrowed to single-agent chemotherapy, clinical trials, or immunotherapy. Studies evaluating single-agent second-line chemotherapy in unselected advanced NSCLC have generally demonstrated low response rates (<10%) with short median PFS (<3 months) (34, 35). Therefore, a significant unmet need exists for more effective and tolerable treatment options for patients with *EGFR*-mutant NSCLC after they exhaust EGFR TKIs.

2.1.2 *ALK*-Rearranged NSCLC

Chromosomal rearrangements involving the *ALK* gene were first identified in a small cohort of Japanese NSCLC patients in 2007 (36). Since then, *ALK* gene fusions have been found in 3-7% of NSCLCs, associated with never or light smoking history, younger age, and adenocarcinoma histology (37). The most common fusion partner for *ALK* in NSCLC is the echinoderm microtubule associated protein-like 4 (*EML4*) gene. More than 10 variants of *EML4-ALK* have been reported, all of which arise from an intrachromosomal inversion event in the short arm of chromosome 2 and preserve the ALK kinase domain (exons 20-29) (38). *ALK* rearrangements result in ligand-independent oligomerization and constitutive activation of ALK, promoting downstream survival and proliferation. Preclinical studies have demonstrated the potent

transforming capacity of *ALK* fusions like EML4-ALK (36, 39). Furthermore, *ALK*-rearranged NSCLC cells are dependent on continued ALK signaling for survival and growth (39).

The remarkable sensitivity of *ALK*-rearranged NSCLCs to ALK inhibition first became clinically evident with crizotinib. Crizotinib was originally synthesized as a potent MET inhibitor, but biochemical kinase assays revealed its additional activity against ALK and ROS1. In the phase I study of 82 patients with *ALK*-rearranged NSCLC, most of whom had received prior treatment, the ORR was 57% with a disease control rate (DCR) of 90% (9). Crizotinib was granted accelerated approval by the U.S. Food and Drug Administration (FDA) in 2011 based on the remarkable anti-tumor efficacy demonstrated in phase I/II studies. Subsequently, two randomized phase III studies demonstrated the superior efficacy of crizotinib over chemotherapy in both the second-line (ORR 65%, median PFS 7.7 months) and first-line setting (ORR 74%, median PFS 10.9 months) (10, 11).

Most patients ultimately relapse on crizotinib due to acquired resistance. Resistance can arise due to a broad array of mechanisms, including secondary *ALK* mutations (including the most common L1196M and G1269A resistance mutations), *ALK* amplification, and bypass signaling track activation (e.g., EGFR, c-KIT activation, MEK activation) (40-42). Once *ALK*-rearranged NSCLC patients progress on (or are intolerant of) crizotinib, they may be treated with next-generation ALK inhibitors such as ceritinib, alectinib, and brigatinib, which are FDA-approved. Responses to ceritinib and alectinib are seen in ~50% of crizotinib-pre-treated *ALK*-rearranged NSCLC patients (12-14). Multiple additional next-generation ALK inhibitors including lorlatinib are in clinical development. Again, acquired resistance to these TKIs due to various mechanisms limits the duration of responses (43).

Following progression on a second-generation ALK TKI (e.g., ceritinib, alectinib, brigatinib) and/or third-generation ALK TKI (e.g., lorlatinib), the resistance mechanism(s) operant in an individual patient's tumor may guide the choice of next-line therapy (43). For example, identification of an *ALK* resistance mutation (e.g., *ALK* G1202R) after failure on ceritinib, alectinib or brigatinib, may suggest lorlatinib as the next therapy, as lorlatinib has been shown to overcome all known resistance mutations. However, patients still relapse on lorlatinib and typically become refractory to all ALK TKIs. In this setting, options may include combination regimens in clinical trials or standard cytotoxic chemotherapy (i.e., platinum-based combination). Once these patients also progress on the platinum-containing chemotherapy, treatment using single-agent chemotherapy is generally ineffective (ORR <10%) (17). Better treatment options are thus needed for *ALK*-rearranged NSCLC patients after they have progressed on the available ALK TKIs.

2.2 Overview of Nivolumab

2.2.1 Nivolumab Pharmacology and Nonclinical Data

Nivolumab (also referred to as BMS-936558 or MDX-1106) is a fully human, immunoglobulin G4 (IgG4) isotype monoclonal antibody directed against the immune checkpoint cell surface receptor, programmed death-1 (PD-1) (44). PD-1 is predominantly expressed on activated T and B lymphocytes and memory T cells. It binds to two known ligands, programmed death-ligand 1

(PD-L1, also called B7-H1) and programmed death-ligand 2 (PD-L2, also called B7-DC), expressed on antigen-presenting cells (APCs) and dendritic cells (DCs). This interaction leads to the inhibition of CD28-mediated IL-2/IL-10/IL-13 and interferon-γ (IFN-γ) upregulation, and inhibition of T cell activation and proliferation, effectively modulating the physiologic peripheral T cell response and mediating tolerance to self-antigens (45).

While PD-1 belongs to the CD28 family of receptors including CD28, CD28 inducible co-stimulator (ICOS), cytotoxic T-lymphocyte antigen 4 (CTLA-4), and B and T lymphocyte attenuator (BTLA), nivolumab has been shown to bind specifically to PD-1 and not to the related CD28 family members. *In vitro* studies have demonstrated that nivolumab binds PD-1 with high affinity (EC_{50} 0.39-2.6 nM) and disrupts its interaction with PD-L1 and PD-L2 with an IC_{50} of ~1 nM (44). This results in abrogation of the inhibitory signals, enhanced T-cell proliferation and IFN-γ release *in vitro* (46-48). In mouse tumor models, expression of PD-L1 promotes immune resistance and tumor growth, and PD-1/PD-L1 blockade using monoclonal antibodies leads to anti-tumor immune responses (48-50). Repeat-dose toxicology studies of nivolumab in cynomolgus monkeys suggested that the drug was well tolerated at tested doses, with no clinical effects on body weight, food consumption, or vital sign parameters (44).

2.2.2 **Nivolumab Clinical Data**

The dose escalation study of nivolumab provided preliminary evidence for its clinical anti-tumor efficacy. In a phase I study of nivolumab in refractory solid tumors (including metastatic melanoma (n = 104), NSCLC (n = 122), castration-resistant prostate cancer (n = 17), renal cell carcinoma (n = 34), and colorectal cancer (n = 19)), a total of 296 patients were treated with nivolumab at doses of 0.1-10 mg/kg every 2 weeks (51). Nivolumab was generally well tolerated, and a maximal tolerated dose (MTD) was not defined. Most frequent adverse events (AEs) were fatigue, decreased appetite, diarrhea, nausea, cough, dyspnea, constipation, and nausea. Common treatment-related AEs included fatigue, rash, diarrhea, pruritus, decreased appetite, and nausea. Treatment-related AEs of special interest, including pneumonitis, colitis, hepatitis, hypophysitis, vitiligo, uveitis, and thyroiditis, occurred in 44% of patients. Grade ≥3 AEs were noted in a total of 14% of patients, and drug-related serious AEs occurred in 11% of patients. The spectrum, frequency, and severity of AEs did not differ across doses (51). In this study, anti-tumor activity of nivolumab was observed at all doses in NSCLC, melanoma, and renal cell carcinoma. In 76 patients with lung cancer, ORRs of 6%, 32%, and 18% were observed at doses of 1.0, 3.0, or 10.0 mg/kg, respectively. Responses were seen in 6 of 18 patients (33%) with squamous NSCLC, and 7 of 56 patients (12%) with non-squamous NSCLC (51).

In the phase I dose escalation cohort expansion trial, 129 patients with pretreated advanced NSCLC (at least one line of platinum- or taxane-based regimen) were treated with nivolumab at doses of 1, 3, or 10 mg/kg every 2 weeks (52). The ORR was 17% across all doses, 24% at the 3 mg/kg and 20% at the 10 mg/kg dose levels. The median duration of response was 17 months, and median PFS among the responders was 20.6 months. Median OS for all patients was 9.9 months, but in the patients receiving nivolumab 3 mg/kg (n = 37), median OS was 14.9 months. The most common treatment-related AEs were fatigue (24%), decreased appetite (12%), and diarrhea (10%). Among the 14% of patients who experienced graded ≥3 treatment-related AEs, the most common was fatigue, which occurred in 3%. In 41% of 129 patients, treatment-related

select AEs of any grade were noted, including most commonly, skin (16%), GI (12%), and pulmonary events. Four patients (3%) experienced treatment-related grade ≥3 pneumonitis, and three treatment-related deaths occurred, associated with pneumonitis (52).

Subsequently, two randomized phase III trials demonstrated the superior activity of nivolumab versus docetaxel in advanced non-squamous (CheckMate 057) and squamous (CheckMate 017) NSCLC (18, 19). In CheckMate 057, 582 patients with advanced non-squamous NSCLC who progressed on or after one prior chemotherapy regimen (platinum-based doublet) were randomized to nivolumab (3 mg/kg every 2 weeks) versus docetaxel. ORR was significant higher for nivolumab compared to docetaxel (19% versus 12%), and median duration of response was 17.2 months versus 5.6 months, respectively (19). OS was also improved with nivolumab (median, 12.2 months versus 9.4 months; hazard ratio (HR), 0.73). Notably, the benefit from nivolumab correlated with PD-L1 expression in the tumor. In 53% of patients with PD-L1-expressing tumor (at the cut-off of PD-L1 ≥1%), ORR to nivolumab was 31%, and in 41% of patients with PD-L1 ≥5%, ORR was 36%. There was similarly a significant correlation between OS and PD-L1 expression (19). Because the study met its primary endpoint of superior OS, it was stopped at a pre-planned interim analysis by the Independent Data Monitoring Committee.

In the CheckMate 017 study, 272 patients with advanced squamous NSCLC who progressed on first-line platinum-based chemotherapy were randomized to nivolumab versus docetaxel (18). Again, nivolumab demonstrated a superior clinical efficacy with ORR of 20% (versus 9% for docetaxel). Median OS was 9.2 months with nivolumab compared to 6.0 months with docetaxel (HR for risk of death, 0.59). Although the PD-L1 expression did not significantly correlate with clinical benefit, there was a trend for longer survival in the PD-L1-expressing subgroups (18). Based on the data from these two phase III trials, nivolumab was granted approval by the U.S. FDA for use in both squamous and non-squamous metastatic NSCLC after progression on or after platinum-based chemotherapy.

Most recently, activity of nivolumab monotherapy as first-line therapy for advanced NSCLC was investigated. In the phase I CheckMate 012 study, 52 treatment-naïve patients received nivolumab 3 mg/kg every 2 weeks until progression or unacceptable toxicity (53). The primary endpoint was safety. The most common treatment-related AEs of any grade included fatigue (29%), rash (19%), nausea (14%), diarrhea and pruritus (12% each), and arthralgia (10%). Grade ≥3 treatment-related AEs occurred in 19% of patients, including rash (4%), increased amylase and lipase, increased liver enzymes, hyperglycemia, cardiac failure, dehydration and diarrhea, hyponatremia, lung infection, and pneumonitis (1 patient each). Six patients (12%) discontinued treatment due to drug-related toxicity. The confirmed ORR was 23% with 4 ongoing responses. ORR was 28% in patients with PD-L1 expressing tumors (versus 14% in PD-L1 non-expressors). Responses were durable (median DOR, not reached, range 4.2-25.8+ months). The median OS was 19.4 months, with 1-year OS rate of 73% and 18-month OS rate of 57% (53). Based on these findings, nivolumab monotherapy as first-line therapy is being evaluated in phase III trials (CheckMate 227, NCT02477826; CheckMate 026, NCT02041533).

2.2.3 **Nivolumab Pharmacokinetics (PK)**

The single-dose PK of nivolumab was investigated in 39 patients with cancer, and found to be

linear and dose-proportional at doses ranging 0.3 mg/kg to 10 mg/kg (44, 54). The median T_{max} ranged from 1.6 to 3 hours. Across the tested doses, the geometric mean total clearance ranged from 0.13 mL/h/kg to 0.19 mL/h/kg, and the mean volume of distribution during the terminal phase (V_z) varied from 83 mL/kg to 113 mL/kg, demonstrating approximate dose proportionality. The mean terminal elimination half-life ($t_{1/2}$) was 17 to 25 days, consistent with the half-life of IgG4.

Single- and multiple-dose PK of nivolumab was studied in patients with various tumor types including melanoma and NSCLC, at doses ranging 0.1 to 10 mg/kg (single dose, or multiple doses given every 2 or 3 weeks) (44). After the first dose, geometric mean of C_{max} ranged 1.9 to 191.2 μg/mL, and AUC ranged 279 to 31095 μg.h/mL. At the steady-state PK on cycle 3 day 1, geometric mean of C_{max} ranged 3.7 to 475 μg/mL, and AUC ranged 1104 to 99621 μg.h/mL. The exposure to nivolumab increased in a dose-proportional manner over the dose levels of 0.1 to 10 mg/kg administered every 2 weeks. The geometric mean AUC was 2.9 to 3.3 μg.h/mL. The geometric mean clearance (CL) was 9.5 mL/h. Geometric mean volume of distribution at steady state (V_{ss}) was 8.0L, and the geometric mean $t_{1/2}$ was 26.7 days.

Based on the population PK analysis, the clearance of nivolumab increased with increasing body weight. It was not dependent on age, gender, race, PD-L1 expression, tumor type, or baseline tumor size. It also did not appear to be affected by renal impairment (as measured using baseline glomerular filtration rate (GFR)) or mild hepatic impairment (total bilirubin 1.0 to 1.5 times the upper limit of normal (ULN) or AST > ULN as defined using the National Cancer Institute criteria of hepatic dysfunction) (44).

Please refer to the Nivolumab Investigator's Brochure for detailed information regarding the pharmacology, toxicology, drug metabolism, and adverse event profile of nivolumab.

2.3 Overview of Carboplatin and Pemetrexed Combination

2.3.1 Carboplatin

Carboplatin is a platinum coordination compound (chemical name: platinum, diammine[1,1-cyclobutane-dicarboxylato(2-)-0,0']-,(SP-4-2)). Like cisplatin, carboplatin predominantly introduces inter-strand DNA cross-links to interfere with DNA repair. Carboplatin is used for the treatment of several cancers including ovarian, endometrial, lung, head and neck, esophageal, bladder, breast, and cervical cancers; it is currently approved by the U.S. FDA for use in ovarian and lung cancers. The most commonly observed side effects include anemia, leukopenia, neutropenia, thrombocytopenia, nausea and vomiting, hypomagnesemia, hyponatremia, hypocalcemia, hypokalemia, and liver enzyme abnormalities. Peripheral neuropathies and nephrotoxicity are significantly less frequent and less severe than with cisplatin (55).

PK studies have revealed that carboplatin plasma levels decline in a biphasic manner after a 30-minute intravenous infusion of 300 to 500 mg/m^2 doses (55). The initial plasma half-life (alpha) was 1.1-2 hours, and the post-distribution plasma half-life (beta) was 2.6-5.9 hours. The total body clearance of carboplatin was 4.4 L/hour, and apparent volume of distribution was 16 L. PK of carboplatin was linear over the tested dose ranges of 300 to 500 mg/m^2. While carboplatin is

not bound to plasma proteins, platinum from carboplatin is irreversibly bound to plasma proteins and eliminated with a minimum half-life of 5 days. The major route of elimination is renal excretion. Therefore, carboplatin doses should be reduced in patients with renal impairment (creatinine clearance <60 mL/min). In patients with normal renal function (creatinine clearance of ≥60 mL/min), 65% of the dose is excreted in the urine within 12 hours, and 71% within 24 hours. Only 3-5% of the administered platinum is excreted in the urine between 24-96 hours.

2.3.2 **Pemetrexed**

Pemetrexed is an anti-folate antineoplastic agent. It disrupts several folate-requiring enzymes essential for cell replication, including thymidylate synthase (TS), dihydrofolate reductase (DHFR), and glycinamide ribonucleotide formyltransferase (GARFT) (56). Pemetrexed has been investigated in a number of tumor types. The most common AEs include fatigue, nausea, and anorexia. When used in combination with cisplatin, additional common AEs include vomiting, neutropenia, leukopenia, anemia, oral mucositis, thrombocytopenia, and constipation. Supplementation with folate and vitamin B_{12} reduces the frequency and severity of drug-related toxicities.

The PK of pemetrexed has been evaluated in 426 cancer patients with solid tumors, at doses ranging from 0.2 to 838 mg/m^2 infused over 10 minutes (56). The total systemic exposure (AUC) and C_{max} were found to increase in a dose-proportional manner. PK parameters did not change over multiple treatment cycles. The V_{ss} of pemetrexed is 16.1 L, and approximately 81% of pemetrexed is bound to plasma proteins. Pemetrexed is primarily excreted in the urine unchanged, with 70% to 90% of the dose excreted within the first 24 hours. The clearance decreases with decreasing renal function, with resultant increase in systemic exposure. The total systemic clearance of pemetrexed is 91.8 mL/min, and $t_{1/2}$ is 3.5 hours in patients with normal renal function (56).

2.3.3 **Carboplatin Plus Pemetrexed Chemotherapy**

Platinum-based combination chemotherapy is the standard first-line treatment for patients with advanced NSCLC without targetable driver mutations. In the phase III study by the Eastern Cooperative Oncology Group (ECOG), E1594, four platinum-based doublet regimens were compared in 1,207 patients with treatment-naïve advanced NSCLC (23). No significant clinical advantage was identified for one specific regimen among cisplatin plus gemcitabine, cisplatin plus docetaxel, carboplatin plus paclitaxel, or cisplatin plus paclitaxel. The ORR was 19% for all patients, with a median OS of 7.9 months.

Subsequently in a multi-centered randomized phase III study, cisplatin (75 mg/m^2) plus pemetrexed (500 mg/m^2) given on day 1 of a 21-day cycle was demonstrated to be non-inferior to cisplatin (75 mg/m^2 on day 1) plus gemcitabine (1250 mg/m^2 on days 1 and 8) of a 21-day cycle, in chemotherapy-naïve patients with advanced NSCLC (25). Notably, in patients with non-squamous histology, cisplatin plus pemetrexed produced statistically superior median OS (11.8 months, versus 10.4 months for cisplatin plus gemcitabine in adenocarcinoma histology; adjusted HR, 0.81). In the squamous patient population, median OS was 9.4 months and 10.8 months for the cisplatin/pemetrexed and cisplatin/gemcitabine arms, respectively (adjusted HR,

1.23). The incidence of grade 3 or 4 hematologic drug-related AEs was significantly lower for cisplatin/pemetrexed compared to cisplatin/gemcitabine. With cisplatin/pemetrexed, neutropenia occurred in 15.1%, anemia in 5.6%, thrombocytopenia in 4.1%, and leukopenia in 4.8%. Drug-related grade ≥3 febrile neutropenia occurred in 1.3%, alopecia of all grades in 11.9%, grade ≥3 nausea in 7.2%, grade ≥3 vomiting in 6.1%, grade ≥3 fatigue in 6.7% (25).

The combination of carboplatin and pemetrexed was found to confer efficacy comparable to cisplatin and pemetrexed in phase II studies (57, 58). In one phase II study, 50 patients with chemotherapy-naïve, advanced NSCLC were treated with carboplatin (AUC = 6) and pemetrexed (500 mg/m^2) given every 3 weeks for 6 cycles (57). Partial responses were seen in 24% of patients, with median OS of 13.5 months and 1-year OS rate of 56%. Grade 3/4 neutropenia occurred in 26%, and grade 3/4 thrombocytopenia occurred in 2% of patients. Three patients (6%) experienced grade 3 non-hematologic AEs including diarrhea, neutropenia pneumonia, and fatigue. In another phase II study, 83 chemotherapy-naïve patients with advanced NSCLC were randomized to receive pemetrexed (500 mg/m^2) plus either oxaliplatin (120 mg/m^2) or carboplatin (AUC = 6) given every 3 weeks for up to 6 cycles (58). In the 39 patients receiving pemetrexed and carboplatin, the ORR was 31.6%, and median OS was 10.5 months with a 1-year OS rate of 43.9%. Common grade ≥3 AEs included neutropenia (25.6%), thrombocytopenia (17.9%), anemia (7.7%), fatigue (7.7%), stomatitis (2.6%), and febrile neutropenia (2.6%). Based on these studies demonstrating its efficacy and tolerability, the carboplatin/pemetrexed doublet has become a commonly used regimen in clinical practice.

2.3.4 **Pemetrexed Maintenance Therapy**

The survival benefit of maintenance therapy using single-agent pemetrexed has been demonstrated in two large trials. In one phase III study, 663 patients with advanced NSCLC who had not progressed on 4 cycles of platinum-based chemotherapy were randomized to receive pemetrexed (500 mg/m^2) or placebo in 21-day cycles (59). Maintenance pemetrexed led to increased median PFS (4.3 months versus 2.6 months; HR, 0.50) and median OS (13.4 months versus 10.6 months; HR, 0.79) compared to placebo. Treatment-related grade ≥3 AEs occurred in 16% of patients treated with pemetrexed, the most common of which included fatigue (24%), anorexia (19%), nausea (19%), anemia (15%), ALT elevation (10%), vomiting (9%), sensory neuropathy (9%), and AST elevation (8%). Treatment discontinuation due to drug-related toxicities was noted in 5% of patients.

In the PARAMOUNT trial, 539 patients with advanced NSCLC who achieved disease control after 4 cycles of cisplatin/pemetrexed were randomized to maintenance pemetrexed (500 mg/m^2 every 21 days) versus placebo (60). The mean number of pemetrexed cycles was 7.9 (range, 1 to 44). Median PFS was significantly increased with pemetrexed compared to placebo (4.1 versus 2.8 months; HR, 0.62). OS was also significantly increased (13.9 versus 11.0 months; 1-year OS rate, 58 versus 45%; HR, 0.78). The most common drug-related grade ≥3 AEs included anemia (6.4%), neutropenia (5.8%), fatigue (4.7%), leukopenia (2.2%), thrombocytopenia (1.9%), and febrile neutropenia (1.9%). Based on these studies, patients who achieve an objective response or stable disease with 4-6 cycles of platinum/pemetrexed typically continue on maintenance pemetrexed, until they develop disease progression or inability to tolerate chemotherapy.

2.4 Overview of Bevacizumab and Combination with Chemotherapy

2.4.1 Bevacizumab

Bevacizumab is a recombinant humanized monoclonal antibody targeting vascular endothelial growth factor (VEGF), an important pro-angiogenic factor (61). EGF has been implicated in angiogenesis associated with tumor growth, and increased levels of VEGF have been detected in multiple tumor types including lung cancer. Bevacizumab may exert a direct anti-angiogenic effect by binding to and clearing VEGF from the tumor environment, and additionally impact tumor vasculature and blood vessel permeability to enhance chemotherapy delivery to tumor cells (62).

Bevacizumab-associated safety signals identified in the initial phase I/II trials include hypertension, proteinuria, thromboembolic events, and hemorrhage. Additional safety signals include congestive heart failure, gastrointestinal perforations, wound healing complications, and arterial thromboembolic events. Reversible posterior leukoencephalopathy syndrome and fistula have also been reported infrequently. Further details on the safety profile of bevacizumab are available in the bevacizumab investigator's brochure.

2.4.2 Bevacizumab in Combination with Chemotherapy

Bevacizumab has been evaluated in phase II and III studies in various types of solid tumors. Two phase III trials have demonstrated the benefit of bevacizumab administered in combination with platinum-based chemotherapy as first-line therapy in advanced non-squamous NSCLC. In the Eastern Cooperative Oncology Group phase III study (E4599), bevacizumab combined with first-line carboplatin/paclitaxel in patients with non-squamous advanced NSCLC demonstrated an improvement in OS and PFS compared to chemotherapy alone (OS 12.3 months versus 10.3 months, respectively, HR 0.79, $p = 0.003$) (63). In the AVAIL study (BO17704), two doses of bevacizumab (7.5 mg/kg and 15 mg/kg every 3 weeks) in combination with cisplatin and gemcitabine were evaluated in comparison to chemotherapy alone, and again demonstrated a PFS benefit (64).

2.5 Study Rationale

2.5.1 Rationale for Doses and Schedules of Nivolumab in Combination with Carboplatin/Pemetrexed

Cancer immunity is regulated by complex interactions between the tumor and its microenvironment. Soluble and membrane-bound molecules on tumors and the tumor microenvironment (such as PD-1/PD-L1, transforming growth factor-ß (TGF-ß), and tumor necrosis factor (TNF)) can induce tumor tolerance, limit tumor antigen presentation, inhibit the cytolytic activity of effector T cells, and increase the immunosuppressive $CD4^+CD25^+FOXP3^+$ regulatory T cells (Tregs) (65). Together, these mechanisms lead to the evasion of immune-mediated tumor killing. Modulation of these interactions may help shift the equilibrium towards

immune activation rather than suppression, and boost anti-tumor immunity.

Cytotoxic chemotherapy can facilitate an anti-tumor immune response through multiple immunomodulatory effects (65). It has been shown that certain chemotherapy drugs—including platinum compounds—can induce immunogenic cell death, mediated by the toll-like receptor-4 (TLR-4) or purinergic receptor P2RX7 (66-68). This process triggers the release of chemotactic signals that recruit dendritic cells (DCs) and macrophages to the tumor site, enhanced expression of co-stimulatory molecules, and increased secretion of pro-inflammatory cytokines. Furthermore, chemotherapy agents can enhance the intrinsic tumor cell immunogenicity (e.g., increase the expression of MHC class I and antigen-processing machinery components, regulate PD-L1 expression), decrease Treg number or function, increase peripheral myeloid-derived suppressor cells, and impact DC phenotype and function (67) Platinum compounds, in particular, have been found to strongly enhance T cell activation by DCs *in vitro*, through the loss of STAT6 phosphorylation and downregulation of PD-L2 (66, 69). STAT3 expression and phosphorylation may also be modulated by platinum compounds (66, 70, 71).

Based on the immunogenic properties of standard chemotherapies and their limited duration of benefit when used alone, various regimens combining platinum-based doublet chemotherapy (PT-DC) with immune checkpoint inhibitors are now being tested. In the CheckMate 012 phase I study, 56 treatment-naïve advanced NSCLC patients received one of 4 regimens: nivolumab 10 mg/kg plus cisplatin/gemcitabine (squamous; n = 12) or cisplatin/pemetrexed (nonsquamous; n = 15), or nivolumab 5 mg/kg or 10 mg/kg plus carboplatin/paclitaxel (all histologies; n = 15 and n = 14, respectively). Nivolumab and PT-DC were given intravenously on day 1 of each 21-day cycle (and also on day 8 for the cisplatin/gemcitabine cohort) for 4 cycles, followed by nivolumab monotherapy every 3 weeks at the same dose (20).

No DLTs were reported during the first 6 weeks of treatment. The overall safety profile reflected the additive side effects of the PT-DC and nivolumab (20). Forty-five percent (45%) of the overall population experienced grade ≥3 treatment-related AEs, the most common of which were pneumonitis, fatigue, and acute renal failure (Table 2.5.1-1).

Table 2.5.1-1: **Treatment-Related AEs Reported in ≥10% of All Patients with Advanced NSCLC Treated with Nivolumab Plus PT-DC, and of Patients Treated with Nivolumab Plus Cisplatin/Pemetrexed**

	No. of Patients (%)			
	Nivolumab + Cis/Pem (n = 15)		**All Patients (n = 56)**	
Treatment-related AE	**Any Grade**	**Grade 3 or 4**	**Any Grade**	**Grade 3 or 4**
Any event	14 (93)	7 (47)	53 (95)	25 (45)
Fatigue	12 (80)	1 (7)	40 (71)	3 (5)
Nausea	10 (67)	1 (7)	26 (46)	1 (2)
Decreased appetite	7 (47)	0	20 (36)	1 (2)
Alopecia	1 (7)	0	17 (30)	0
Anemia	2 (13)	0	15 (27)	2 (4)
Rash	5 (33)	0	15 (27)	1 (2)
Diarrhea	2 (13)	0	12 (21)	1 (2)

Arthralgia	3 (20)	0	12 (21)	0
Constipation	4 (27)	0	11 (20)	0
Peripheral neuropathy	2 (13)	0	11 (20)	0
Dysgeusia	2 (13)	0	8 (14)	0
Hypersensitivity	3 (20)	1 (7)	8 (14)	1 (2)
Vomiting	4 (27)	0	8 (14)	0
Mucosal inflammation	1 (7)	0	7 (13)	0
Myalgia	0	0	7 (13)	0
Pneumonitis	3 (20)	2 (13)	7 (13)	4 (7)
Infusion-related reaction	4 (27)	0	6 (11)	0
Leukopenia	2 (13)	0	6 (11)	0
Lymphopenia	1 (7)	0	6 (11)	0
Peripheral sensory neuropathy	1 (7)	0	6 (11)	0
Pruritus	2 (13)	0	6 (11)	0
Tinnitus	4 (27)	0	5 (9)	0
Cough	2 (13)	0	3 (5)	0
Dry skin	2 (13)	0	2 (4)	0

The immune-related AEs affecting the skin, GI, renal, and pulmonary occurred in 36%, 23%, 14%, and 7% of patients, respectively (Table 2.5.1-2). Among the patients receiving nivolumab with cisplatin/pemetrexed, the immune-related AEs affecting the skin, GI, renal, and pulmonary occurred in 40%, 20%, 20%, and 20% of the patients. Treatment-related AEs led to drug discontinuation in 21% of the patients, including 33% of patients (5 of 15 patients) in the nivolumab plus cisplatin/pemetrexed arm. Most discontinuations were observed during the nivolumab maintenance therapy. The treatment-related AEs including pneumonitis were effectively managed with steroids or infliximab. No treatment-related deaths were reported (20).

Table 2.5.1-2: **Treatment-Related Immune AEs Reported in ≥10% of All Patients with Advanced NSCLC Treated with Nivolumab Plus PT-DC, and of Patients Treated with Nivolumab Plus Cisplatin/Pemetrexed**

	No. of Patients (%)			
	Nivolumab + Cis/Pem (n = 15)		**All Patients (n = 56)**	
Immune AE	**Any Grade**	**Grade 3 or 4**	**Any Grade**	**Grade 3 or 4**
Skin	6 (40)	0	20 (36)	3 (5)
Rash	5 (33)	0	15 (27)	1 (2)
Pruritus	2 (13)	0	6 (11)	0
Rash maculopapular	0	0	3 (5)	2 (4)
Erythema	1 (7)	0	1 (2)	0
Rash pruritic	0	0	1 (2)	0
GI	3 (20)	1 (7)	13 (23)	2 (4)
Diarrhea	2 (13)	0	12 (21)	1 (2)
Colitis	1 (7)	1 (7)	2 (4)	1 (2)
Hypersensitivity/infusion reaction	6 (40)	1 (7)	13 (23)	1 (2)
Hypersensitivity	3 (20)	1 (7)	8 (14)	1 (2)

Infusion-related reaction	4 (27)	0	6 (11)	0
Renal	3 (20)	1 (7)	8 (14)	3 (5)
Blood creatinine increased	1 (7)	0	4 (7)	0
Acute renal failure	1 (7)	1 (7)	3 (5)	3 (5)
Allergic nephritis	1 (7)	1 (7)	2 (4)	2 (4)
Blood urea increased	0	0	1 (2)	0
Creatinine renal clearance decreased	1 (7)	0	1 (2)	0
Renal failure	0	0	1 (2)	0
Tubulointerstitial nephritis	1 (7)	0	1 (2)	0
Pulmonary	3 (20)	2 (13)	7 (13)	4 (7)
Pneumonitis	3 (20)	2 (13)	7 (13)	4 (7)

The ORRs for all nivolumab and chemotherapy arms ranged 33% to 47%, with DCRs ranging 73% to 93% (20). In the nivolumab plus cisplatin/pemetrexed arm, ORR was 47% (7 of 15 patients), and DCR was 93% (14 of 15 patients). The 24-week PFS rate for all arms ranged 38% to 71% (in the nivolumab plus cisplatin/pemetrexed cohort, 71%). The median OS for patients that received nivolumab plus cisplatin/pemetrexed was 19.2 months, with 1-year OS rate of 87% and 2-year OS rate of 33%.

These data suggest that the regimen combining nivolumab with platinum plus pemetrexed is overall tolerable, and effective in patients with advanced NSCLC. Moreover, they provide the rationale for investigating the efficacy of nivolumab plus PT-DC in TKI-pre-treated but chemotherapy-naïve patients with advanced *EGFR*-mutant or *ALK*-rearranged NSCLCs. The majority of patients in the CheckMate 012 study (89%) did not have *EGFR* mutations in the tumor, and were not evaluated for the presence of *ALK* rearrangements (20). The efficacy of combining nivolumab and PT-DC in TKI-pre-treated patient populations is also unknown.

The present study will evaluate the PT-DC regimen of carboplatin (AUC = 5) and pemetrexed (500 mg/m^2) in combination with nivolumab. Carboplatin plus pemetrexed is a standard of care chemotherapeutic regimen for treatment-naïve patients with advanced non-squamous NSCLC without molecular alterations, and also for patients with *EGFR*-mutant or *ALK*-rearranged NSCLC after progression on available TKIs.

Patients will receive 4 cycles of carboplatin and pemetrexed plus nivolumab on an every 3-week cycle, followed by maintenance of pemetrexed plus nivolumab every 3 weeks until disease progression, inability to tolerate, study termination, or death, whichever occurs first. The duration of the initial platinum-based induction is based on multiple trials and a meta-analysis of 5 trials that compared 6 cycles versus 3-4 cycles (72). There was no statistically significant improvement in OS with 6 cycles versus 3-4 cycles (9.5 versus 8.7 months), although there was a modest improvement in the PFS (6.09 versus 5.33 months). Notably, severe anemia occurred more frequently with 6 cycles compared to 3-4 cycles (7.8% versus 2.9%) (72).

Flat dosing of nivolumab will be used at 360 mg every 3 weeks. Based on the nivolumab PK analysis, the simulated steady state concentration at trough (C_{minss}), peak (C_{maxss}), and average (C_{avgss}) with 360 mg are less than those of 10 mg/kg given every 2 weeks. Prior PK data and AE

profiles from multiple trials have demonstrated nivolumab to be safe and well tolerated at doses up to 10 mg/kg every 2 weeks (18-20, 44, 51-53). Therefore, the 360 mg dosing on an every 3-week schedule is expected to be safe and tolerable.

2.5.2 Rationale for the Dosing of Bevacizumab in Combination with Nivolumab and Carboplatin/Pemetrexed

Emerging evidence suggests that VEGF may play a role in cancer immune evasion through several mechanisms. For example, VEGF may reduce lymphocyte adhesion to vessel walls and contribute to decreased immune cell recruitment (73). In a mouse melanoma model, VEGF blockade was shown to synergize with adoptive immunotherapy, resulting in improved anti-tumor activity, prolonged survival, and increased T cell trafficking into tumors (74). Synergistic effects have also been observed in patients with melanoma treated with ipilimumab and bevacizumab (75).

In NSCLC, bevacizumab has been tested in combination with atezolizumab (a PD-L1 antibody) and carboplatin/paclitaxel in metastatic non-squamous NSCLC (IMpower150) (76). In this phase III study, patients were randomized to receive atezolizumab plus chemotherapy, bevacizumab plus chemotherapy, or atezolizumab plus chemotherapy plus bevacizumab. PFS and OS were longer in the atezolizumab plus chemotherapy plus bevacizumab group versus the bevacizumab plus chemotherapy group. Notably, this study allowed patients with EGFR and ALK alterations who had failed prior TKI therapy. Clinical benefit of the combination of atezolizumab plus bevacizumab plus chemotherapy was observed in this subgroup (76).

The dosing of bevacizumab used in the IMpower150 study was 15 mg/kg every 3 weeks, the standard dosing schedule used in metastatic NSCLC (76). With this dosing of bevacizumab, the combination with atezolizumab and chemotherapy was generally well-tolerated. This dosing of bevacizumab (15 mg/kg every 3 weeks) was also tested in combination with nivolumab in previously treated metastatic NSCLC (77). No treatment-related grade 4 AEs were reported; grade 3 AEs included pneumonitis (n = 2) and cough and Tubulointerstitial nephritis (n = 1 each). This study will evaluate the safety and efficacy of bevacizumab 15 mg/kg every 3 weeks combined with nivolumab 360 mg every 3 weeks plus carboplatin/pemetrexed.

2.5.3 Rationale for Assessing PD-L1 Expression in Baseline Tumor Tissue

Numerous studies have suggested a correlation between the level of PD-L1 expression in tumor and clinical benefit from nivolumab (and other PD-1/PD-L1 inhibitors) (18-21, 51-53). As an example, in the CheckMate 057 phase III study of nivolumab in patients with advanced NSCLC progressing on platinum-based chemotherapy, ORR to nivolumab was 9% in patients with PD-L1 non-expressing tumors (47% of the study cohort), 31% in those with PD-L1 ≥1% (53% of the study cohort), and 36% in those with PD-L1 ≥5% (41% of the study cohort) (19). Median OS was 10.5 months in PD-L1 non-expressors, 17.7 months in patients with PD-L1 ≥1%, and 19.4 months in patients with PD-L1 ≥5% (19).

Similarly, in the CheckMate 012 study, efficacy of nivolumab plus ipilimumab was enhanced with increasing PD-L1 expression (78). The ORR of the N3 Q2W + I1 Q6W regimen was 0%

(0/7) in PD-L1 non-expressing tumors, 57% (13/23) in tumors with ≥1% PD-L1, and 86% (6/7) with ≥50% PD-L1. Efficacy of first-line nivolumab plus ipilimumab in advanced NSCLC by tumor PD-L1 expression is shown in Table 2.5.3-1.

Table 2.5.3-1: **Efficacy of First-Line Nivolumab Plus Ipilimumab in NSCLC by Tumor PD-L1 Expression**

	N3 Q2W + I1 Q12W (n = 38)	N3 Q2W + I1 Q6W (n = 39)	N3 Q2W (n = 52)
ORR, % (n/N)			
<1% PD-L1	30 (3/10)	0 (0/7)	14 (2/14)
≥1% PD-L1	57 (12/21)	57 (13/23)	28 (9/32)
≥50% PD-L1	100 (6/6)	86 (6/7)	50 (6/12)
Median PFS, mo			
<1% PD-L1	4.7	2.4	6.6
≥1% PD-L1	8.1	10.6	3.5
≥50% PD-L1	13.6	NR	8.4
1-year OS rate, %			
<1% PD-L1	NC	NC	79
≥1% PD-L1	90	83	69
≥50% PD-L1	NC	100	83

NR, not reached; NC, not calculated

However, not all studies have shown a correlation between PD-L1 expression and nivolumab activity. In the CheckMate 012 trial evaluating first-line nivolumab plus PT-DC chemotherapy, for example, a clear association between PD-L1 and ORR, PFS, and OS endpoints could not be detected (20).

Therefore, the current study will require a baseline tumor tissue for examination of the PD-L1 expression status. Exploratory analysis will be performed to look for any association between clinical benefit from the nivolumab combination regimens and tumor PD-L1 positivity (defined as PD-L1 ≥1%).

2.5.4 Rationale for Allowing Continued Treatment in Select Cases of Progressive Disease

Studies have shown that up to ~10% of patients treated with immunotherapeutic agents may manifest an atypical, immune-related pattern of response, whereby there is initial increase in tumor burden (progressive disease based on the conventional RECIST criteria) before disease control is achieved (79-81). This phenomenon has been termed tumor pseudoprogression. Tumor lesions may initially increase in size—or new lesions may appear—because of inflammatory cell infiltrates or necrosis within the tumor. Furthermore, in some cases, patients may have subtle radiographic progression of disease but continue to benefit clinically.

Therefore, patients in this study will be allowed to continue study therapy after a RECIST v1.1-defined progression if they are tolerating the study drug(s) and are deemed to be deriving clinical

benefit based on the investigator assessment.

2.6 Correlative Studies Background

Although immunotherapies using anti-PD-1/PD-L1 antibodies are demonstrating efficacy across a spectrum of malignancies, the response rates have been variable. Therefore, intensive efforts are underway to identify blood- and tumor-based biomarkers that may predict response to these agents.

One of the first potential tumor-based biomarkers explored was PD-L1 status in the tumor cells. A number of clinical studies have suggested a correlation between the level of PD-L1 expression in tumors and responses to nivolumab (18-20, 51-53, 78), as detailed in Section 2.5.3. However, this correlation is imperfect. Patients who have PD-L1 non-expressing tumors may still respond to anti-PD-1/PD-L1 therapies such as nivolumab; conversely, patients with tumors expressing a high level of PD-L1 may fail to respond. At least partially, this discrepancy may be due to the dynamic nature of PD-L1 expression, influenced by concurrent and/or prior treatments and timing of the biopsy (82-85). There is also spatial heterogeneity in the expression of PD-L1. Therefore, alternative biomarker approaches are being investigated.

Other potential biomarkers aside from PD-L1 have been proposed, derived from tumor cells or immune cells in the tumor microenvironment. These biomarkers, detectable by IHC, include immunoregulatory molecules PD-L2, FOXP3, PD-1, CTLA-4, LAG-3, co-stimulatory molecules and tumor-associated antigens (85, 86). Furthermore, several studies have found that the mutational load and/or the number of predicted neoantigens are relevant in predicting response to checkpoint inhibition. The total burden of nonsynonymous mutations as determined by whole genome or exome sequencing of tumor DNA has been shown to correlate with clinical benefit of anti-PD-1 therapy in various cancers including NSCLC. Similarly, the number of candidate tumor neoantigens, predicted using *in silico* algorithms that account for MHC binding, is associated with response to anti-PD-1/PD-L1 and anti-CTLA-4 therapies (87-89). Other tumor-associated biomarkers that have been proposed include tumor-based multigene signatures and the presence of tumor-infiltrating lymphocytes (TILs) measured using multiplex IHC or immunofluorescence (IF) for molecules such as CD3, CD4, CD8, FOXP3, PD-L1 (86, 90).

Biomarkers derived from the blood are also being explored, given the relative ease of collection and potential for serial monitoring. Soluble mediator detection methods such as enzyme-linked immunoabsorbent assay (ELISA) and enzyme-linked immunospot (ELISPOT) can be used to detect the relative abundance of cytokines and chemokines (e.g., IFN-ϒ, IL-2, IL-5, IL-10, IL-17, granzyme B, TNF, GM-CSF) and tumor antigen-specific antibodies in the peripheral blood (86).

As part of this study, we will collect pre-treatment archival (within 6 months of starting the study) or fresh FFPE tumor biopsy specimens. These biopsies will be evaluated for potential biomarkers of response to the study drugs in the study population. Specifically, the level of PD-L1 expression in the tumor cells will be determined using IHC. Additional IHC on FFPE tissue may be performed to detect the expression of immunoregulatory proteins such as, but not limited to, PD-L2, PD-1, and other markers associated with tumor-infiltrating lymphocytes (TILs) (e.g., CD4, CD8, FOXP3). FFPE tissue and/or peripheral blood sample may be further evaluated by

molecular techniques including but not limited to: IF, QPCR, and/or genetic sequencing. Because of the evolving nature of the field, not all of the potential biomarkers of interest can be pre-specified in this document.

3. PARTICIPANT SELECTION

3.1 Eligibility Criteria

Participants must meet the following eligibility criteria for study entry:

- Histologically or cytologically confirmed advanced (stage IIIB or IV) non-small-cell lung cancer (NSCLC).
    - *ALK*-rearranged NSCLC: *ALK* rearrangement as assessed by *ALK* FISH, IHC, or next-generation sequencing (NGS). For *ALK* FISH, rearrangements must be detected in >15% of tumor cells.
    - *EGFR*-mutant NSCLC: *EGFR* activating gene mutation (e.g., L858R, exon 19 deletion) per local testing.
- Patients receiving bevacizumab (Cohorts E and F) must have non-squamous histology NSCLC.
- Presence of at least one measurable lesion as defined by RECIST v1.1. A previously irradiated site lesion may only be counted as a target lesion if there is clear sign of progression since the completion of irradiation.
- Prior treatment with appropriate tyrosine kinase inhibitors (TKIs) as follows:
    - *ALK*-positive NSCLC (Cohorts F and H): Participants must have progressed on or after 1 or more next-generation ALK-TKI(s).
    - *EGFR*-mutant NSCLC (Cohorts E and G): Participants must have progressed on or after 1 or more third-generation EGFR-TKI(s).
- No prior systemic chemotherapy is allowed.
  NOTE: Prior adjuvant or neoadjuvant chemotherapy is allowed if received more than 12 months prior to the study. In addition, one prior cycle (dose) of chemotherapy is allowed if there was no evidence of disease progression following the dose.
- Tumor tissue sample is required within 6 months prior to study enrollment. Tissue sample may be fresh (core needle, excisional, or incisional biopsy), or archival if obtained within 6 months prior to enrollment. If a tissue sample is available but it has been > 6 months, the

Principal Investigator may approve the sample after discussion. PD-L1 IHC testing will be performed on the tumor tissue, but positivity on the PD-L1 IHC testing is not required to enroll in the study.

- Clinically asymptomatic and stable central nervous system (CNS) metastases are allowed (including untreated CNS metastases) if they have not required increasing doses of steroids or stable doses equivalent to prednisone > 10 mg daily within 2 weeks prior to study entry for CNS symptoms.

- Prior palliative radiotherapy must have been completed at least 2 weeks prior to study entry.

- Subjects must have been off any prior TKIs for at least 5 half-lives of that drug.

- Age ≥ 18 years old.

- ECOG performance status of 0 or 1.

- Life expectancy ≥ 12 weeks.

- Screening laboratory values must meet the following criteria:

  - WBC ≥ 2.0 x 10^9/L
  - Neutrophils ≥ 1.5 x 10^9/L
  - Platelet ≥ 100 x 10^9/L
  - Hemoglobin ≥ 9/dL
  - Serum creatinine ≤ 1.5 x ULN or calculated creatinine clearance using Cockcroft-Gault formula ≥ 50 mL/min

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

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

  - Total bilirubin ≤ 1.5 x ULN (except in patients with Gilbert's syndrome who may have total bilirubin < 3.0 mg/dL)
  - AST and ALT ≤ 3.0 x ULN (or ≤ 5.0 x ULN if liver metastases are present)

- Females of child-bearing potential (defined as a sexually mature woman who has not undergone a hysterectomy or bilateral oophorectomy or has not been naturally post-menopausal for at least 24 consecutive months) must:
  - Have a negative serum or urine pregnancy test obtained within 24 hours prior to starting the investigational drug.
  - Not be breastfeeding.
  - Agree to use, and be able to comply with, highly effective contraception (failure rate less than 1% per year) without interruption while on study treatment plus 5 half-lives of

nivolumab (half-life up to 25 days) plus 30 days (duration of ovulatory cycle) for a total of 23 weeks post treatment completion. Complete abstinence is acceptable if it is in line with the preferred and usual lifestyle of the patient. Period abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not acceptable methods of contraception. Examples of non-hormonal contraceptive methods with a failure rate of < 1% per year include bilateral tubal ligation, male sterilization, hormonal implants, established and proper use of combined oral or injected hormonal contraceptives, and certain intrauterine devices. Alternatively, two methods (e.g., two barrier methods from the options of diaphragm, cervical cap, vaginal sponge, and condom, or progesterone-only oral hormonal contraception where inhibition of ovulation is not the primary mode of action) may be combined to achieve a failure rate of < 1% per year. Barrier methods must always be supplemented with the use of a spermicide.

- Male subjects agree to remain abstinent or use a condom plus an additional contraceptive method that result in a failure rate of <1% per year during sexual contact with a female of childbearing potential while participating in the study, during dose interruptions, and for 31 weeks following the last dose of the study treatment, even if he has undergone a successful vasectomy. Abstinence is only acceptable if it is in line with the preferred and usual lifestyle of the patient. Periodic abstinence and withdrawal are not acceptable.

- Subject has the ability to understand and provide signed informed consent.

- Subject has the willingness and ability to comply with scheduled visits, treatment plans, laboratory tests, and other study procedures.

3.2 Exclusion Criteria

Participants who meet any of the following criteria will be excluded from the study entry:

- Subjects previously treated with T cell immune-modulating antibodies, including anti-CTLA-4, anti-PD-1 and/or anti-PD-L1 agents.

- Subjects with symptomatic brain metastases, carcinomatous meningitis, spinal cord compression, or intractable back pain due to compression of destructive mass.

- Subjects with active, known, or suspected autoimmune disease. Subjects with type I diabetes mellitus, hypothyroidism only requiring hormone replacement, skin disorders (such as vitiligo, psoriasis, or alopecia) not requiring systemic treatment, or conditions not expected to recur in the absence of an external trigger are permitted to enroll.

- Subjects with a condition requiring systemic treatment with either corticosteroids (> 10 mg daily prednisone equivalent) or other immunosuppressive medications within 14 days of randomization (unless used to treat investigational drug-related adverse events). Inhaled or topical steroids, and adrenal replacement steroid doses > 10 mg daily prednisone equivalent, are permitted in the absence of active autoimmune disease.

- Subjects with interstitial lung disease or interstitial pneumonitis that is symptomatic or may interfere with the detection or management of suspected drug-related pulmonary toxicity.

- For Cohorts E and F (bevacizumab cohorts) only (not applicable to cohorts G and H):

    - Previous history of hemoptysis (expectoration of more than 2.5 mL of blood) within 3 months prior to enrollment.
    - History of hemorrhagic CNS metastases or intracranial hemorrhage.
    - History of or genetic predisposition to a bleeding diathesis or coagulopathy.
    - Therapeutic anticoagulation, including but not limited to: low-molecular weight heparin, heparin, or warfarin. Anticoagulants must be discontinued 10 days prior to the first administration of bevacizumab. Prophylactic use of anticoagulants is allowed.
    - Current or recent (within 10 days of first dose of bevacizumab) use of aspirin (> 325 mg/day) or other non-steroidal anti-inflammatories known to inhibit platelet function.
    - Clinically significant heart disease (i.e., active), stroke or myocardial infarction within 6 months prior to enrollment, unstable angina pectoris, congestive heart failure of grade > II according to the New York Heart Association (NYHA), or cardiac arrhythmia requiring specific treatment during the study and that may interfere with the follow-up of the study treatment or poorly controlled by treatment.
    - Arterial or venous thromboembolic events within 6 months of study enrollment.
    - Poorly controlled arterial hypertension (systolic > 150 mm Hg and/or diastolic > 100 mm Hg), with or without antihypertensive medication. Patients presenting with high blood pressure are eligible if the dose or adjustment of anti-hypertensives lowers blood pressure to meet the inclusion criteria of the study.
    - Minor surgical intervention, including placement of a permanent catheter, within 24 hours prior to the first infusion of bevacizumab.
    - Non-healing wound, active peptic ulcer, or untreated bone fracture.
    - Previous history of abdominal fistula, tracheoesophageal fistula or other fistula with grade 4 severity, gastrointestinal perforation or intra-abdominal abscess within 6 months prior to enrollment.
    - Proteinuria at baseline. Subjects unexpectedly found to have 2+ or greater proteinuria on a urine dipstick at baseline should undergo a 24-hour urine which must be an adequate collection and must demonstrate <2 g of protein/24 hr to allow participation in the study.
    - Patients who have received previous anti-angiogenic treatment (experimental or marketed: bevacizumab, thalidomide, CP-547632, sunitinib, sorafenib, or others).

- Subjects must have recovered from the effects of major surgery or significant traumatic injury at least 14 days prior to screening. No major surgery, other than diagnostic surgery, is allowed within 4 weeks prior to treatment in the study.

- Co-administration of anti-cancer therapies other than those administered in the study.

- Subjects with other active malignancy requiring concurrent intervention.

- Known history of testing positive for human immunodeficiency virus (HIV) or known acquired immunodeficiency syndrome (AIDS). HIV-positive participants are ineligible because these participants are at increased risk of lethal infections when treated with marrow-suppressive therapy, and because there is the potential for pharmacokinetic interactions with combination antiretroviral therapy and study drugs.

- Any positive test for hepatitis B virus or hepatitis C virus indicating acute or chronic infection.

- Subjects with ≥ grade 2 peripheral neuropathy at enrollment per the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE).

- Pregnant or lactating women. Pregnant women are excluded from this study because the study drugs (i.e., nivolumab, carboplatin, pemetrexed, and/or bevacizumab) have the potential for teratogenic or abortifacient effects. Because there is an unknown but potential risk for adverse events in nursing infants secondary to treatment of the mother with these agents, breastfeeding should be discontinued.

- Subjects currently enrolled in any other clinical protocol or investigational trial that involves administration of experimental therapy and/or therapeutic devices, or investigational drug.

- History of allergy or hypersensitivity to any study drugs or their excipients.

- Any known clinically significant concomitant medical condition, laboratory abnormality, or psychiatric illness that, in the investigator's opinion, would prevent the subject from participating in the study, pose an unacceptable risk to the patient in this study, or interfere with the interpretation of safety results.

3.3 Inclusion of Women and Minorities

Both men and women of all races and ethnic groups are eligible for this trial.

4. REGISTRATION PROCEDURES

4.1 General Guidelines for DF/HCC Institutions

Institutions will register eligible participants in the Clinical Trials Management System (CTMS) OnCore. Registrations must occur prior to the initiation of protocol therapy. Any participant not registered to the protocol before protocol therapy begins will be considered ineligible and registration will be denied.

An investigator will confirm eligibility criteria and a member of the study team will complete the protocol-specific eligibility checklist.

Following registration, participants may begin protocol therapy. Issues that would cause treatment delays should be discussed with the Overall Principal Investigator (PI). If a participant does not receive protocol therapy following registration, the participant's registration on the study must be canceled. Registration cancellations must be made in OnCore as soon as possible.

4.2 Registration Process for DF/HCC Institutions

DF/HCC Standard Operating Procedure for Human Subject Research Titled *Subject Protocol Registration* (SOP #: REGIST-101) must be followed.

5. TREATMENT PLAN

In this phase II trial, subjects with TKI-pre-treated, advanced *EGFR*-mutant or *ALK*-rearranged NSCLC will be enrolled. Subjects must be chemotherapy-naïve, and have *EGFR*-mutant NSCLC which progressed on a third-generation EGFR TKI, or *ALK*-rearranged NSCLC which progressed on at least one next-generation ALK TKI. We will evaluate the efficacy of nivolumab plus carboplatin and pemetrexed plus bevacizumab in patients who are bevacizumab-eligible, and the efficacy of nivolumab plus carboplatin and pemetrexed in patients who are bevacizumab-ineligible. Cohorts of the study are as specified below:

Nivolumab Plus Carboplatin and Pemetrexed Plus Bevacizumab:

- **Cohort E**: *EGFR*-mutant advanced NSCLC, previously treated with at least one third-generation EGFR TKI and chemotherapy-naïve, who are bevacizumab-eligible.
- **Cohort F**: *ALK*-rearranged advanced NSCLC, previously treated with at least one next-generation ALK TKI and chemotherapy-naïve, who are bevacizumab-eligible.

Nivolumab Plus Carboplatin and Pemetrexed:

- **Cohort G**: *EGFR*-mutant advanced NSCLC, previously treated with at least one third-generation EGFR TKI and chemotherapy-naïve, who are bevacizumab-ineligible.
- **Cohort H**: *ALK*-rearranged advanced NSCLC, previously treated with at least one next-generation ALK TKI and chemotherapy-naïve, who are bevacizumab-ineligible.

5.1 Treatment Regimen

Nivolumab, carboplatin and pemetrexed, with or without bevacizumab will be administered every 3 weeks, with 21 consecutive days defined as a treatment cycle, until disease progression, unacceptable toxicity, or completion of 4 cycles, whichever comes first. A ±3-day window period will be authorized throughout the study period. Treatment will be administered as intravenous (IV) infusion. On Day 1 of each cycle, all eligible patients will receive the drug

infusions in the following order:

Cohorts E and F: Nivolumab 360 mg will be administered IV over approximately 30 minutes (with a window of ±5 minutes), followed at least 30 minutes later by bevacizumab (15 mg/kg) IV over 90 minutes (with a window of ±15 minutes) for the first infusion shortening to 60 (±10) minutes then 30 (±10) minutes for subsequent infusions if tolerated, followed by pemetrexed (500 mg/m^2) IV over approximately 10 minutes and carboplatin (AUC 5) IV over approximately 60 minutes.

Cohorts G and H: Nivolumab 360 mg will be administered IV over approximately 30 minutes (with a window of ±5 minutes), followed at least 30 minutes later by pemetrexed (500 mg/m^2) IV over approximately 10 minutes and carboplatin (AUC 5) IV over approximately 60 minutes.

Subjects who have stable disease or response after 4 cycles will continue nivolumab and pemetrexed with bevacizumab (Cohorts E and F) or without bevacizumab (Cohorts G and H) at the same doses as maintenance therapy on Day 1 every 3 weeks, until disease progression, unacceptable toxicity, or withdrawal of consent, whichever occurs first.

Pemetrexed and carboplatin and bevacizumab may be prepared and administered according to institutional standards.

Reported adverse events and potential risks are described in Section 7. Appropriate dose modifications are described in Section 6. No investigational or commercial agents or therapies other than those described below may be administered with the intent to treat the participant's malignancy.

Please see Table 5.1.1 and Table 5.1.2 for the Regimen Description.

Table 5.1.1: **Regimen of Nivolumab Plus Bevacizumab Plus Carboplatin and Pemetrexed**

Regimen Description					
Agent	***Premedications; Precautions***	***Dose***	***Route***	***Schedule***	***Cycle Length***
Nivolumab	N/A	360 mg	IV over approximately 30 minutes before bevacizumab	Day 1, week 1	21 days (3 weeks)
Bevacizumab	N/A	15 mg/kg	IV over approximately 90 minutes before carboplatin and	Day 1,week 1	

			pemetrexed for the first infusion – if tolerated, can shorten to IV over approximately 60 minutes and then over approximately 30 minutes for the subsequent infusions		
Carboplatin	Anti-emetics per local standards, including dexamethasone and 5-HT_3 receptor antagonist.	AUC 5	IV over approximately 60 minutes, to start at least 30 minutes after the completion of nivolumab	Day 1, week 1, for 4 cycles	
Pemetrexed	Premedicate with dexamethasone on the day before, day of, and day after pemetrexed. Oral folic acid (continued daily) and IM vitamin B12 (every 3 cycles) should be initiated 1 week prior to pemetrexed treatment.	500 mg/m^2	IV over approximately 10 minutes, to start at least 30 minutes after the completion of nivolumab	Day 1, week 1	

Table 5.1.2: **Regimen of Nivolumab Plus Carboplatin and Pemetrexed**

Regimen Description					
Agent	***Premedications; Precautions***	***Dose***	***Route***	***Schedule***	***Cycle Length***
Nivolumab	N/A	360 mg	IV over approximately 30 minutes before carboplatin and pemetrexed	Day 1, week 1	21 days (3 weeks)
Carboplatin	Anti-emetics per local standards, including	AUC 5	IV over approximately	Day 1, week 1, for	

	dexamethasone and 5-HT_3 receptor antagonist.		60 minutes, to start at least 30 minutes after the completion of nivolumab	4 cycles	
Pemetrexed	Premedicate with dexamethasone on the day before, day of, and day after pemetrexed. Oral folic acid (continued daily) and IM vitamin B12 (every 3 cycles) should be initiated 1 week prior to pemetrexed treatment.	500 mg/m^2	IV over approximately 10 minutes, to start at least 30 minutes after the completion of nivolumab	Day 1, week 1	

5.2 Agent Administration

For subjects enrolled in Cohorts E and F, nivolumab 360 mg will be administered IV over 30 minutes (with a window of ±5 minutes), followed by bevacizumab (15 mg/kg) IV (over the time period as specified above), followed by pemetrexed (500 mg/m^2) IV over 10 minutes and carboplatin (AUC 5) IV over 30 minutes, on Day 1 of each 21-day cycle. For subjects enrolled in Cohorts G and H, nivolumab 360 mg will be administered IV over 30 minutes (with a window of ±5 minutes), followed by pemetrexed (500 mg/m^2) IV over 10 minutes and carboplatin (AUC 5) IV over 30 minutes, on Day 1 of each 21-day cycle. A ±3-day window period will be authorized throughout the study period.

This combination will continue until disease progression, unacceptable toxicity, or completion of 4 cycles, whichever comes first. Subjects who have stable disease or response after 4 cycles will discontinue carboplatin, and continue nivolumab 360 mg and pemetrexed 500 mg/m^2 with (Cohorts E and F) or without (Cohorts G and H) bevacizumab as maintenance therapy on Day 1 every 3 weeks. Again, a ±3-day window period will be authorized throughout the study period. Treatment will continue until disease progression, unacceptable toxicity, or withdrawal of consent, whichever occurs first.

In subjects who require pemetrexed dose reduction, the dose of pemetrexed may be escalated to 500 mg/m^2 after the discontinuation of carboplatin at the investigator's discretion, if the prior toxicity was felt to be related mainly to carboplatin.

If a subject receiving nivolumab and pemetrexed (with or without bevacizumab) maintenance experiences an adverse event, and the investigator can attribute it to either nivolumab or pemetrexed or bevacizumab, then that agent can be discontinued and the remaining agent(s) can be continued until disease progression or unacceptable toxicity.

On the day of the infusion, nivolumab is to be administered first. Infusion of the bevacizumab and/or platinum-doublet chemotherapy will start at least 30 minutes after the completion of

nivolumab infusion. Pemetrexed and carboplatin and bevacizumab may be prepared and administered according to institutional standard.

Pemetrexed dosing calculations are based on the body weight. If the subject's weight on the day of the dosing differs by >10% from the weight used to calculate the prior dose, the pemetrexed dose must be re-calculated. All doses should be rounded to the nearest milligram or per institutional standard for bevacizumab, carboplatin and pemetrexed. It is permissible to re-calculate the doses more frequently for weight changes greater than 5%.

The carboplatin dose is calculated using the Calvert formula as follows:

- Carboplatin dose (mg) = Target AUC x [(CrCl (mL/min) + 25]
- Creatinine clearance (CrCl) calculation is based on the Cockroft-Gault formula (see Inclusion Criteria in Section 3.1) and should include the most recent serum creatinine and most recent weight. If calculation of the CrCl by the Cockroft-Gault formula yields a result of > 125 mL/min, then a CrCl should be calculated by an alternative formula per institutional standards or capped at 125 mL/min.
- The dose of carboplatin may be capped per local standards.

Pre-medication for use with pemetrexed: Oral corticosteroid should be given according to local standards at a dose equivalent to dexamethasone 4 mg BID on the day prior to, day of, and day after the administration of pemetrexed during the carboplatin, pemetrexed, and nivolumab induction cycles. Once participants are receiving maintenance therapy of pemetrexed plus nivolumab, steroid dose ≤ dexamethasone 4 mg BID on the day prior to, day of, and day after the administration of pemetrexed will be allowed.

Oral folic acid 350 to 1000 mcg daily should be given starting 1 week prior to the first dose of pemetrexed, with at least 5 doses of folic acid administered in the 7 days prior to the first dose. Folic acid should be continued daily for the duration of pemetrexed treatment, and for 21 days after the last dose of pemetrexed. Intramuscular (IM) injection of vitamin B12 1000 mcg should be administered approximately 1 week prior to the first dose of pemetrexed, and repeated every 3 cycles (every 9 weeks) thereafter during pemetrexed treatment. Subsequent injections of vitamin B12 may be given on the same day as pemetrexed.

Pre-medications are allowed to be administered during the wait time after the nivolumab infusion.

Pre-medications for use with carboplatin/pemetrexed: Anti-emetic premedication(s) will be administered according to local standards. Recommended anti-emetic treatments are dexamethasone (dosing according to local standards, and an equivalent dose of another corticosteroid may be substituted) and a 5-HT_3 receptor antagonist (type per investigator discretion and local standards of care). Additional use of anti-emetic medications is allowed at the investigator's discretion.

Pre-medications are allowed to be administered during the wait time after the nivolumab infusion.

Guidelines for appropriate dose modifications and treatment interruptions or discontinuation due to specific adverse events are provided in Section 6..

5.3 General Concomitant Medication and Supportive Care Guidelines

5.3.1 Permitted Therapy

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

Regular concomitant use of bisphophosphonates and RANK-L inhibitors for prevention or reduction of skeletal-related events in patients with bone metastases is allowed if initiated prior to first dose of study therapy.

Caution should be exercised when the following are administered with bevacizumab:

- Aspirin and NSAIDs: Since the most serious toxicities observed with bevacizumab to date are hemorrhages, thrombosis, and gastrointestinal perforations, the use of aspirin and NSAIDs must be limited.
    - Participants who require long-term administration of aspirin (>325 mg/day) or non-steroidal anti-inflammatory drugs that inhibit platelet function at doses used to treat chronic inflammatory diseases will not be included in the study (see inclusion and exclusion criteria).
    - Administration of low doses of aspirin (≤325 mg/day), occasional administration of non-steroidal anti-inflammatory drugs or non-steroidal anti-inflammatory drugs inhibiting platelet function is authorized. Patients presenting with a venous thromboembolic accident during the trial will be withdrawn from bevacizumab treatment.

5.3.2 Prohibited and/or Restricted Therapy

The following medications are prohibited during the study, unless utilized to treat a drug-related adverse event:

- Immunosuppressive agents;
- Immunosuppressive doses of systemic corticosteroids, except as stated in Section 5.3.1;
- Any concurrent anti-neoplastic therapy (i.e., chemotherapy, hormonal therapy, immunotherapy, extensive or non-palliative radiation therapy, or standard or investigational agents for the treatment of NSCLC).

For patients receiving bevacizumab, the following medications are prohibited during the study and for at least 14 days prior to initiation of the study treatment unless otherwise specified below.

- Anticoagulants (e.g., LMWH, warfarin) are prohibited within 10 days of the first administration of bevacizumab and for the entire duration of treatment with bevacizumab.

- Anti-platelet agents (e.g., ticlopidine, clopidogrel).

Caution should be used regarding the use of herbal medications, as there may be as of yet unknown interactions with nivolumab. Discontinuation of the use of herbal medications prior to study enrollment is encouraged.

Investigators should refer to the product labeling for carboplatin and pemetrexed for additional prohibited and restricted concomitant medications. Non-steroidal anti-inflammatory drugs (NSAIDs) can be administered with pemetrexed in patients with normal renal function, but caution should be used when administering NSAIDs concurrently with pemetrexed in patients with mild to moderate renal insufficiency. Further information is available in the Pemetrexed Package Insert.

5.3.3 **Supportive Care Guidelines**

Participants should receive full supportive care including transfusions of blood and blood products, antibiotics, analgesia, etc., according to local practice/institutional guidelines where appropriate. Anti-emetic medications should be prescribed according to local practice.

Treatments received prior to the study entry and that are not prohibited by the protocol will be continued by the patients during the study, depending on their physician's recommendations. All concomitant medication(s) must be reported in the Case Report Form.

Palliative local radiation therapy will be permitted for participants with symptomatic bone metastases, skin lesions, or CNS lesions, provided that the participant continues to derive clinical benefit from the study drugs in the opinion of the investigator. Palliative radiation to lesions causing hemoptysis may also be permitted in subjects who do not have evidence of overall clinical or radiographic progression, provided that the lesions undergoing local therapy are not the only sites of measurable disease, upon discussion with the Principal Investigator.

The potential for overlapping toxicities with radiotherapy and nivolumab is currently not known, although anecdotal data suggests that it is tolerable. In the absence of formal evaluation, in cases where palliative radiation is required for a tumor lesion, nivolumab should be withheld for at least 1 week before, during, and 1 week after radiation. Subjects should be closely monitored for any potential toxicity during and after receiving radiotherapy, and AEs should resolve to grade $\leq$ 1 prior to resuming study drugs. For patients undergoing cerebral radiotherapy, bevacizumab should be held for 14 days following completion of radiation.

5.4 Criteria for Taking a Participant Off Protocol Therapy

Duration of therapy will depend on individual response, evidence of disease progression and tolerance. In the absence of treatment delays due to adverse event(s), treatment may continue until one of the following criteria applies:

- Disease progression.
  Note: In select cases, subjects may be continued on study drugs (including the chemotherapy agents pemetrexed and carboplatin) despite an initial investigator-assessed, RECIST v1.1-defined progression, if they are tolerating the study drugs and deemed to be deriving clinical benefit by the investigator. The following criteria must be met in order to continue the study drug treatment through RECIST v1.1-defined radiological progression of disease:
    - Absence of clinical symptoms or signs indicating clinically significant disease progression;
    - No decline in performance status;
    - Absence of rapid disease progression or threat to vital organs or critical anatomical sites (e.g., progression in the central nervous system, respiratory failure due to tumor compression, spinal cord compression) requiring urgent alternative medical intervention;
    - No significant, unacceptable or irreversible toxicities related to study treatment.

- Intercurrent illness that prevents further administration of treatment

- Unacceptable adverse event(s)

- Participant demonstrates an inability or unwillingness to comply with the oral medication regimen and/or documentation requirements

- Participant decides to withdraw from the protocol therapy

- General or specific changes in the participant's condition render the participant unacceptable for further treatment in the judgment of the treating investigator

Participants will be removed from the protocol therapy when any of these criteria apply. The reason for removal from protocol therapy, and the date the participant was removed, must be documented in the case report form (CRF). Alternative care options will be discussed with the participant.

An ODQ Treatment Ended/Off Study Form will be filled out when a participant is removed from protocol therapy. This form can be found on the ODQ website or obtained from the ODQ registration staff.

In the event of unusual or life-threatening complications, treating investigators must immediately notify the Overall PI, Alice T. Shaw, MD, PhD, at [redacted].

5.5 Duration of Follow Up

The follow-up period for a participant begins after the last completed assessment during the active study period. Any participant who discontinued study treatment for any reason other than disease progression, death, or withdrawal of consent will continue to have tumor assessments every 12 weeks (±14 days) until disease progression, death, or withdrawal of consent, whichever occurs first.

All participants will be followed for safety on day 30 (±7 days) and on day 100 (±7 days) after the last dose of the study drugs with an office visit. The following laboratory tests will be performed on days 30 and 100 (±7 days) after the last dose of the study drugs: complete blood count (CBC) with differential, and chemistry panel including but not limited to sodium, potassium, calcium, chloride, BUN, creatinine, glucose, albumin, total protein, alkaline phosphatase, bilirubin (total and direct), AST/SGOT, ALT/SGPT, LDH, lipase, and TSH (reflex testing [T3 and free T4] to be done if TSH abnormal).

All subjects will be followed for survival every 3 months (±7 days) following the last safety follow-up visit (on day 100) until death, withdrawal of consent from the study, or up to 2 years after the last participant is enrolled, whichever occurs first. Survival follow-up visits may be performed by record review (including public records), telephone contact (with the subject, family, or the subject's treating physician), or office visit. Information on new anti-cancer therapies should be collected. New anti-cancer therapy includes (but is not limited to) any systemic or local medication, surgery, radiation, or any other therapy intended to treat the subject's cancer.

5.6 Criteria for Taking a Participant Off Study

Participants will be removed from study when any of the following criteria apply:

- Lost to follow-up
- Withdrawal of consent for data submission
- Death

The reason for taking a participant off study, and the date the participant was removed, must be documented in the case report form (CRF).

For Centralized Subject Registrations, the research team must submit a completed Off Treatment/Off Study form to ODQ when a participant comes off study. This form can be found on the ODQ website or obtained from the ODQ registration staff.

For Decentralized Subject Registrations, the research team updates the relevant Off Treatment/Off Study information in OnCore.

6. DOSING DELAYS/DOSE MODIFICATIONS

Dose delays and modifications will be made as specified below. For all cohorts, a ±3-day visit and treatment window is allowed. Per DF/HCC guidelines, delays for state/federal holidays, inclement weather, or circumstances beyond the control of the research team and/or participant are not considered protocol deviations.

The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized for dose delays and dose modifications. A copy of the CTCAE version 4.0 can be downloaded from the CTEP website http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

6.1 Dose Delay Criteria

6.1.1 Dose Delays for Nivolumab Plus Carboplatin and Pemetrexed

Nivolumab and carboplatin/pemetrexed administration should be delayed for the following:

- Absolute neutrophil count (ANC) < 1500/µl
- Platelets < 100,000/mm^3
- Any Grade ≥ 2 non-skin, non-hematologic, drug-related AE, except for fatigue and laboratory abnormalities
- Any Grade ≥ 3 skin drug-related AE
- Any Grade ≥ 3 drug-related laboratory abnormality with the following exceptions:
  - Grade 3 lymphopenia does not require a dose delay
  - 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 AE, laboratory abnormality or inter-current illness which, in the judgment of the investigator, warrants dose delays of the study medications. Investigator should consult local labeling for carboplatin and pemetrexed for additional guidance on dose delays.

Of note, in subjects receiving carboplatin and pemetrexed with nivolumab, if any non-hematologic AE meeting the dose delay criteria above is felt to be related to only one particular agent in the platinum-double chemotherapy, then that agent alone may be omitted for that cycle while the other agent(s) are 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 re-treatment criteria are met.

Subjects who require dosing delay should be re-evaluated weekly or more frequently if clinically indicated, and resume study treatment when re-treatment criteria are met, as specified in Section 6.3.1.
.

6.1.2 **Toxicity Related to Bevacizumab**

Temporary suspension of bevacizumab must occur if a patient experiences a serious adverse event or a grade 3 or 4 non-serious adverse event assessed by the investigator as related to bevacizumab. If the event resolves to grade ≤1, bevacizumab may be restarted at the same dose level. If bevacizumab is delayed due to toxicity for >42 days beyond when the next dose should have been given, the patient must be permanently discontinued from bevacizumab.

The appropriate interval between the last dose of bevacizumab and major surgery is unknown. Because bevacizumab has a half-life of approximately 21 days, elective surgery should be delayed whenever possible, but if necessary, bevacizumab should be held for ≥28 days prior to the procedure. Re-initiation of bevacizumab following surgery should not occur for ≥28 days and until wounds have fully healed. Re-initiation of bevacizumab after surgery requires documented approval from the sponsor.

Infusion of bevacizumab should be interrupted in patients who develop dyspnea or clinically significant hypotension. Patients who experience an NCI CTCAE grade 3 or 4 allergic reaction/hypersensitivity, adult respiratory distress syndrome, or bronchospasm (regardless of grade) will be discontinued from bevacizumab treatment.

Bevacizumab infusion should be slowed to ≤50% or interrupted for patients who experience any infusion-associated symptoms not specified above. If the infusion is interrupted, it may be resumed at ≤50% of the rate prior to the reaction after the patient's symptoms have adequately resolved and increased in 50% increments up to the full rate if well tolerated. Infusions may be restarted at the full rate during the next cycle.

Table 6.1.2-1: **Bevacizumab Dose Management for Adverse Events**

CTCAE grade	**Action to be taken**
Hypertension	
Grade 1 or 2	No treatment modifications.
Grade 3	If not controlled at ≤150 mm Hg with anti-hypertensive treatment, do not administer bevacizumab.
Grade 4	Discontinue bevacizumab.
Sign of posterior reversible leukoencephalopathy syndrome (PRLS)	
Any grade (confirmed on an MRI)	Discontinue bevacizumab.
Hemorrhaging of the CNS	
Any grade	Discontinue bevacizumab.
Pulmonary hemorrhage	
Any grade	Discontinue bevacizumab
Non-pulmonary, non-CNS hemorrhage	
Grade 1	No dose modifications.
Grade ≥2	Discontinue bevacizumab.

Venous thrombosis	
Any grade	Discontinue bevacizumab.
Arterial thromboembolic event (angina pectoris, myocardial infarction, ischemic heart attack, arterial thromboembolic attack or any other arterial thromboembolic event)	
Any grade	Discontinue bevacizumab.
Proteinuria	
Grade 1 or 2	No dose modifications.
Grade 3	Suspend bevacizumab until resolution of grade to ≤2.
Grade 4 (nephrotic syndrome)	Discontinue bevacizumab.
GI perforation	
Grade ≥2 (requiring medical or surgical intervention)	Discontinue bevacizumab.
Intestinal obstruction	
Grade 1	Continue bevacizumab for partial obstruction NOT requiring medical/surgical intervention.
Grade 2	Suspend bevacizumab for partial obstruction requiring medical/clinical intervention. The administration of treatment will resume after full resolution.
Grade 3 or 4	Discontinue bevacizumab for total obstruction. If surgical intervention is needed, the patient will resume treatment after wounds are healed and the assessment of investigator.
Dehiscence of wounds requiring medical or surgical treatment (if the wound comes from incision of a cavity)	
Any grade	Discontinue bevacizumab.
Left ventricular systolic dysfunction	
Grade 1 or 2	No dose modifications.
Grade 3	Suspend bevacizumab until resolution of grade to ≤1.
Grade 4	Discontinue bevacizumab.
Fistula	
TE fistula Any grade	Discontinue bevacizumab.
Any other events of grade 3/4 that may be related to bevacizumab according to the investigator	
Grade 3	Discontinue bevacizumab until resolution of grade to ≤1.
Grade 4	Discontinue bevacizumab.

6.2 Dose Reduction Criteria

6.2.1 Dose Reductions for Nivolumab

There will be no dose reductions for nivolumab.

6.2.2 Dose Reductions for Bevacizumab

There will be no dose reductions for bevacizumab. Please refer to section 6.1.2 for criteria for treatment modification and guidelines for the management of bevacizumab-related toxicities.

6.2.3 Dose Reductions for Carboplatin and Pemetrexed

Carboplatin and pemetrexed chemotherapy may be dose reduced based on toxicities, according to Table 6.2.1-1. Once the dose of a chemotherapeutic agent is reduced, it may not be re-escalated in subsequent cycles, except when starting the pemetrexed maintenance therapy. Any subject with two prior dose reductions who experiences a toxicity requiring a third dose reduction must be discontinued from the study drug.

Table 6.2.3-1: **Dose Reductions of Carboplatin and Pemetrexed**

Dose Level	Carboplatin	Pemetrexed
Starting dose	AUC 5	500 mg/m^2
First dose reduction	AUC 4	375 mg/m^2
Second dose reduction	AUC 3	250 mg/m^2
Third dose reduction	Discontinue	Discontinue

Dose modifications for toxicities according to CTCAE version 4.0 are summarized in Table 6.2.1-2. Dose level adjustments for carboplatin and pemetrexed are relative to that of the preceding administration. All dose reductions should be made based on the worst grade toxicity (and nadir blood counts as per local standards). Subjects experiencing any of the toxicities detailed in Table 6.2.1-2 during the previous cycle should have their chemotherapy delayed until re-treatment criteria are met, and then dose reduced for all subsequent cycles by one dose level or discontinued as appropriate.

Dose levels for carboplatin and pemetrexed may be reduced independently for the non-hematologic toxicities as summarized in the table. For hematologic toxicities, growth factors may be used after the first cycle to assist blood count recovery. Local standards of care in supportive measures should be utilized. Prophylactic antibiotics may also be used according to local standards of care. Any antibiotic or growth factor use should be reported on the eCRF.

Table 6.2.3-2: **Dose Modification Guidelines for Carboplatin and Pemetrexed Based on Toxicity**

Toxicity	Carboplatin	Pemetrexed
Neutropenia Grade 4	Reduce one dose level	Reduce one dose level
Thrombocytopenia Grade ≥ 3	Reduce one dose level	Reduce one dose level
Thrombocytopenia Grade ≥ 3,	Reduce two dose levels	Reduce two dose levels

Grade ≥ 2 with bleeding		
Febrile Neutropenia Grade ≥ 3	Reduce one dose level	Reduce one dose level
Diarrhea Grade ≥ 3	No change	Reduce one dose level
Allergic reaction Grade ≥ 3	Discontinue	Discontinue
Neuropathy Grade ≥ 3	Discontinue	Discontinue
Transaminase elevation Grade 3	Reduce one dose level	Reduce one dose level
Transaminase elevation Grade 4	Discontinue	Discontinue
Calculated creatinine clearance < 20 mL/min	Discontinue	No change
Mucositis Grade ≥ 3	No change	Reduce two dose levels
Other Grade ≥ 3 toxicity (except for fatigue and transient arthralgia and myalgia)	Adjust as medically indicated	Adjust as medically indicated

6.3 Criteria to Resume Dosing

6.3.1 Criteria to Resume Nivolumab Plus Carboplatin and Pemetrexed

- ANC ≥ 1500/µl, platelet ≥ 100,000/mm^3
- All other drug-related toxicities returned to baseline or Grade ≤ 1, with exceptions as noted below.
- Grade ≤ 2 alopecia and fatigue.
- Subjects who have not experienced a Grade 3 drug-related skin AE may resume treatment in the presence of Grade 2 skin toxicity.
- Drug-related pulmonary toxicity, diarrhea, or colitis must have resolved to baseline before treatment is resumed. Subjects with persistent Grade 1 pneumonitis after completion of a steroid taper over at least 1 month may be eligible for re-treatment if discussed with and approved by the Principal Investigator.
- Subjects who received systemic corticosteroids for management of any drug-related toxicity must be off corticosteroids or have tapered down to an equivalent dose of prednisone ≤ 10 mg/day.
- Drug-related endocrinopathies adequately controlled with only physiologic hormone replacement may resume treatment after consultation with the Principal Investigator.
- If a subject fails to meet criteria for re-treatment, then re-treatment should be delayed, and the subject should be re-evaluated weekly or more frequently as clinically indicated. Dose delay of nivolumab and/or carboplatin and pemetrexed which results in treatment interruption of > 6 weeks requires treatment discontinuation, with exceptions as noted in

Section 6.4.

6.3.2 Criteria to Resume Bevacizumab

Please refer to Section 6.1.2.

6.4 Criteria to Discontinue Treatment

The assessment for discontinuation of nivolumab should be made separately from the assessment for discontinuation of carboplatin/pemetrexed or from the assessment for discontinuation of bevacizumab. If the investigator can attribute an adverse event to a specific agent and the criteria for discontinuation of that drug are met, then that agent can be discontinued and the other agent(s) continued until disease progression or unacceptable toxicity. If the investigator is unable to determine whether an adverse event is related to one drug only, then the subject should discontinue all drugs in the combination regimen and be taken off the treatment phase of the study.

6.4.1 Criteria for Nivolumab Discontinuation

- 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 ≥ 2 drug-related pneumonitis or interstitial lung disease that does not resolve to dose delay and systemic steroids.
- Any Grade 3 drug-related bronchospasm, hypersensitivity reaction, or infusion reaction, regardless of duration.
- Any Grade 3 non-skin, drug-related adverse event lasting > 7 days, with the following exceptions for uveitis, pneumonitis, bronchospasm, diarrhea, colitis, neurologic toxicity, hypersensitivity reactions, infusion reactions, endocrinopathies, and laboratory abnormalities:
    - Grade 3 drug-related uveitis, pneumonitis, bronchospasm, diarrhea, colitis, neurologic toxicity, hypersensitivity reaction, or infusion reaction of any duration requires discontinuation.
    - Grade 3 drug-related endocrinopathies adequately controlled with only physiologic hormone replacement do not require discontinuation.
    - Grade 3 drug-related laboratory abnormalities do not require treatment discontinuation except:
        - Grade 3 drug-related thrombocytopenia > 7 days or associated with bleeding requires discontinuation.
        - Any drug-related liver function test (LFT) abnormality that meets the following criteria require discontinuation:
            - AST or ALT > 5-10x ULN for > 2 weeks
            - AST or ALT > 10x ULN
            - Total bilirubin > 5x ULN
            - Concurrent AST or ALT > 3x ULN and total bilirubin > 2x ULN

- Any Grade 4 drug-related adverse event or laboratory abnormality, except for the following events which do not require discontinuation:
    - Grade 4 neutropenia ≤ 7 days
    - Grade 4 lymphopenia or leukopenia
    - Isolated Grade 4 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. The Principal Investigator should be consulted for Grade 4 amylase or lipase abnormalities.
    - Isolated Grade 4 electrolyte imbalances/abnormalities that are not associated with clinical sequelae and are corrected with supplementation/appropriate management within 72 hours of their onset.
    - Grade 4 drug-related endocrinopathy adverse events such as adrenal insufficiency, ACTH deficiency, hyper- or hypothyroidism, or glucose intolerance, which resolve or are adequately controlled with physiologic hormone replacement (corticosteroids, thyroid hormones) or glucose-controlling agents, respectively, may not require discontinuation after discussion with the Principal Investigator.
- Dosing delays lasting > 6 weeks from the previous dose that occur for non-drug-related reasons may be allowed if approved by the Principal Investigator. Prior to re-initiating treatment in a subject with a dosing delay lasting > 6 weeks, the Principal Investigator must be consulted. Tumor assessments should continue per protocol even if the dosing is delayed.
- 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 dosing.

6.4.2 **Criteria for Carboplatin/Pemetrexed Discontinuation**

Except where specified below, both agents (carboplatin and pemetrexed) should be discontinued for any of the following:

- Any Grade ≥ 3 peripheral neuropathy.
- Grade ≥ 3 drug-related thrombocytopenia associated with clinically significant bleeding.
- Any drug-related liver function test (LFT) abnormality that meets the following criteria:
    - AST or ALT > 5-10x ULN for > 2 weeks
    - AST or ALT > 10x ULN
    - Total bilirubin > 5x ULN
    - Concurrent AST or ALT > 3x ULN and total bilirubin > 2x ULN
- Any drug-related adverse event which recurs after two prior dose reductions for the same drug-related adverse event requires discontinuation of the drug(s) which was/were previously dose reduced.
- Any Grade ≥ 3 drug-related hypersensitivity reaction or infusion reaction requires discontinuation of the drug(s) felt to be causing the reaction. The drug not felt to be related to the hypersensitivity reaction or infusion reaction may be continued.
- Any Grade 4 drug-related adverse event which the investigator deems is inappropriate to be managed by dose reduction(s) requires discontinuation of the drug(s) felt to be causing

the event. The drug not felt to be related to the event may be continued.

- Any event that leads to delay in dosing of any study drug(s) for > 6 weeks from the previous dose requires discontinuation of that drug(s) with the following exception:
    - Dosing delays lasting > 6 weeks from the previous dose that occur for non-drug-related reasons may be allowed if approved by the Principal Investigator. Prior to re-initiating treatment in a subject with a dosing delay lasting > 6 weeks, the Principal Investigator must be consulted.
- 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 carboplatin and pemetrexed dosing. Investigators should consult local labeling for the chemotherapy agents for additional guidance on dose discontinuation.

6.4.3 Criteria for Bevacizumab Discontinuation

Please refer to Section 6.1.2.

6.5 Management Algorithms for Immuno-Oncology Agents

Immuno-oncology (I-O) agents are associated with AEs that can differ in severity and duration than AEs caused by other therapeutic classes. Nivolumab is considered an immune-oncology agent in this protocol. Early recognition and management of AEs associated with I-O agents may mitigate severe toxicity. Management algorithms have been developed to assist investigators in assessing and managing the following groups of AEs:

- Gastrointestinal
- Renal
- Pulmonary
- Hepatic
- Endocrinopathy
- Skin
- Neurological

The above algorithms are found in the nivolumab Investigator Brochure, as well as in **Appendix B.**

6.6 Treatment of Nivolumab Infusion Reactions

Since nivolumab contains 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 may manifest with fevers, chills, rigors, headache, rash, pruritus, arthralgias, hypo- or hypertension, bronchospasm or other symptoms. All Grade 3 or 4 infusion reactions should be reported within 24 hours to the Principal Investigator and reported as an SAE if criteria are met. Infusion reactions should be graded according to NCI CTCAE (version 4.0) guidelines.

Treatment recommendations are provided below and may be modified based on local treatment

standards and guidelines, as appropriate:

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

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

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

- Stop the nivolumab infusion. Begin an intravenous infusion of normal saline, and treat the subject with diphenhydramine 50 mg IV (or equivalent) and/or acetaminophen/paracetamol 325 to 1000 mg. Remain at bedside and monitor subject until resolution of symptoms. Corticosteroid and/or bronchodilator therapy may also be administered as appropriate. If the infusion is interrupted, then restart the infusion at 50% of the original infusion rate when symptoms resolve. If no further complications ensue after 30 minutes, the rate may be increased to 100% of the original infusion rate. Monitor subject closely. If symptoms recur, then no further nivolumab will be administered at that visit. Administer diphenhydramine 50 mg IV, and remain at bedside and monitor the subject until resolution of symptoms. The amount of study drug infused must be recorded on the electronic case report form (eCRF).
- For future infusions, the following prophylactic pre-medications are recommended: diphenhydramine 50 mg (or equivalent) and/or acetaminophen/paracetamol 325 to 1000 mg should be administered at least 30 minutes before nivolumab infusions. If necessary, corticosteroids (up to 25 mg of SoluCortef or equivalent) may be used.

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

- Immediately discontinue infusion of nivolumab. Begin an IV infusion of normal saline and treat the subject as follows: Recommend bronchodilators, epinephrine 0.2 to 1 mg of a 1:1000 solution for subcutaneous administration or 0.1 to 0.25 mg of a 1:10,000 solution injected slowly for IV administration, and/or diphenhydramine 50 mg IV with methylprednisolone 100 mg IV (or equivalent), as needed. Subject should be monitored until the investigator is comfortable that the symptoms will not recur. Nivolumab will be permanently discontinued. Investigators should follow their institutional guidelines for the treatment of anaphylaxis. Remain at bedside and monitor subject until recovery of the symptoms.

In case of late-occurring hypersensitivity symptoms (e.g., appearance of a localized or

generalized pruritus within 1 week after treatment), symptomatic treatment may be given (e.g., oral anti-histamine or corticosteroids).

7. ADVERSE EVENTS: LIST AND REPORTING REQUIREMENTS

Adverse event (AE) monitoring and reporting is a routine part of every clinical trial. The following list of reported and/or potential AEs (Section 7.1) and the characteristics of an observed AE (Section 7.2) will determine whether the event requires expedited reporting **in addition** to routine reporting.

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

7.1 Adverse Events

7.1.1 Adverse Events for Nivolumab

The following treatment-related adverse events (AEs) of any grade and of grade ≥ 3 were reported in patients with advanced NSCLC treated with nivolumab monotherapy at 3 mg/kg administered every 2 weeks, according to a pooled safety analysis (total 535 subjects) (44):

Table 7.1.1: **Summary of Adverse Events with Nivolumab Monotherapy in Subjects with Advanced NSCLC**

Event	Any Grade, n (%)	Grade 3-4, n (%)
Drug-related AEs in ≥5% of subjects		
Fatigue	105 (19.6)	9 (1.7)
Decreased appetite	66 (12.3)	1 (0.2)
Nausea	64 (12.0)	2 (0.4)
Asthenia	56 (10.5)	1 (0.2)
Rash	45 (8.4)	2 (0.4)
Diarrhea	44 (8.2)	5 (0.9)
Pruritus	34 (6.4)	1 (0.2)
Arthralgia	28 (5.2)	0
Hypothyroidism	27 (5.0)	0
Drug-related AEs leading to discontinuation	32 (6.0)	25 (4.7)
Drug-related AEs leading to discontinuation in > 1 subject		
Pneumonitis	10 (1.9)	7 (1.3)

Fatigue	3 (0.6)	1 (0.2)
Interstitial lung disease	2 (0.4)	1 (0.2)
Rash	2 (0.4)	1 (0.2)
Drug-related SAEs	42 (7.9)	27 (5.0)
Drug-related SAEs in >1 subject		
Pneumonitis	10 (1.9)	7 (1.3)
Colitis	2 (0.4)	1 (0.2)
Diarrhea	2 (0.4)	2 (0.4)
Infusion-related reaction	2 (0.4)	0
Interstitial lung disease	2 (0.4)	1 (0.2)
Nausea	2 (0.4)	1 (0.2)
Pyrexia	2 (0.4)	0
Select AEs		
Drug-related endocrine select AEs	39 (7.3)	1 (0.2)
Thyroid disorder	38 (7.1)	0
Hypothyroidism	27 (5.0)	0
Blood TSH increased	7 (1.3)	0
Hyperthyroidism	4 (0.7)	0
Blood TSH decreased	2 (0.4)	0
Thyroiditis	2 (0.4)	0
Adrenal disorder	1 (0.2)	1 (0.2)
Adrenal insufficiency	1 (0.2)	1 (0.2)
Drug-related gastrointestinal select AEs	45 (8.4)	6 (1.1)
Diarrhea	44 (8.2)	5 (0.9)
Colitis	3 (0.6)	2 (0.4)
Drug-related hepatic select AEs	21 (3.9)	3 (0.6)
ALT increased	12 (2.2)	0
AST increased	11 (2.1)	1 (0.2)
Blood ALP increased	5 (0.9)	0
GGT increased	2 (0.4)	2 (0.4)
Transaminases increased	2 (0.4)	1 (0.2)
Blood bilirubin increased	1 (0.2)	0
Hepatotoxicity	1 (0.2)	0
Hyperbilirubinemia	1 (0.2)	0
Drug-related hypersensitivity/infusion reactions	12 (2.2)	2 (0.4)
Infusion-related reaction	9 (1.7)	0
Hypersensitivity	3 (0.6)	1 (0.2)
Anaphylactic reaction	1 (0.2)	1 (0.2)
Drug-related pulmonary select AEs	22 (4.1)	8 (1.5)
Pneumonitis	19 (3.6)	7 (1.3)
Interstitial lung disease	2 (0.4)	1 (0.2)
Lung infiltration	1 (0.2)	0
Drug-related renal select AEs	15 (2.8)	1 (0.2)
Blood creatinine increased	11 (2.1)	0
Renal failure	2 (0.4)	0
Renal failure acute	2 (0.4)	0

Tubulointerstitial nephritis	1 (0.2)	1 (0.2)
Drug-related skin select AEs	81 (15.1)	4 (0.7)
Drug-related skin select AEs in ≥ 1% of subjects		
Rash	45 (8.4)	2 (0.4)
Pruritus	34 (6.4)	1 (0.2)
Rash, maculopapular	8 (1.5)	0

Of note, "select AEs" were identified based on the following 4 principles:

- AEs that may differ in type, frequency, and severity from AEs caused by non-immunotherapies
- AEs that may require immunosuppression (e.g., corticosteroids) as part of their management
- AEs whose early recognition and management may mitigate severe toxicity
- AEs for which multiple event terms may be used to describe a single type of AE, thereby necessitating the pooling of terms for full characterization.

7.1.2 Adverse Events for Pemetrexed

Table 7.1.3 provides the list of AEs reported in >5% of advanced NSCLC patients who received pemetrexed maintenance (a total of 333 patients) following platinum-based induction chemotherapy (56).

Table 7.1.3: **Summary of Adverse Events with Pemetrexed Monotherapy in Subjects with Advanced NSCLC Following Platinum/Pemetrexed Induction Therapy**

Event	Any Grade, %	Grade 3-4, %
Laboratory		
Hematologic		
Anemia	15	4.8
Neutropenia	9	3.9
Leukopenia	6	2
Clinical		
Constitutional symptoms		
Fatigue	18	4.5
Gastrointestinal		
Nausea	12	0.3
Vomiting	6	0
Mucositis/stomatitis	5	0.3
General disorders		
Edema	5	0

The following additional grade 3 or 4 AEs were observed in patients with NSCLC who received pemetrexed:

- Incidence of 1-5%:

  - Blood/bone marrow – Thrombocytopenia
  - General disorders – Febrile neutropenia
- Incidence less than 1%:
  - Cardiovascular – Ventricular tachycardia, syncope
  - General disorders – Pain
  - Gastrointestinal – Gastrointestinal obstruction, ALT or AST elevation, diarrhea
  - Neurology – Depression, neuropathy
  - Renal – Renal failure
  - Vascular – Pulmonary embolism

7.1.3 **Adverse Events for Carboplatin**

The following list of AEs and their incidences have been described based on data from 1893 patients with various types of tumors who received carboplatin as single-agent therapy (55):

Table 7.1.4-1: **Summary of Adverse Events with Carboplatin Monotherapy in Subjects with Various Tumors**

Event	**%**
Hematologic	
Thrombocytopenia (platelet < 50,000/mm^3)	25
Neutropenia (ANC < 1000/mm^3)	16
Leukopenia (WBC < 2000/mm^3)	15
Anemia (Hgb < 11 g/dL)	71
Gastrointestinal	
Vomiting	65
Nausea alone	10-15
Neurologic	
Peripheral neuropathy	4
Renal	
Abnormal serum creatinine value	6
Abnormal blood urea nitrogen value	14
Decreased creatinine clearance	27
Hepatic	
Abnormal total bilirubin	5
Abnormal AST	5
Abnormal alkaline phosphatase	24
Electrolyte changes	
Low sodium	29
Low potassium	20
Low calcium	22
Low magnesium	29
Allergic reactions	
Hypersensitivity	2

Other events that have been reported include injection site reactions, pain and asthenia, alopecia (3%). Malaise, anorexia, and hypertension have been reported as part of post-marketing surveillance. Cardiovascular, respiratory, genitourinary, and mucosal side effects have occurred in < 6% of the patients.

Among patients with advanced NSCLC treated with carboplatin and pemetrexed combination chemotherapy for 6 or more cycles (total of 50 patients), the following AEs were noted (57):

Table 7.1.4-2: **Summary of Adverse Events with Carboplatin and Pemetrexed Combination Chemotherapy in Subjects with NSCLC**

Event	Any Grade, n (%)	Grade 3-4, n (%)
Hematologic		
Anemia	42 (84)	1 (2)
Neutropenia	31 (62)	13 (26)
Thrombocytopenia	27 (54)	1 (2)
Non-hematologic		
Nausea	34 (68)	1 (2)
Fatigue	27 (54)	2 (4)
Alopecia	24 (48)	0
Watery eyes	21 (42)	0
Stomatitis	18 (36)	0
Diarrhea	14 (28)	1 (2)
Vomiting	14 (28)	1 (2)
Dry eyes	10 (20)	0
Anorexia	9 (18)	0
Rash	8 (16)	0
Sensory neuropathy	8 (16)	0
Constipation	7 (14)	0
Pruritus	4 (8)	0
Thrush	2 (4)	0
Pneumonia	1 (2)	0
Upper respiratory tract infection	1 (2)	0

7.1.4 Adverse Events for Bevacizumab

Hypertension: An increased incidence of hypertension has been observed in patients treated with bevacizumab. Grade 4 and 5 hypertensive events are rare. Clinical sequelae of hypertension are rare but have included hypertensive crisis, hypertensive encephalopathy, and reversible posterior leukoencephalopathy syndrome (RPLS). There is no information on the effect of bevacizumab in patients with uncontrolled hypertension at the time of initiating bevacizumab therapy. Therefore, caution should be exercised before initiating bevacizumab therapy in these patients. Monitoring of blood pressure

is recommended during bevacizumab therapy. Optimal control of blood pressure according to standard public health guidelines is recommended for patients on treatment with or without bevacizumab. Temporary interruption of bevacizumab therapy is recommended in patients with hypertension requiring medical therapy until adequate control is achieved. If hypertension cannot be controlled with medical therapy, bevacizumab therapy should be permanently discontinued. Bevacizumab should be permanently discontinued in patients who develop hypertensive crisis or hypertensive encephalopathy.

Proteinuria: An increased incidence of proteinuria has been observed in patients treated with bevacizumab compared with control arm patients. In the bevacizumab-containing treatment arms of clinical trials (across all indications), the incidence of proteinuria (reported as an adverse event) was up to 38% (metastatic CRC Study AVF2192g). The severity of proteinuria has ranged from asymptomatic and transient events detected on routine dipstick urinalysis to nephrotic syndrome; the majority of proteinuria events have been grade 1. NCI-CTC Grade 3 proteinuria was reported in up to 3% of bevacizumab-treated patients, and Grade 4 in up to 1.4% of bevacizumab-treated patients. The proteinuria seen in bevacizumab clinical trials was not associated with renal impairment and rarely required permanent discontinuation of bevacizumab therapy. Bevacizumab should be discontinued in patients who develop Grade 4 proteinuria (nephrotic syndrome). Patients with a history of hypertension may be at increased risk for the development of proteinuria when treated with bevacizumab. There is evidence from the dose-finding, Phase II trials (AVF0780g, AVF0809s, and AVF0757g) suggesting that
Grade 1 proteinuria may be related to bevacizumab dose.

Thromboembolic Events: Both venous and arterial thromboembolic (TE) events, ranging in severity from catheter-associated phlebitis to fatal events, have been reported in patients treated with bevacizumab in the colorectal cancer trials and, to a lesser extent, in patients treated with bevacizumab in NSCLC and breast cancer trials.

Venous thromboembolism (including deep venous thrombosis, pulmonary embolism, and thrombophlebitis): In the pivotal Phase III trial in metastatic CRC, there was a slightly higher rate of venous TE events in patients treated with bevacizumab plus chemotherapy compared with chemotherapy alone (19% vs. 16%). In Study AVF2107g, a Phase III, pivotal trial in metastatic CRC, VTE events, including deep venous thrombosis, pulmonary embolism, and thrombophlebitis, occurred in 15.2% of patients receiving chemotherapy alone and 16.6% of patients receiving chemotherapy and□bevacizumab.

The incidence of NCI-CTC Grade ≥□3 venous VTE events in one NSCLC trial (E4599) was higher in the bevacizumab-containing arm compared to the chemotherapy control arm (5.6% vs. 3.2%). One event (0.2%) was fatal in the bevacizumab-containing arm; no fatal events were reported in the carboplatin/paclitaxel arm (see bevacizumab Investigator Brochure).

In metastatic CRC clinical trials, the incidence of VTE events was similar in patients receiving chemotherapy plus bevacizumab and those receiving the control chemotherapy alone. In clinical trials across all indications the overall incidence of VTE events was 2.8 - 17.3% in the bevacizumab-containing arms compared with 3.2 - 15.6% in the chemotherapy control arms. The use of bevacizumab with chemotherapy does not substantially increase the risk of VTE event compared with chemotherapy alone. However, patients with metastatic CRC who receive bevacizumab and experienced a VTE event may be at higher risk for recurrence of VTE event.

Arterial Thromboembolic Events: An increased incidence of ATE events was observed in patients treated with bevacizumab compared with those receiving control treatment. ATE events include cerebrovascular accidents, myocardial infarction, transient ischemic attacks (TIAs), and other ATE events. In a pooled analysis of data from five randomized Phase II and III trials (mCRC [AVF2107g, AVF2192g, AVF0780g]; locally advanced or metastatic NSCLC [AVF0757g]; and metastatic breast cancer [AVF2119g]), the incidence of ATE events was 3.8% (37 of 963) in patients who received chemotherapy and bevacizumab compared with 1.7% (13 of 782) in patients treated with chemotherapy alone. ATE events led to a fatal outcome in 0.8% (8 of 963) of patients treated with chemotherapy and bevacizumab and 0.5% (4 of 782) of patients treated with chemotherapy alone. Cerebrovascular accidents (including TIAs) occurred in 2.3% of patients treated with chemotherapy and bevacizumab and 0.5% of patients treated with chemotherapy alone. Myocardial infarction occurred in 1.4% of patients treated with chemotherapy plus bevacizumab compared with 0.7% of patients treated with chemotherapy alone (see the bevacizumab Investigator Brochure for additional details).

Aspirin is a standard therapy for primary and secondary prophylaxis of arterial thromboembolic events in patients at high risk of such events, and the use of aspirin ≤ 325 mg daily was allowed in the five randomized studies discussed above. Use of aspirin was assessed routinely as a baseline or concomitant medication in these trials, though safety analyses specifically

regarding aspirin use were not preplanned. Due to the relatively small numbers of aspirin users and arterial thromboembolic events, retrospective analyses of the ability of aspirin to affect the risk of such events were inconclusive. However, similarly retrospective analyses suggested that the use of up to 325 mg of aspirin daily does not increase the risk of grade 1-2 or grade 3-4 bleeding events, and similar data with respect to metastatic colorectal cancer patients were presented at ASCO 2005 (Hambleton et al., 2005). Further analyses of the effects of concomitant use of bevacizumab and aspirin in colorectal and other tumor types are ongoing.

Gastrointestinal perforation: Patients with metastatic carcinoma may be at increased risk for the development of gastrointestinal perforation and fistula when treated with bevacizumab and chemotherapy. Bevacizumab should be permanently discontinued in patients who develop gastrointestinal perforation. A causal association of intra-abdominal inflammatory processes and gastrointestinal perforation to bevacizumab treatment has not been established. Nevertheless, caution should be exercised when treating patients with intra-abdominal inflammatory processes with bevacizumab. Gastrointestinal perforation has been reported in other trials in non-colorectal cancer populations (e.g., ovarian, renal cell, pancreas, breast, and NSCLC) and may be higher in incidence in some tumor types.

Fistula: Bevacizumab use has been associated with serious cases of fistulae including events resulting in death. Fistulae in the GI tract are common (1%-10% incidence) in patients with metastatic CRC, but uncommon (0.1 - 1%) or rare (0.01%-0.1%) in other indications. In addition, fistulae that involve areas of the body other than the GI tract (e.g., tracheoesophageal, bronchopleural, urogenital, biliary) have been reported uncommonly (0.1%-1%) in patients receiving bevacizumab in clinical studies and postmarketing reports. Events were reported at various timepoints during treatment, ranging from 1 week to >□1 year following initiation of bevacizumab, with most events occurring within the first 6 months of therapy. Bevacizumab should be permanently discontinued in patients with tracheoesophageal fistulae or any Grade 4 fistula. Limited information is available on the continued use of bevacizumab in patients with other fistulae. In cases of internal fistula not arising in the GI tract, discontinuation of bevacizumab should be considered.

Wound healing complications: Wound healing complications such as wound dehiscence have been reported in patients receiving bevacizumab. In an analysis of pooled data from two trials in metastatic colorectal cancer, patients undergoing surgery 28-60 days before study treatment with 5-FU/LV

plus bevacizumab did not appear to have an increased risk of wound healing complications compared to those treated with chemotherapy alone. Surgery in patients currently receiving bevacizumab is not recommended. No definitive data are available to define a safe interval after bevacizumab exposure with respect to wound healing risk in patients receiving elective surgery; however, the estimated half life of bevacizumab is 21 days. Bevacizumab should be discontinued in patients with severe wound healing complications.

If patients receiving treatment with bevacizumab require elective major surgery, it is recommended that bevacizumab be held for 4-8 weeks prior to the surgical procedure. Patients undergoing a major surgical procedure should not begin or restart bevacizumab until 4 weeks after that procedure (in the case of high-risk procedures such as liver resection, thoracotomy, or neurosurgery, it is recommended that chemotherapy be restarted no earlier than 6 weeks and bevacizumab no earlier than 8 weeks after surgery).

Hemorrhage: Overall, Grade 3 and 4 bleeding events were observed in 4.0% of 1132 patients treated with bevacizumab in a pooled database from eight Phase I, II, and III clinical trials in multiple tumor types (bevacizumab Investigator Brochure). The hemorrhagic events that have been observed in bevacizumab clinical studies were predominantly tumor-associated hemorrhage (see below) and minor mucocutaneous hemorrhage.

Tumor-Associated Hemorrhage: Major or massive pulmonary hemorrhage or hemoptysis has been observed primarily in patients with NSCLC. Life-threatening and fatal hemoptysis was identified as a bevacizumab-related adverse event in NSCLC trials. These events occurred suddenly and presented as major or massive hemoptysis. Among the possible risk factors evaluated (include squamous cell histology, treatment with anti-rheumatic/anti-inflammatory drugs, treatment with anticoagulants, prior radiotherapy, bevacizumab therapy, previous medical history of atherosclerosis, central tumor location, and cavitation of tumors during therapy), the only variables that showed statistically significant correlations with bleeding were bevacizumab therapy and squamous cell histology.

Of patients experiencing pulmonary hemorrhages requiring medical intervention, many had cavitation and/or necrosis of the tumor, either preexisting or developing during bevacizumab therapy. Patients developing lung cavitation on treatment should be assessed by the treating physician for risk-benefit. In

Study E4599, in which squamous cell carcinoma was excluded, the rate of any type of Grade ≥□3 hemorrhage was 1.0% in the control arm (carboplatin and paclitaxel) versus 4.1% in the carboplatin and paclitaxel plus□bevacizumab arm.

GI hemorrhages, including rectal bleeding and melena have been reported in patients with CRC, and have been assessed as tumor-associated hemorrhages.

Tumor-associated hemorrhages were also seen rarely in other tumor types and locations, including a case of CNS bleeding in a patient with hepatoma with occult CNS metastases and a patient who developed continuous oozing of blood from a thigh sarcoma with necrosis. A recent review examined the risk of CNS hemorrhage in association with anti-VEGF therapy. Among 669 patients treated on Phase I and II studies of bevacizumab that excluded brain metastases, only 1 case (0.2%) of CNS bleeding was reported.

Mucocutaneous Hemorrhage: Across all bevacizumab clinical trials, mucocutaneous hemorrhage has been seen in 20%-40% of patients treated with bevacizumab. These were most commonly NCI-CTC Grade 1 epistaxis that lasted less than 5 minutes, resolved without medical intervention and did not require any changes in bevacizumab treatment regimen. There have also been less common events of minor mucocutaneous hemorrhage in other locations, such as gingival bleeding and vaginal bleeding.

Reversible Posterior Leukoencephalopathy Syndrome: There have been rare reports of bevacizumab-treated patients developing signs and symptoms that are consistent with RPLS, a rare neurological disorder that can present with the following signs and symptoms (among others): seizures, headache, altered mental status, visual disturbance, or cortical blindness, with or without associated hypertension. Brain imaging is mandatory to confirm the diagnosis of RPLS. In patients who develop RPLS, treatment of specific symptoms, including control of hypertension, is recommended along with discontinuation of bevacizumab. The safety of reinitiating bevacizumab therapy in patients previously experiencing RPLS is not known.

Congestive heart failure: In clinical trials, CHF was observed in all cancer indications studied to date, but predominantly in patients with metastatic breast cancer. In the Phase III clinical trial of metastatic breast cancer (AVF2119g), 7 (3%) bevacizumab-treated patients experienced CHF, compared with two (1%) control arm patients. These events varied in severity from asymptomatic declines in left ventricular ejection fraction (LVEF) to

symptomatic CHF requiring hospitalization and treatment. All the patients treated with bevacizumab were previously treated with anthracyclines (doxorubicin cumulative dose of 240□360 mg/m²). Many of these patients also had prior radiotherapy to the left chest wall. Most of these patients showed improved symptoms and/or left ventricular function following appropriate medical therapy.

In a randomized, Phase III trial of patients with previously untreated metastatic breast cancer (E2100), the incidence of LVEF decrease (defined as NCI-CTC Grade 3 or 4) in the paclitaxel □□bevacizumab arm was 0.3% versus 0% for the paclitaxel alone arm. No information is available on patients with preexisting CHF of New York Heart Association (NYHA) Class II□IV at the time of initiating bevacizumab therapy, as these patients were excluded from clinical trials. Prior anthracyclines exposure and/or prior radiotherapy to the chest wall may be possible risk factors for the development of CHF. Caution should be exercised before initiating bevacizumab therapy in patients with these risk factors. A Phase II trial in patients with refractory acute myelogenous leukemia reported 5 cases of cardiac dysfunction (CHF or LVEF decrease to <□40%) among 48 patients treated with sequential cytarabine, mitoxantrone, and bevacizumab. All but 1 of these patients had significant prior exposure to anthracyclines as well.

Two additional studies investigated concurrent administration of anthracyclines and bevacizumab. In 21 patients with inflammatory breast cancer treated with neoadjuvant docetaxel, doxorubicin, and bevacizumab, no patients developed clinically apparent CHF; however, patients had asymptomatic decreases in LVEF to < 40%. In a small Phase II study in patients with soft tissue sarcoma, 2 of the 17 patients treated with bevacizumab and high-dose doxorubicin (75 mg/m²) developed CHF (one Grade 3 event after a cumulative doxorubicin dose of 591 mg/m2, one Grade 4 event after a cumulative doxorubicin dose of 420 mg/m²); an additional 4 patients had asymptomatic decreases in LVEF. Other studies in patients with various tumor types and either a history of anthracycline exposure or concomitant use with bevacizumab are ongoing. Patients receiving concomitant anthracyclines or with prior exposure to anthracyclines should have a baseline MUGA scans or echocardiograms (Echo’s) with a normal LVEF.

Neutropenia: Increased rates of severe neutropenia, febrile neutropenia, or infection with severe neutropenia (including some fatalities) have been

observed in patients treated with some myelotoxic chemotherapy regimens plus bevacizumab in comparison to chemotherapy alone.

Additional Adverse Events: See the bevacizumab Investigator Brochure for additional details regarding the safety experience with bevacizumab.

7.2 Adverse Event Characteristics

- **CTCAE term (AE description) and grade:** The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized for AE reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 4.0. A copy of the CTCAE version 4.0 can be downloaded from the CTEP web site http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

- **For expedited reporting purposes only:**
  - AEs for the agent(s) that are listed above should be reported only if the adverse event varies in nature, intensity or frequency from the expected toxicity information which is provided.
  - Other AEs for the protocol that do not require expedited reporting are outlined in the next section (Expedited Adverse Event Reporting) under the sub-heading of Protocol-Specific Expedited Adverse Event Reporting Exclusions.

- **Serious adverse event (SAE):**
  - A ***Serious Adverse Event (SAE)*** is any untoward medical occurrence that, at any dose:
    - results in death
    - is life-threatening (defined as an event in which the participant was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe)
    - requires inpatient hospitalization or causes prolongation of existing hospitalization (see **NOTE** below)
    - results in persistent or significant disability/incapacity
    - is a congenital anomaly/birth defect
    - is an important medical event (defined as a medical event(s) that may not be immediately life-threatening or result in death or hospitalization but, based upon appropriate medical and scientific judgment, may jeopardize the subject or may require intervention [eg, medical, surgical] to prevent one of the other serious outcomes listed in the definition above.) Examples of such events include, but are not limited to, intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization.)
    - Suspected transmission of an infectious agent (eg, pathogenic or nonpathogenic) via the study drug is an SAE.
  - Although pregnancy, overdose, potential drug-induced liver injury (DILI) and cancer are not always serious by regulatory definition, these events must be handled as SAEs.

- Any component of a study endpoint that is considered related to study therapy should be reported as an SAE (e.g., death is an endpoint; if death occurred due to anaphylaxis, anaphylaxis must be reported).

- **Attribution** of the AE:
  - Definite – The AE *is clearly related* to the study treatment.
  - Probable – The AE *is likely related* to the study treatment.
  - Possible – The AE *may be related* to the study treatment.
  - Unlikely – The AE *is doubtfully related* to the study treatment.
  - Unrelated – The AE *is clearly NOT related* to the study treatment.

7.3 Expedited Adverse Event Reporting

7.3.1 Investigators **must** report to the Overall PI any serious adverse event (SAE, defined above) that occurs during screening, after the initial dose of study treatment, during treatment, or within 30 days of the last dose of treatment on the local institutional SAE form. Events after these time periods must also be reported to the Overall PI if they are believed to be related to the study drugs.

7.3.2 SAEs, whether related or not related to study drug, and pregnancies must be reported to BMS within 24 hours. SAEs must be recorded on BMS or an approved form; pregnancies must be reported on a Pregnancy Surveillance Form.

7.3.3 All SAEs must be reported by confirmed facsimile (fax) transmission or reported via electronic mail to:

SAE Email Address: [redacted]
SAE Facsimile Number: [redacted]

- 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.

7.3.4 DF/HCC Expedited Reporting Guidelines

Investigative sites within DF/HCC will report AEs directly to the DFCI Office for Human Research Studies (OHRS) per the DFCI IRB reporting policy.

7.4 Pregnancy

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

The investigator must immediately notify [redacted] of this event via the Pregnancy Surveillance Form in accordance with SAE reporting procedures.

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

Follow-up information regarding the course of the pregnancy, including perinatal and neonatal outcome and, where applicable, offspring information must be reported on the 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. In order for Sponsor or designee to collect any pregnancy surveillance information from the female partner, the female partner must sign an informed consent form for disclosure of this information.

7.5 Expedited Reporting to the Food and Drug Administration (FDA)

The Overall PI, as study sponsor, will be responsible for all communications with the FDA. The Overall PI will report to the FDA, regardless of the site of occurrence, any serious adverse event that meets the FDA's criteria for expedited reporting following the reporting requirements and timelines set by the FDA.

7.6 Expedited Reporting to Hospital Risk Management

Participating investigators will report to their local Risk Management office any participant

safety reports or sentinel events that require reporting according to institutional policy.

7.7 Routine Adverse Event Reporting

All Adverse Events **must** be reported in routine study data submissions to the Overall PI on the toxicity case report forms. **AEs reported through expedited processes (e.g., reported to the IRB, FDA, etc.) must <u>also</u> be reported in routine study data submissions.**

Investigators should report to the responsible regulatory authority as appropriate.

8. PHARMACEUTICAL INFORMATION

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

8.1 Nivolumab

8.1.1 Description

Nivolumab (BMS-936558, MDX-1106, ONO-4538) anti-PD-1 monoclonal antibody is a soluble protein consisting of 4 polypeptide chains, including 2 identical heavy chains and 2 identical light chains. Its molecular weight is 146,221 daltons.

8.1.2 Form

Nivolumab is provided as solution for injection, 10 mL per vial (100 mg per vial). It is a clear to opalescent, colorless to pale yellow liquid, which may contain light (few) particulates. The drug product is a sterile, non-pyrogenic, single-use, isotonic aqueous solution formulated at 10 mg/mL in sodium citrate, sodium chloride, mannitol, diethylenetriaminepentacetic acid (pentetic acid), and polysorbate 80 (Tween^{TM} 80), pH 6.0, and includes an overfill to account for vial, needle, and syringe holdup. It is supplied in 10-cc Type I flint glass vials, stoppered with butyl rubber stoppers and sealed with aluminum seals.

8.1.3 Storage and Stability

Nivolumab vials must be stored at 2°C to 8°C (36°F to 46°F) and protected from light and freezing.

The administration of nivolumab infusion must be completed within 24 hours of preparation. If not used immediately, the infusion solution may be stored under refrigeration conditions (2°C to 8°C, 36°F to 46°F) for up to 24 hours, and a maximum of

4 hours of the total 24 hours can be at room temperature (20°C to 25°C, 68°F to 77°F) and room light. The maximum 4-hour period under room temperature and room light conditions includes the product administration period.

8.1.4 **Compatibility**

Nivolumab can be diluted with 0.9% sodium chloride injection, USP or 5% dextrose injection, USP to protein concentrations. No incompatibilities between nivolumab and polyvinyl chloride (PVC) and non-PVC/non-DEHP (di(2-ethylhexyl)phthalate) containers/IV components or glass bottles have been observed.

8.1.5 **Handling**

During drug product preparation and handling, vigorous mixing or shaking is to be avoided. Qualified personnel, familiar with procedures that minimize undue exposure to themselves and the environment, should undertake the preparation, handling, and safe disposal of the study agent in a self-contained and protective environment.

8.1.6 **Availability**

Nivolumab will be provided by Bristol-Myers Squibb.

8.1.7 **Preparation**

Nivolumab injection can be infused undiluted (10 mg/mL) or diluted with 0.9% sodium chloride injection, USP or 5% dextrose injection, USP to protein concentrations as low as 0.35 mg/mL. During drug product preparation and handling, vigorous mixing or shaking is to be avoided. Care must be taken to assure sterility of the prepared solution as the product does not contain any antimicrobial preservative or bacteriostatic agent.

8.1.8 **Administration**

See Section 5.2. Nivolumab is to be administered as an IV infusion through a 0.2-micron to 1.2-micron pore size, low-protein binding in-line filter at the protocol-specified doses and infusion times. It is not to be administered as an IV push or bolus injection.

8.1.9 **Ordering**

Investigative site(s) will order nivolumab directly through Bristol-Myers Squibb. Shipments will be at appropriate intervals, depending on patient accrual. The site(s) must use an appropriate accountability form provided by the Sponsor, or an acceptable substitute provided by the Sponsor.

8.1.10 **Accountability**

The investigator, or a responsible party designated by the investigator, should maintain a

careful record of the inventory and disposition of the agent using the NCI Drug Accountability Record Form (DARF) or another comparable drug accountability form. (See the NCI Investigator's Handbook for Procedures for Drug Accountability and Storage.)

8.1.11 **Destruction and Return**

If the study agent is 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. Appropriate records of the disposal must be maintained. Please consult with the Principal Investigator for instructions on the disposal of unused nivolumab.

8.2 Bevacizumab

8.2.1 **Description**

Bevacizumab is a recombinant monoclonal antibody targeting vascular endothelial growth factor (VEGF).

8.2.2 **Form**

Pharmaceutical form: solution for dilution for infusion

Bevacizumab 25 mg per mL
Trehalose dihydrate
Sodium phosphate
Polysorbate 20
Water for injection
Clear to slightly opalescent liquid, colourless to pale brown.

8.2.3 **Storage and Stability**

Chemical and physical stability during use has been demonstrated for 48 hours between 2°C and 30°C in an injectable solution of sodium chloride at 9 mg/mL (0.9%). From a microbiological point of view, immediate use is recommended. If the product is not used immediately after reconstitution, the storage period and conditions are the responsibility of the user and must not normally exceed 24 hours in the refrigerator between 2°C and 8°C, unless the dilution has been performed in controlled, aseptic conditions.

Do not freeze.

Store the vial in the outer packaging away from light.

8.2.4 **Compatibility**

No incompatibility between bevacizumab and infusion bags or devices made of polyvinyl chloride or polyolefin has been observed.

8.2.5 **Handling**

Procedures for proper handling and disposal of anticancer drugs should be considered.

Bevacizumab must be prepared by a health professional observing aseptic precautions. Take the volume of bevacizumab needed for the preparation of one dose of 15 mg/kg of body weight every 3 weeks and dilute it with an injectable solution of sodium chloride at 9 mg/mL (0.9%) up to a total volume of 100 mL. Dispose of any unused amount remaining in the vial, since the product does not contain a preservative. Medicinal products intended for parenteral route must be visually examined, looking for particles and colour deviations, before their administration.

No incompatibility between bevacizumab and infusion bags or devices made of polyvinyl chloride or polyolefin has been observed.

When bevacizumab has been mixed with a sterile saline solution bag, the solution must be administered within 8 hours.

Bevacizumab must not be administered or mixed with glycated solutions (see investigator's brochure).

A mechanism regulating the speed of the infusions will be used for all infusions. When the bag is empty, a volume of 50 mL of sodium at 0.9% will be added or another bag will be added, and the infusion will be continued for a volume equal to that of the tube in order to ensure the complete administration of bevacizumab. Saline solution, which will then be injected to empty the tube, will not influence the infusion time of the study treatment.

8.2.6 **Availability**

Bevacizumab will be provided by the local site supplier. This medication is not funded by the study, and will be charged to the patient's insurance.

8.2.7 **Administration**

See Section 5.2.

8.2.8 **Ordering**

Investigative site(s) will order pemetrexed directly through the local supplier. Shipments will be at appropriate intervals, depending on patient accrual.

8.2.9 **Accountability**

The investigator, or a responsible party designated by the investigator, should maintain a careful record of the inventory and disposition of the agent using the NCI Drug Accountability Record Form (DARF) or another comparable drug accountability form. (See the NCI Investigator's Handbook for Procedures for Drug Accountability and Storage.)

8.2.10 **Destruction and Return**

If the study agent is 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. Appropriate records of the disposal must be maintained. Please consult with the Principal Investigator for instructions on the disposal of unused bevacizumab.

8.3 Pemetrexed

8.3.1 **Description**

Pemetrexed (Alimta®) is an antifolate anti-neoplastic agent.

[Chemical name] L-glutamic acid, N-[4-2-(2-amino-4,7-dihydro-4-oxo-1H-pyrrolo[2,3-d]pyrimidin-5-yl)ethyl]benzoyl]-,disodium salt, heptahydrate.

[Molecular formula] $C_{20}H_{19}N_5O_6 \bullet 2Na \bullet 7H_2O$.

8.3.2 **Form**

Pemetrexed is supplied as lysophilized powder in glass vials (100 mg in a 10-mL size vial, or 500 mg in a 50-mL size vial). The product vials contain pemetrexed and mannitol in a 1:1 ratio. Sodium hydroxide and/or hydrochloric acid solution may have been added during processing to adjust the pH. The product is a white to either light-yellowish or green-yellow lysophilized solid.

8.3.3 **Storage and Stability**

The drug product is stable when stored at room temperature, not to exceed 30°C, and normal lighting conditions. Chemical and physical stability of reconstituted and infusion solutions of pemetrexed were demonstrated for up to 24 hours following initial reconstitution, when stored refrigerated, 2-8°C.

8.3.4 **Compatibility**

Pemetrexed can be reconstituted in 0.9% sodium chloride solution, without preservative, for injection. No incompatibilities between pemetrexed and polyvinyl chloride (PVC) and

polyolefin line administration sets and infusion bags have been observed. Pemetrexed is physically incompatible with diluents containing calcium, including Lactated Ringer's injection and Ringer's Injection. Co-administration of pemetrexed with other drugs and diluents has not been studied, and therefore, is not recommended.

8.3.5 **Handling**

Qualified personnel, familiar with procedures that minimize undue exposure to themselves and the environment, should undertake the preparation, handling, and safe disposal of the study agent in a self-contained and protective environment.

8.3.6 **Availability**

Pemetrexed will be provided by the local site supplier. This medication is not funded by the study, and will be charged to the patient's insurance.

8.3.7 **Preparation**

Pemetrexed vial must be reconstituted with 0.9% sodium chloride solution for injection, without preservative, resulting in a solution containing 10 mg/mL to 50 mg/mL. Gently swirl each vial until the powder is completely dissolved. The resulting solution is clear and ranges in color from colorless to yellow or green-yellow without adversely affecting product quality. The pH of the reconstituted solution is between 6.6 and 7.8. Further dilution is required.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration. If particulate matter or dark green color is observed, do not administer.

The appropriate volume of reconstituted pemetrexed solution should be further diluted to 75 to 125 mL with 0.9% sodium chloride solution without preservative for injection.

8.3.8 **Administration**

See Section 5.2. Pemetrexed is to be administered as an IV infusion over 10 minutes.

8.3.9 **Ordering**

Investigative site(s) will order pemetrexed directly through the local supplier. Shipments will be at appropriate intervals, depending on patient accrual.

8.3.10 **Accountability**

The investigator, or a responsible party designated by the investigator, should maintain a careful record of the inventory and disposition of the agent using the NCI Drug Accountability Record Form (DARF) or another comparable drug accountability form.

(See the NCI Investigator's Handbook for Procedures for Drug Accountability and Storage.)

8.3.11 **Destruction and Return**

If the study agent is 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. Appropriate records of the disposal must be maintained. Please consult with the Principal Investigator for instructions on the disposal of unused pemetrexed.

8.4 Carboplatin

8.4.1 **Description**

Carboplatin (Paraplatin®) is a platinum coordination compound. It produces DNA cross-links to have a cell-cycle non-specific, anti-neoplastic effect.

[Chemical name] platinum, diammine [1,1-cyclobutane-dicarboxylato(2-)-0,0']-,(SP-4-2).

[Molecular formula] $C_6H_{12}N_2O_4Pt$

8.4.2 **Form**

Carboplatin is supplied as a sterile 10 mg/mL aqueous solution in vials.

8.4.3 **Storage and Stability**

Unopened vials of carboplatin aqueous solution injection are stable to the date indicated on the package when stored at 25°C (77°F); excursions permitted from 15°C to 30 °C. Carboplatin must be protected from light. When diluted further, aqueous solutions are stable for 8 hours at room temperature (25°C).

8.4.4 **Compatibility**

Carboplatin can be further diluted with 5% dextrose in water or 0.9% sodium chloride injection, USP.

8.4.5 **Handling**

Qualified personnel, familiar with procedures that minimize undue exposure to themselves and the environment, should undertake the preparation, handling, and safe disposal of the study agent in a self-contained and protective environment.

8.4.6 **Availability**

Carboplatin will be provided by the local site supplier. This medication is not funded by the study, and will be charged to the patient's insurance.

8.4.7 **Preparation**

Carboplatin vial is a pre-mixed aqueous solution of 10 mg/mL. It can be further diluted to concentrations as low as 0.5 mg/mL with 5% dextrose in water or 0.9% sodium chloride injection, USP.

8.4.8 **Administration**

See Section 5.2. Carboplatin is to be administered as an IV infusion over 60 minutes with standard anti-emetics per local practice guidelines.

8.4.9 **Ordering**

Investigative site(s) will order carboplatin directly through the local supplier. Shipments will be at appropriate intervals, depending on patient accrual.

8.4.10 **Accountability**

The investigator, or a responsible party designated by the investigator, should maintain a careful record of the inventory and disposition of the agent using the NCI Drug Accountability Record Form (DARF) or another comparable drug accountability form. (See the NCI Investigator's Handbook for Procedures for Drug Accountability and Storage.)

8.4.11 **Destruction and Return**

If the study agent is 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. Appropriate records of the disposal must be maintained. Please consult with the Principal Investigator for instructions on the disposal of unused carboplatin.

9. BIOMARKER, CORRELATIVE, AND SPECIAL STUDIES

9.1 Tumor Tissue Collection

Archival or fresh FFPE tumor tissue collected within 6 months prior to enrollment must be submitted for determination of the PD-L1 status using the analytically validated IHC assay. PD-L1 stained tissue samples will be assessed by a pathologist at a lab identified by the Principal Investigator, and scored as PD-L1 expressing if membrane staining is observed in ≥ 1% tumor

cells among a minimum of 100 evaluable tumor cells.

Baseline tumor tissue may be stored for additional analyses of molecular markers that may influence response and/or resistance to the study therapies, which may include the following: IHC or immunofluorescence (IF) to determine the abundance of immunoregulatory proteins such as PD-L2, PD-1, and other markers associated with tumor-infiltrating lymphocytes (TILs) (e.g., CD4, CD8, FOXP3); ELISA/ELISPOT; and/or genetic sequencing to look for total mutation burden and resistance mutations to EGFR or ALK inhibitors. The rationale for these studies is outlined in Section 2.6. Because of the evolving nature of the field, not all of potential biomarkers can be pre-specified in this document.

Biopsies samples should be formalin-fixed and paraffin-embedded per routine local procedures. At least 12 (preferably 15) unstained FFPE slides will be collected (5 microns thickness) for DNA extraction. If fewer are available, patients may still enroll after discussion with the principal investigator. Specimens will be labeled and identified with the DF/HCC protocol number, patient ID, specimen type and date.

9.2 Blood for Germline DNA Collection

Germline DNA will be extracted from peripheral leukocytes obtained from a peripheral blood sample and studied as a control for tumor tissue sequencing/tumor mutation burden analysis. The blood for germline DNA testing is to be collected on Cycle 1 Day 1.

9.3 Handling and Shipping of Specimens

Tumor tissue: At least 12 (preferably 15) unstained FFPE slides should be sent at room temperature during the screening period to:

Massachusetts General Hospital – Dr. Mino-Kenudson's Lab

[redacted]

Blood: A germline DNA specimen should be collected in one 10 ml EDTA-containing ("purple top") tube and shipped at room temperature to:

Massachusetts General Hospital – Dr. Mino-Kenudson's Lab

[redacted]

Please contact the lab prior to sending the specimens to the lab. Please e-mail: Bryan Northam [redacted] and Marina Kem [redacted].

10. STUDY CALENDAR

Screening evaluations (including scans) are to be conducted within 28 days prior to start of protocol therapy. In the event that the participant's condition is deteriorating, laboratory

evaluations should be repeated within 48 hours prior to initiation of the next cycle of therapy. Assessments must be performed prior to administration of any study agent. Study visits and agents should be administered within ± 3 days of the protocol-specified date, unless otherwise noted. For tumor assessments with scans and survival follow-up, a ±7-day window is allowed. Please note that once the participant's screening labs meet the eligibility criteria, the cycle 1 day 1 labs do not need to re-meet the eligibility criteria.

Table 10-1: **Study Calendar**

	Screening Period	**Treatment Period Every 21-day cycle[1]**				**Follow-Up Period**		
Assessment	**Screening**	**Cycle 1 Day 1**	**Cycle 1 Day 8**	**Subsequent Cycles Day 1**	**EOT**	**30 Day Follow-Up**	**100 Day Follow-Up**	**Survival Follow-Up**
Informed consent	X							
Demographics	X							
Inclusion/exclusion criteria	X							
Relevant medical history & current medical conditions	X							
Diagnosis/extent of cancer	X							
Prior antineoplastic therapy	X							
Documentation of *EGFR* or *ALK* status	X							
Smoking history	X							
Concomitant medications	X	X	X	X	X	X	X	
Antineoplastic therapies					X	X	X	X
Vital signs	X	X	X	X	X	X	X	
Weight	X	X		X	X	X	X	
Height	X							
ECOG performance status	X	X	X	X	X	X	X	
Physical exam	X	X	X	X	X	X	X	
Hematology/chemistry	X	X	X	X	X	X	X	
TSH	X	X[2]		X	X			
Urinalysis	X	X		X	X			
Hepatitis B and C testing[3]	X							
12-lead ECG	X				X			
Pregnancy test	X							
Disease assessments[4]	X	X[4]			X			
Tumor Biopsy[5]	X							
Blood for germline DNA		X						
Adverse events	X	X	X	X	X	X	X	
Survival follow-up[6]								X[6]
Nivolumab (IV)		X		X				
Carboplatin and Pemetrexed (IV)[7]		X		X[7]				
Bevacizumab (IV) [8]		X		X[8]				

1. Each cycle is 21 consecutive days. A ±3-day window period will be authorized throughout the study period.

2. Thyroid function testing is to be done at screening and every 6 weeks (TSH only, unless abnormal in which case reflex free T3 and free T4 testing is to be performed). Infusion administrations can begin as long as the thyroid function test has been drawn. The thyroid function test needs not have resulted prior to the infusions.

3. Hepatitis B and C testing consist of HBV sAg and HCV Ab or HCV RNA.

4. Disease assessments will include CT/MRI of the chest and abdomen (and pelvis if clinically indicated) every 6 weeks (± 7 days) for the first 6 months, followed by every 12 weeks until disease progression, lost to follow-up, withdrawal of consent or study termination, whichever occurs first. MRI of brain will be performed at the same time intervals in patients with known metastatic disease in the brain per the baseline screening MRI brain. In patients without known metastatic intracranial disease on the baseline screening MRI brain, repeat MRI brain will be performed every 6 months. For all disease assessments, a ±7-day window is allowed.

5. Tumor tissue sample may be fresh, or archival if obtained within 6 months prior to enrollment. If a tissue sample is available but it has been >6 months and there has been no intervening therapy, the Principal Investigator may approve the sample after discussion. PD-L1 IHC testing will be performed on the tumor tissue, but positivity on the PD-L1 IHC testing is not required to enroll in the study.

6. Survival follow-up may be conducted by phone or visit, every 3 months (± 7 days) until death, lost to follow-up, withdrawal of study consent or up to 2 years from the enrollment of the last subject, whichever occurs first.

7. Patients will receive nivolumab with carboplatin and pemetrexed on Day 1 of every cycle for 4 cycles. Starting with cycle 5, patients will receive pemetrexed with nivolumab on Day 1 of every cycle. A ±3-day window is allowed for the study treatment.

8. Patients in Cohorts E and F only (NOT cohorts G and H) will receive bevacizumab on Day 1 of every cycle. A ±3-day window is allowed for the study treatment.

10.1 Study Assessments

- **Informed consent**: Informed consent, documented by a signed consent form, must be obtained prior to any screening activities not otherwise part of the participant's care. A note documenting the informed consent procedure should be included in the participant's medical record.

- **Demographics**: Demographic information consists of the participant's age, gender, race, and ethnicity (as allowed by local law and regulations).

- **Relevant medical history and current medical conditions**: Medical and surgical history includes diagnoses, therapies, and medical/surgical treatments.

- **Diagnosis and extent of cancer**: The initial cancer diagnosis and the current cancer diagnosis at the time of screening (if different), along with dates of diagnosis need to be recorded.

- **Prior antineoplastic therapy**: Prior cancer therapy history consists of the specific oncologic regimens a patient has received, the dates of the regimen and the best response to the regimen, and the reason for failure or intolerance to each regimen. Stem cell transplant or experimental or investigational therapy history must also be recorded.

  - **Documentation of an *EGFR* mutation or *ALK* rearrangement**: Documentation of an *EGFR* activating gene mutation (e.g., L858R, exon 19 deletion) is required per local testing. *ALK* status is to be determined using *ALK* FISH, IHC, or next generation sequencing (NGS). For *ALK* FISH, positivity will be defined as > 15% positive tumor cells. Local *ALK* testing is acceptable, provided that archival tissue is available for patients deemed *ALK* positive on the basis of NGS.

- **Concomitant medications:** Concomitant medications for all ongoing medical conditions or AEs must be reported from the date the informed consent is signed until at least 30 days after the end of treatment, and for all concomitant medications related to serious or study drug-related toxicities until the medication is no longer taken or until the patient contact discontinues.

- **Vital signs**: Vital signs include temperature, pulse, respiratory rate, and blood pressure (when patient is seated). In addition, screening assessment includes height and weight.

- **ECOG performance status**: The participant's performance status must be assessed using the ECOG performance scale (Appendix A).

- **Physical exam**: A physical examination will be performed, the extent of which should be consistent with the medical history and the participant's underlying disease.

- **Hematology**: Hematology assessments of the parameters listed in Table 10.1-1 will be tested as per the schedule of assessments (Table 10-1).

Table 10.1-1: **Local Clinical Laboratory Parameters Collection Plan**

Test Category	**Test Name**
Hematology	Hemoglobin (Hgb), platelets, white blood cells (WBC), red blood cells (RBC), differential (basophils, eosinophils, lymphocytes, monocytes, neutrophils (% or absolute))
Chemistry	Albumin, ALT, AST, calcium, creatinine, total bilirubin, direct bilirubin (only if total bilirubin is ≥ grade 2), blood urea nitrogen (BUN) or urea, magnesium, potassium, sodium, glucose, phosphate (inorganic phosphorus), alkaline phosphatase, lipase, and LDH
Thyroid function test	TSH Free T4 and free T3 by reflex if TSH is abnormal
Urinalysis	Macroscopic panel (color, total bilirubin, blood, glucose, ketones, leukocyte esterase, nitrite, pH, protein, specific gravity, urobilinogen) Microscopic panel (RBC, WBC, casts, crystals, bacteria, epithelial cells)
Pregnancy test	Serum pregnancy test

- **Chemistry**: Clinical chemistry assessments of the parameters listed in Table 10.1-1 will be tested as per the schedule of assessments (Table 10-1).

- **Thyroid function testing:** Thyroid function assessment listed in Table 10.1-1 will be tested as per the schedule of assessments (Table 10-1).

- **Urinalysis:** Urine measurements will be performed as per Table 10.1-1 and according to the schedule of assessments (Table 10-1).

- **Electrocardiogram**: 12-lead ECGs will be performed at baseline during the screening visit, and again at the end of treatment. Additional ECGs may be performed as clinically indicated throughout the study.

- **Pregnancy test:** A serum pregnancy test will be completed at baseline during the screening.

- **Disease assessments**: Tumor assessments will take place in accordance with the schedule outlined in Table 10-1. A ±7-day window is permitted. At screening, disease assessment must include imaging of the chest and abdomen. Imaging of the pelvis should also be performed if clinically indicated. Contrast-enhanced CT with PO/IV contrast or contrast-enhanced MRI are the preferred imaging modalities for assessing radiographic tumor response. If a subject has a known allergy to contrast material, local prophylaxis standard should be used to obtain the assessment with contrast if at all possible. In cases where contrast is strictly contraindicated, a non-contrast scan will suffice. Should a subject have a contraindication for CT IV contrast, a non-contrast CT of the chest and a contrast-

enhanced MRI of the abdomen may be obtained. Every attempt should be made to image each subject using an identical acquisition protocol on the same scanner for all imaging time points.

MRI of the brain is required at screening in order to rule out active metastatic disease. If disease is identified, then MRI of the brain should be repeated as outlined in Table 10-1. If no brain disease is identified on screening MRI brain, participants will undergo repeat MRI brain every 6 months as surveillance.

Target and non-target lesions must be selected at study start and followed throughout the course of treatment for response assessment according to RECIST version 1.1 guidelines (See Section 11). Imaging assessment is also required to be performed at the End of Treatment.

- **Tumor biopsy**: Tumor tissue sample is within 6 months prior to enrollment. Tissue sample may be fresh, or archival if obtained within 6 months prior to enrollment.

- **Adverse events**: Participants must be followed for all adverse events (AEs) from the start of study treatment until the safety follow-up phase (day 30 and day 100 since end of treatment), and for all serious or study drug-related toxicities until the AEs are resolved and are considered chronic or stable or until patient contact discontinues. Serious adverse events (SAEs) should be monitored and reported. Type, incidence, severity (graded in accordance with the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 4.0), timing, seriousness and relatedness, outcome, action taken with the study drug, and treatment will be assessed and documented by the investigator throughout the study. Malignancy-related signs and symptoms noted at study entry will be recorded as AEs during the trial if they worsen in severity or increase in frequency.

11. MEASUREMENT OF EFFECT

11.1 Antitumor Effect – Solid Tumors

For the purposes of this study, participants should be re-evaluated for response every 6 weeks for the first 6 months, and then every 12 weeks thereafter. Response and progression will be evaluated in this study using the new international criteria proposed by the Response Evaluation Criteria in Solid Tumors (RECIST) guideline (version 1.1) [*Eur J Ca* 45:228-247, 2009]. Changes in the largest diameter (unidimensional measurement) of the tumor lesions and the shortest diameter in the case of malignant lymph nodes are used in the RECIST criteria.

11.1.1 **Definitions**

Evaluable for Target Disease response. Only those participants who have measurable disease present at baseline, have received at least one cycle of therapy, and have had their disease re-evaluated will be considered evaluable for target disease response. These

participants will have their response classified according to the definitions stated below. (Note: Participants who exhibit objective disease progression prior to the end of cycle 1 will also be considered evaluable.)

11.1.2 **Disease Parameters**

Measurable disease. Measurable lesions are defined as those that can be accurately measured in at least one dimension (longest diameter to be recorded) as ≥10 mm with CT scan or MRI (excluding lymph nodes – see below). All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters).

Note: Tumor lesions that are situated in a previously irradiated area are not eligible for measurable disease unless there is objective evidence of progression of the lesion prior to study enrollment. Lesions in previously irradiated areas must be clearly identified as such.

Malignant lymph nodes. To be considered pathologically enlarged and measurable, a lymph node must be ≥15 mm in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). At baseline and in follow-up, only the short axis will be measured and followed.

Non-measurable disease. All other lesions (or sites of disease), including small lesions (longest diameter <10 mm or pathological lymph nodes with ≥10 to <15 mm short axis), are considered non-measurable disease. Bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonitis, inflammatory breast disease, abdominal masses (not followed by CT or MRI), and cystic lesions are all considered non-measurable.

Note: Cystic lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts.

'Cystic lesions' thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same participant, these are preferred for selection as target lesions.

Target lesions. All measurable lesions up to a maximum of 2 lesions per organ and 5 lesions in total, representative of all involved organs, should be identified as **target lesions** and recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, but in addition should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion which can be measured reproducibly should be selected. A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported

as the baseline sum diameters. If lymph nodes are to be included in the sum, then only the short axis is added into the sum. The baseline sum diameters will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease.

Non-target lesions. All other lesions (or sites of disease) including any measurable lesions over and above the 5 target lesions should be identified as **non-target lesions** and should also be recorded at baseline. Measurements of these lesions are not required, but the presence, absence, or in rare cases unequivocal progression of each should be noted throughout follow up.

11.1.3 Methods for Evaluation of Disease

All measurements should be taken and recorded in metric notation using a ruler, calipers, or a digital measurement tool. All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 4 weeks before the beginning of the treatment.

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging-based evaluation is preferred to evaluation by clinical examination unless the lesion(s) being followed cannot be imaged but are assessable by clinical exam.

This guideline has defined measurability of lesions on CT scan based on the assumption that CT thickness is 5mm or less. If CT scans have slice thickness greater than 5 mm, the minimum size of a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situations (*e.g.* for body scans).

11.1.4 Response Criteria

11.1.4.1 Evaluation of Target Lesions

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

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

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

Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient

increase to qualify for PD, taking as reference the smallest sum diameters while on study.

11.1.4.2 **Evaluation of Non-Target Lesions**

Complete Response (CR): Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (<10 mm short axis).

Note: If tumor markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response.

Non-CR/Non-PD: Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits.

Progressive Disease (PD): Appearance of one or more new lesions and/or *unequivocal progression* of existing non-target lesions. *Unequivocal progression* should not normally trump target lesion status. It must be representative of overall disease status change, not a single lesion increase.

Although a clear progression of "non-target" lesions only is exceptional, the opinion of the treating physician should prevail in such circumstances, and the progression status should be confirmed at a later time by the review panel (or Principal Investigator).

11.1.4.3 **Evaluation of New Lesions**

The finding of a new lesion should be unequivocal (i.e. not due to difference in scanning technique, imaging modality, or findings thought to represent something other than tumor (for example, some 'new' bone lesions may be simply healing or flare of pre-existing lesions). However, a lesion identified on a follow-up scan in an anatomical location that was not scanned at baseline is considered new and will indicate PD. If a new lesion is equivocal (because of small size etc.), follow-up evaluation will clarify if it truly represents new disease and if PD is confirmed, progression should be declared using the date of the initial scan on which the lesion was discovered.

11.1.4.4 **Evaluation of Best Overall Response**

The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for progressive disease the smallest measurements recorded since the treatment started). The patient's best response assignment will depend on the achievement of both measurement and confirmation criteria.

For Participants with Measurable Disease (*i.e.*, Target Disease)

Target Lesions	Non-Target Lesions	New Lesions	Overall Response	Best Overall Response when Confirmation is Required*
CR	CR	No	CR	≥4 wks Confirmation**
CR	Non-CR/Non-PD	No	PR	≥4 wks Confirmation**
CR	Not evaluated	No	PR	
PR	Non-CR/Non-PD/not evaluated	No	PR	
SD	Non-CR/Non-PD/not evaluated	No	SD	Documented at least once ≥4 wks from baseline**
PD	Any	Yes or No	PD	no prior SD, PR or CR
Any	PD***	Yes or No	PD	
Any	Any	Yes	PD	

* See RECIST 1.1 manuscript for further details on what is evidence of a new lesion.
** Only for non-randomized trials with response as primary endpoint.
*** In exceptional circumstances, unequivocal progression in non-target lesions may be accepted as disease progression.

Note: Participants with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as "*symptomatic deterioration.*" Every effort should be made to document the objective progression even after discontinuation of treatment.

11.1.5 **Duration of Response**

Duration of overall response: The duration of overall response is measured from the time measurement criteria are met for CR or PR (whichever is first recorded) until the first date that recurrent or progressive disease is objectively documented (taking as reference for progressive disease the smallest measurements recorded since the treatment started, or death due to any cause. Participants without events reported are censored at the last disease evaluation).

Duration of overall complete response: The duration of overall CR is measured from the time measurement criteria are first met for CR until the first date that progressive disease is objectively documented, or death due to any cause. Participants without events reported are censored at the last disease evaluation.

Duration of stable disease: Stable disease is measured from the start of the treatment until the criteria for progression are met, taking as reference the smallest measurements recorded since the treatment started, including the baseline measurements.

11.1.6 **Progression-Free Survival**

Overall Survival: Overall Survival (OS) is defined as the time from randomization (or registration) to death due to any cause, or censored at date last known alive.

Progression-Free Survival: Progression-Free Survival (PFS) is defined as the time from the day treatment starts to the earlier of progression or death due to any cause. Participants alive without disease progression are censored at date of last disease evaluation.

Time to Progression: Time to Progression (TTP) is defined as the time from the day treatment starts to progression, or censored at date of last disease evaluation for those without progression reported.

12. DATA REPORTING / REGULATORY REQUIREMENTS

Adverse event lists, guidelines, and instructions for AE reporting can be found in Section 7.0 (Adverse Events: List and Reporting Requirements).

12.1 Data Reporting

12.1.1 **Method**

The Office of Data Quality (ODQ) will collect, manage, and perform quality checks on the data for this study.

12.1.2 **Responsibility for Data Submission**

Investigative sites within DF/HCC or DF/PCC are responsible for submitting data and/or data forms to the Office of Data Quality in accordance with DF/HCC SOPs.

12.2 Data Safety Monitoring

The DF/HCC Data and Safety Monitoring Board (DSMB) will review and monitor study progress, toxicity, safety and other data from this study. The board is chaired by a medical oncologist from outside of DF/HCC and has external and internal representation. Information that raises any questions about participant safety or protocol performance will be addressed by the Overall PI, statistician and study team. Should any major concerns arise, the DSMB will offer recommendations regarding whether or not to suspend the study.

The DSMB will meet twice a year to review accrual, toxicity, response and reporting information. Information to be provided to the DSMB may include: participant accrual; treatment regimen information; adverse events and serious adverse events reported by category; summary of any deaths on study; audit results; and a summary provided by the study team. Other information (e.g. scans, laboratory values) will be provided upon request.

13. STATISTICAL CONSIDERATIONS

13.1 Study Design/Endpoints

This is a phase II trial evaluating the efficacy and safety of nivolumab administered in combination with platinum-doublet chemotherapy, with or without bevacizumab, in TKI-pre-treated, chemotherapy-naïve, *EGFR*-mutant or *ALK*-positive patients. The patients must have advanced *EGFR*-mutant NSCLC which progressed on a third-generation EGFR TKI, or advanced *ALK*-rearranged NSCLC which progressed on at least one next-generation ALK TKI.

- Eligible patients who are chemotherapy-naïve and bevacizumab–eligible will receive nivolumab plus carboplatin and pemetrexed plus bevacizumab for 4 cycles, followed by nivolumab plus bevacizumab plus pemetrexed maintenance therapy at the pre-specified doses (Cohorts E and F).

- Eligible patients who are chemotherapy-naïve and bevacizumab–ineligible will receive nivolumab plus carboplatin and pemetrexed for 4 cycles, followed by nivolumab plus pemetrexed maintenance therapy at the pre-specified doses (Cohorts G and H).

Our primary objective will be to evaluate the efficacy of these combinations using an objective response rate (ORR). ORR will be determined using efficacy assessments (CT chest/abdomen) performed every 6 weeks for the first 6 months, after which assessments will be performed every 12 weeks until disease progression, unacceptable toxicity, patient withdrawal, death or discontinuation from the study for any other reason, or study termination, whichever comes first. ORR is defined as the number of subjects with the best overall response (BOR) of complete response (CR) or partial response (PR) divided by the number of treated subjects in each cohort. The BOR is assessed per RECIST 1.1. For subjects who continue study medication beyond progression, the BOR should be determined based on response designations recorded at the time of the initial RECIST 1.1-defined progression.

Secondary endpoints that will be investigated include the disease control rate (DCR), duration of response (DOR), duration on treatment, progression-free survival (PFS) (including PFS rates at 6 months and at 12 months), and overall survival (OS) (including OS rates at 1 year and at 2 years). Safety and tolerability of the combination regimen will also be assessed. Exploratory analysis will include evaluation of the efficacy endpoints in subjects with PD-L1-expressing or non-expressing tumors. Baseline tumor tissue and peripheral blood samples will be evaluated for biomarkers of response or resistance to the combination therapy (e.g., PD-L1, PD-L2, CD4, CD8, FOXP3, cytokines, T-cell subsets, genetic sequencing).

13.2 Sample Size, Accrual Rate and Study Duration

This study will be comprised of four cohorts as specified above. Each cohort will be considered as independent for efficacy and will be analyzed independently. The study will be conducted using a two-stage design.

For each cohort, in the first stage, 9 patients will be enrolled in each cohort. Enrollment to the second stage will proceed in each cohort only if at least 3 of the evaluable patients were to have CR or PR. Should the study proceed to the second stage, 16 more patients will be enrolled for a total of 25 in each cohort. If 12 (or more) of 25 evaluable patients were to have a confirmed CR or PR, the combination of nivolumab plus carboplatin and pemetrexed would be considered to have a promising anti-tumor activity. This design is associated with 80% power if 55% of the patients truly were to have a response to nivolumab plus carboplatin and pemetrexed. The overall type 1 error rate is 4.2% if the underlying rate of responses were 30% or less. The probability of early termination is 0.463. The null hypothesis is based on the data from prior studies suggesting that platinum-based doublet chemotherapy following progression on a prior TKI in oncogene-driven NSCLC generally leads to responses in 20-30% of patients (2, 15, 16).

Accrual Rate and Study Duration:
EGFR mutations and *ALK* rearrangements are identified in approximately 10-15% and 3-7% of patients with NSCLC, respectively. At MGH alone, approximately 500 patients with NSCLC undergo genotyping annually. Additionally, DF/HCC is a referral center for patients with *EGFR*-mutant and *ALK*-positive NSCLC. Therefore, across the participating institutions, we expect to enroll 3-4 subjects per month. Therefore, we expect to complete enrollment in approximately 25-33 months.

All subjects will be followed for survival every 3 months (± 7 days) for up to 2 years after the last participant is enrolled.

13.3 Interim Monitoring Plan

Please refer to Section 13.2 for the two-stage study design with an early termination rule based on efficacy.

13.4 Analysis of Primary Endpoints

See Section 13.1. Analysis of the primary endpoint will follow the trial design. Response rates will be calculated at each stage, and the decision to continue will be based on the criteria specified in Section 13.1. In addition, 95% exact binomial CI will be reported. Response rates will be reported by cohort and for the pooled groups of E+F and G+H to obtain a tighter CI for the ORR estimate.

13.5 Analysis of Secondary Endpoints

Secondary endpoints will be analyzed for exploratory purposes only. These analyses are applicable to the entire cohort as well as PD-L1 expressing (staining positive for PD-L1 in ≥1% of tumor cells) and PD-L1 non-expressing subset cohorts.

Disease control rate (DCR) – DCR is defined as the percentage of subjects who have either a complete response (CR), partial response (PR), or stable disease (SD) as assessed by RECIST v1.1.

Duration of response (DOR) – DOR is measured from the first time measurement criteria are met for CR or PR (whichever is recorded first), based on RECIST 1.1 guidelines, until the first date that progressive disease (PD) is objectively documented. The duration of CR is measured from the time measurement criteria are first met for CR until the first date that PD is objectively documented. Subjects who are non-responders (i.e., do not achieve at least a PR) will be excluded from the analysis of the endpoint of interest for DOR. Subjects who have achieved at least a PR and do not have disease progression as of the data cutoff date for statistical analysis will be censored at the date of the last radiographic assessment prior to the data cutoff date.

Duration on therapy (DOT) – DOT is measured from the date of initiation on study therapy until study drug discontinuation, death, or withdrawal of consent, whichever occurs first.

Progression-free survival (PFS) – PFS is defined as the time from the start date of the study drug treatment to the date of first documented progression or death due to any cause. Subjects who do not have disease progression and are alive as of the data cutoff date for the statistical analysis will be censored at the date of the last radiographic assessment prior to the data cutoff date. PFS will be summarized in each treatment cohort using the Kaplan-Meier method with median PFS time (including two-sided 95% CI). The PFS rates at 6 months and at 12 months will be estimated with two-sided 95% CIs.

Overall survival (OS) – OS is defined as the time from the start date of the study drug treatment to death due to any cause. All subjects who are lost to follow-up prior to the end of the study or who have withdrawn from the study will be censored at the time of last contact. Subjects who are still receiving treatment as of the data cutoff date will be censored at the cutoff date. OS will be summarized for each treatment cohort using the Kaplan-Meier method with median OS time (including two-sided 95% CI). The OS rates at 1 year and at 2 years will be estimated with two-sided 95% CIs.

Safety – All participants who receive any study drug will be evaluable for toxicity. Toxicities (including laboratory parameter abnormalities) will be assessed using CTCAE v4.0. Summary tables of adverse events and serious adverse events will be created. The number and percentage of participants who experience any AE, SAE, treatment-related AE, and treatment-related SAE will be summarized according to worst toxicity grades. The incidence and reasons for dose reductions, interruptions, and discontinuations will be recorded.

Frequency, management, and resolution of select (immunologic) AEs will be analyzed (e.g., pneumonitis IMAEs, diarrhea/colitis IMAEs, hepatitis IMAEs, nephritis and renal dysfunction IMAEs, rash IMAEs, endocrine IMAEs). A tabular summary of overall immunologic AEs and serious immunologic AEs will be provided. Time-to-onset, severity, duration of IMAEs, action taken with the study drug, dosing delays, corticosteroid details and re-challenge information will be described.

Exploratory biomarker analyses – Exploratory analyses will be performed to correlate any findings from the various potential biomarker studies listed in Section 9 with the study endpoints above.

The goal of the biomarker/correlative studies is to establish the relationship between PD-L1

expression level (and potentially other biomarkers, such as the presence of tumor infiltrating lymphocytes or tumor mutational burden) and response to the study drugs. The rationale for these studies is outlined in Section 2.6. In the recent large randomized trials of checkpoint inhibitors including KEYNOTE-024 (103), patients with *EGFR*-mutant or *ALK*-rearranged metastatic NSCLC were excluded. Thus, it will be important to investigate the potential biomarkers of response to immunotherapies among the *EGFR*-mutant or *ALK*-rearranged NSCLC patients in a systematic manner.

PD-L1 expression level will be estimated and binned into a binary variable of positive (expressed in $\geq$ 1% of tumor cells) or negative (expressed in <1% of tumor cells). A Fisher's Exact Test will be used to test the relationship between response and PD-L1 status, and p-values will be calculated to test for statistical significance. All analyses will be done by cohort and also by treatment groups (cohorts E+F and cohorts G+H). A sample of 25 subjects will have a 95% one-sided lower limit of 74.3% for a desired sensitivity rate of 90%; for a sample of 50 subjects, the lower limit is 80%.

14. PUBLICATION PLAN

It is anticipated that the results of this study will first be reported in abstract form, followed by presentation in a peer-reviewed manuscript.

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APPENDIX A PERFORMANCE STATUS CRITERIA

ECOG Performance Status Scale		**Karnofsky Performance Scale**	
Grade	Descriptions	Percent	Description
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.	100	Normal, no complaints, no evidence of disease.
		90	Able to carry on normal activity; minor signs or symptoms of disease.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (*e.g.*, light housework, office work).	80	Normal activity with effort; some signs or symptoms of disease.
		70	Cares for self, unable to carry on normal activity or to do active work.
2	In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.	60	Requires occasional assistance, but is able to care for most of his/her needs.
		50	Requires considerable assistance and frequent medical care.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.	40	Disabled, requires special care and assistance.
		30	Severely disabled, hospitalization indicated. Death not imminent.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.	20	Very sick, hospitalization indicated. Death not imminent.
		10	Moribund, fatal processes progressing rapidly.
5	Dead.	0	Dead.

APPENDIX B MANAGEMENT ALGORITHMS FOR IMMUNO-ONCOLOGY AGENTS

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 immune-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.

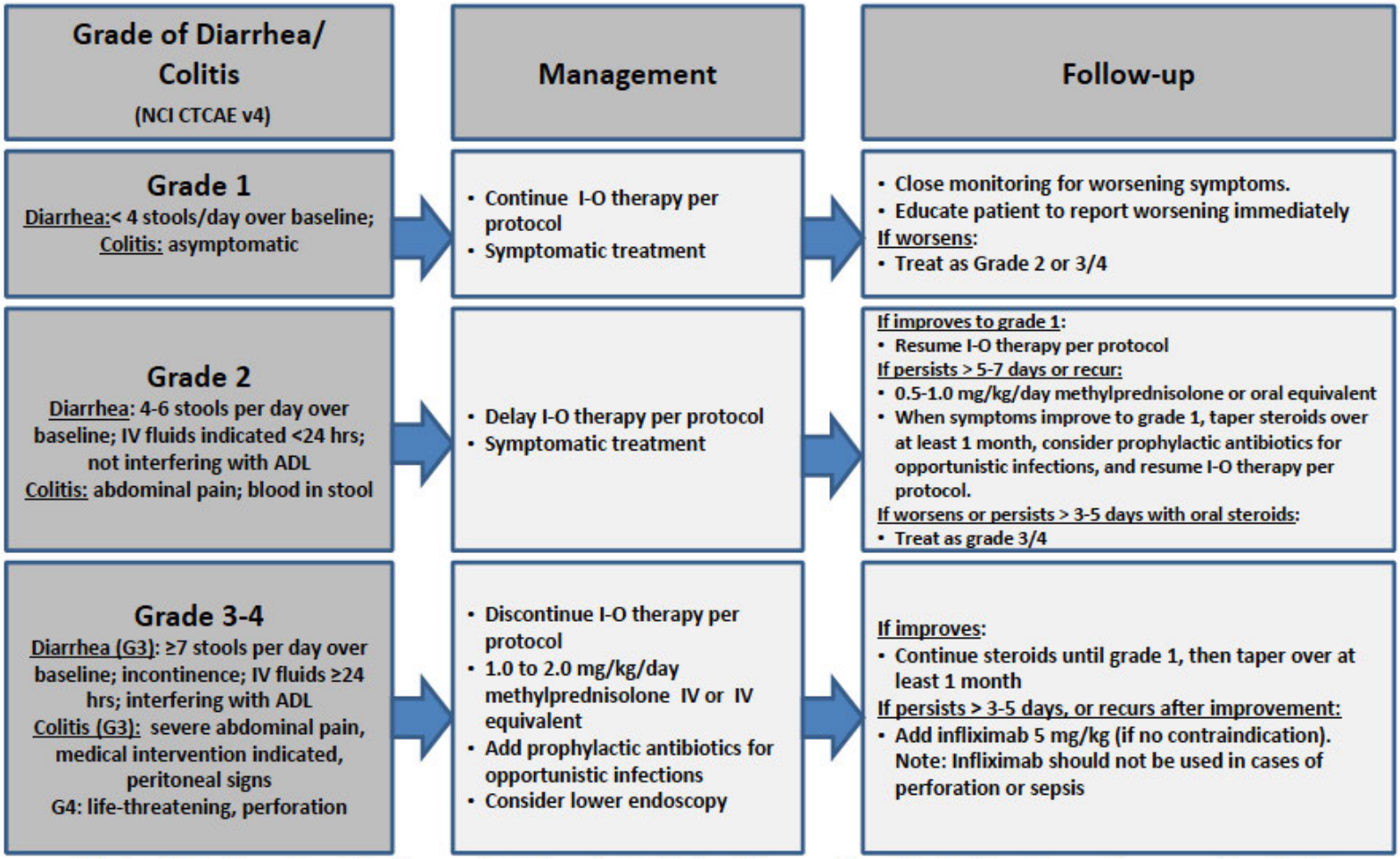
Corticosteroids are a primary therapy for immune-oncology drug-related adverse events. The oral equivalent of the recommended IV doses may be considered for ambulatory patients with low-grade toxicity. The lower bioavailability of oral corticosteroids should be taken into account when switching to the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

GI Adverse Event Management Algorithm

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

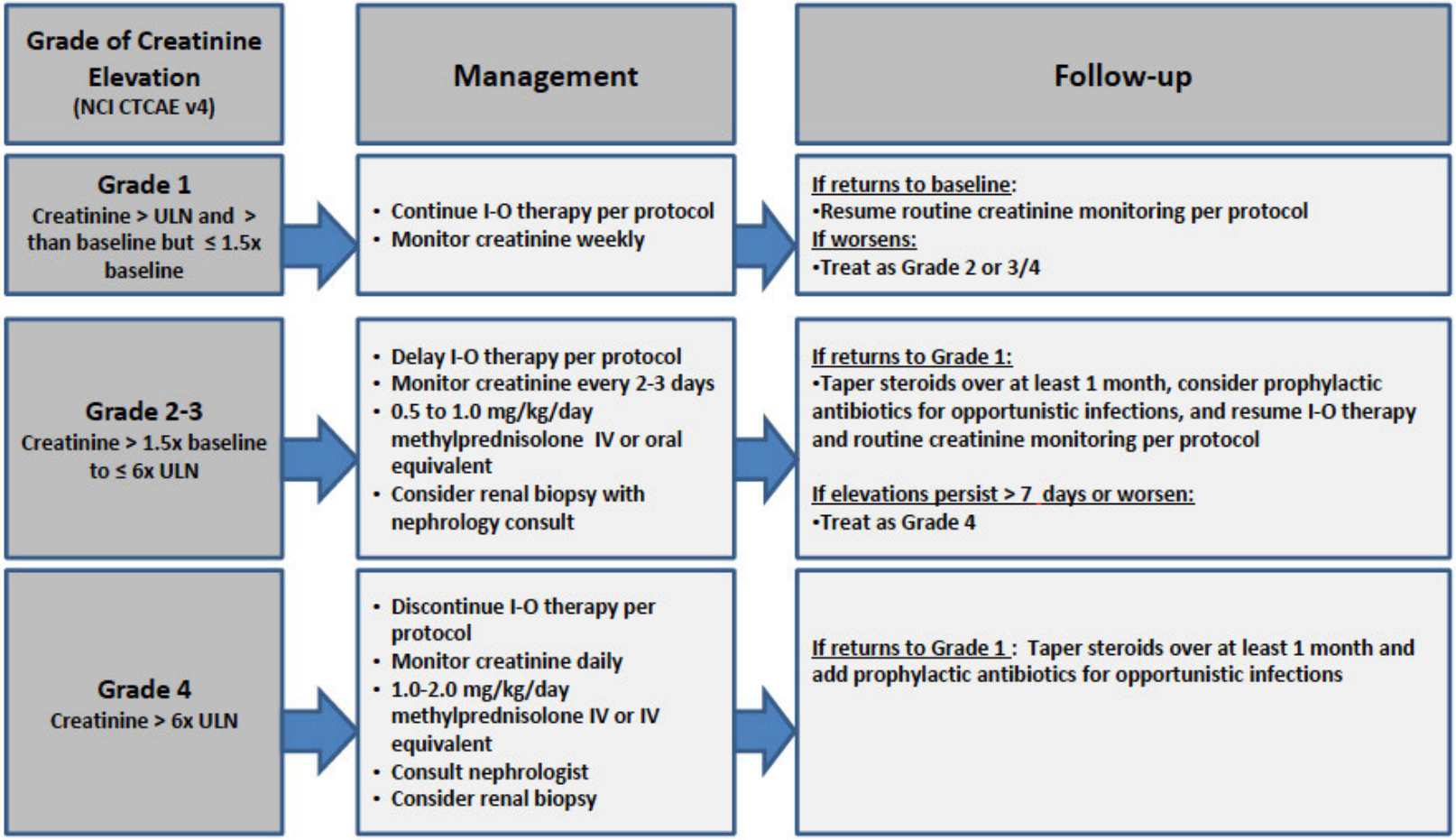


Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of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

Updated 05-Jul-2016

Renal Adverse Event Management Algorithm

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



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

Updated 05-Jul-2016

Pulmonary Adverse Event Management Algorithm

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

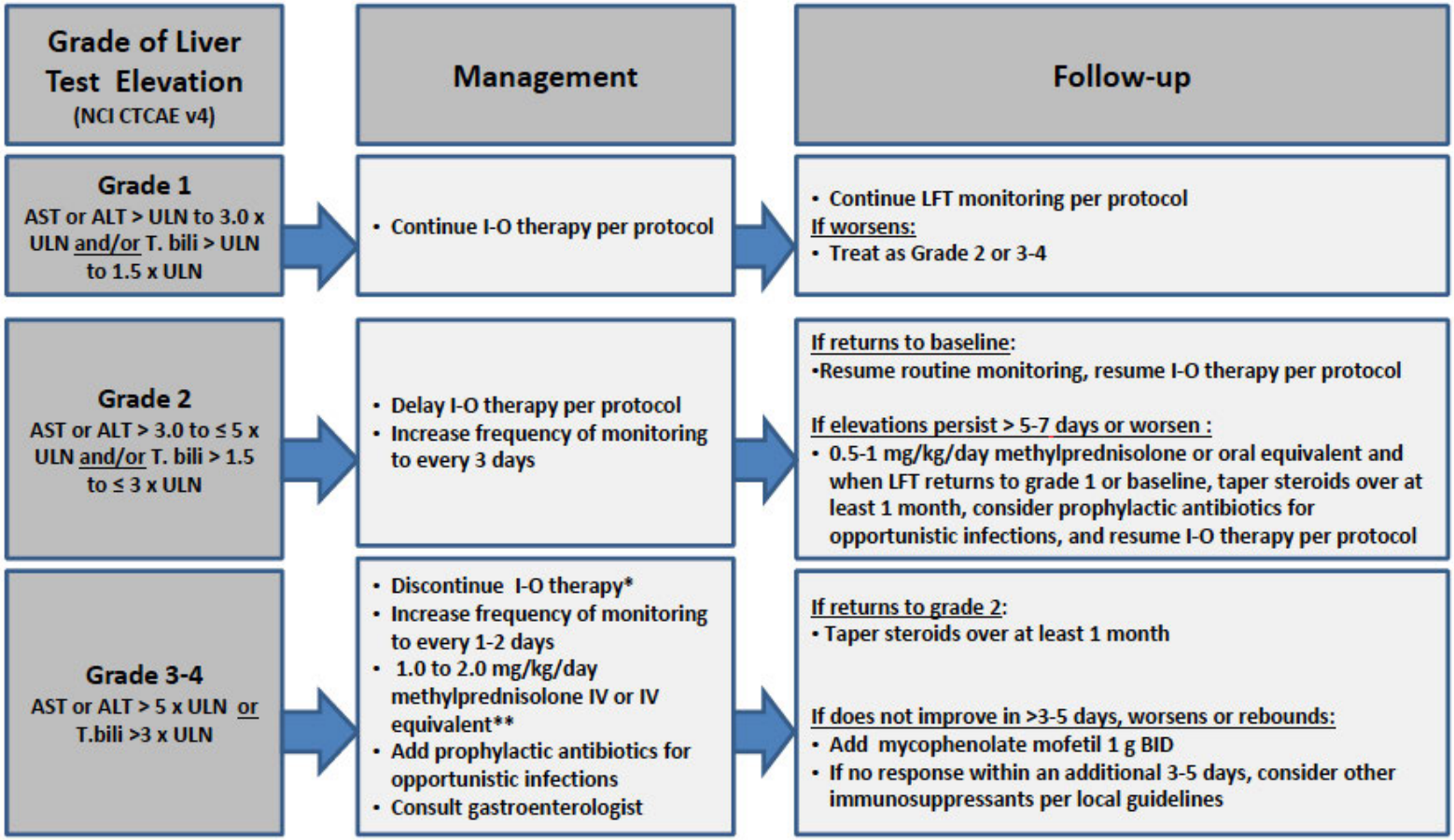
Grade of Pneumonitis (NCI CTCAE v4)	Management	Follow-up
Grade 1 Radiographic changes only	• Consider delay of I-O therapy • Monitor for symptoms every 2-3 days • Consider Pulmonary and ID consults	• Re-image at least every 3 weeks If worsens: • Treat as Grade 2 or 3-4
Grade 2 Mild to moderate new symptoms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

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

Updated 05-Jul-2016

Hepatic Adverse Event Management Algorithm

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



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

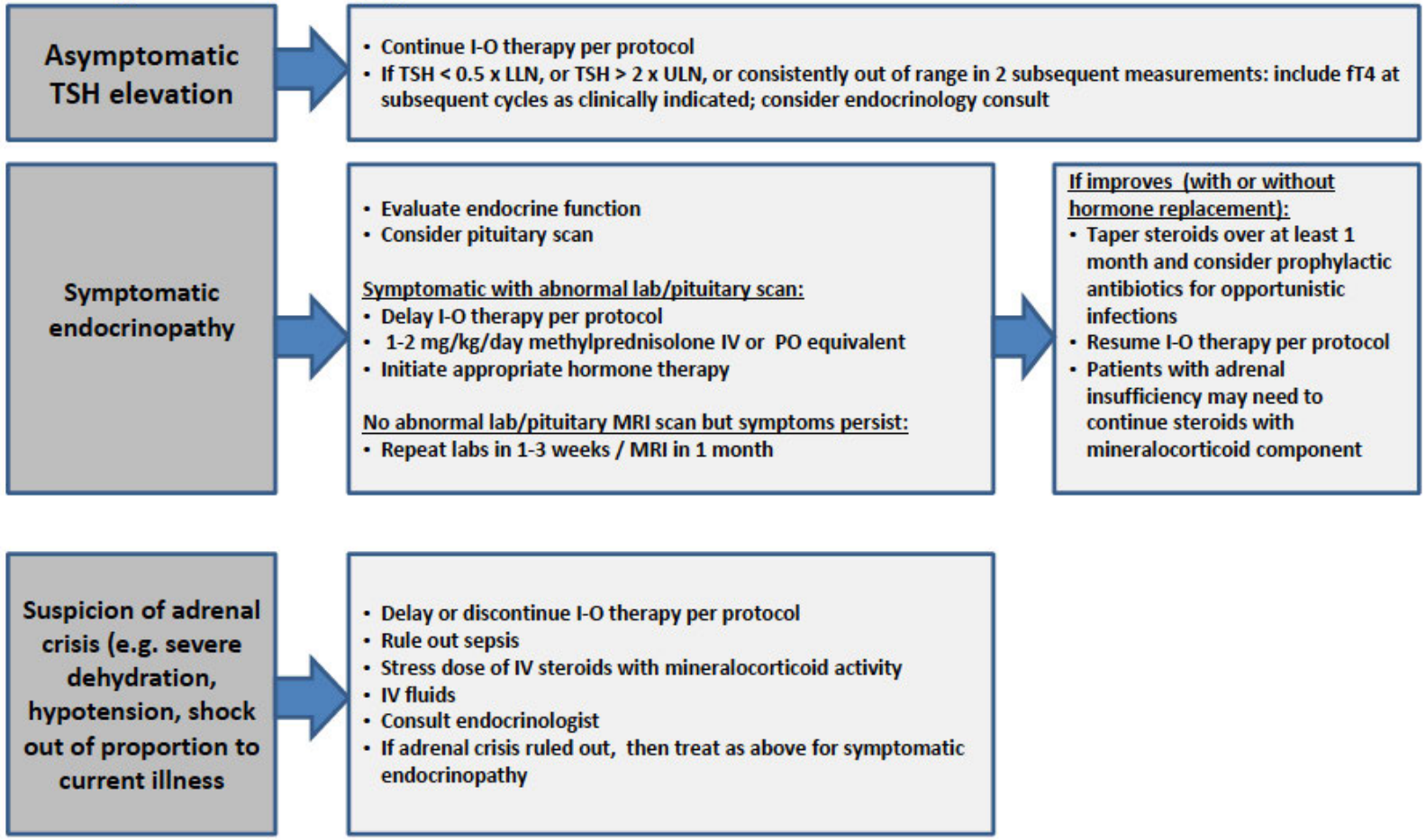
***I-O therapy may be delayed rather than discontinued if AST/ALT ≤ 8 x ULN or T.bili ≤ 5 x ULN.**

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

Updated 05-Jul-2016

Endocrinopathy Management Algorithm

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

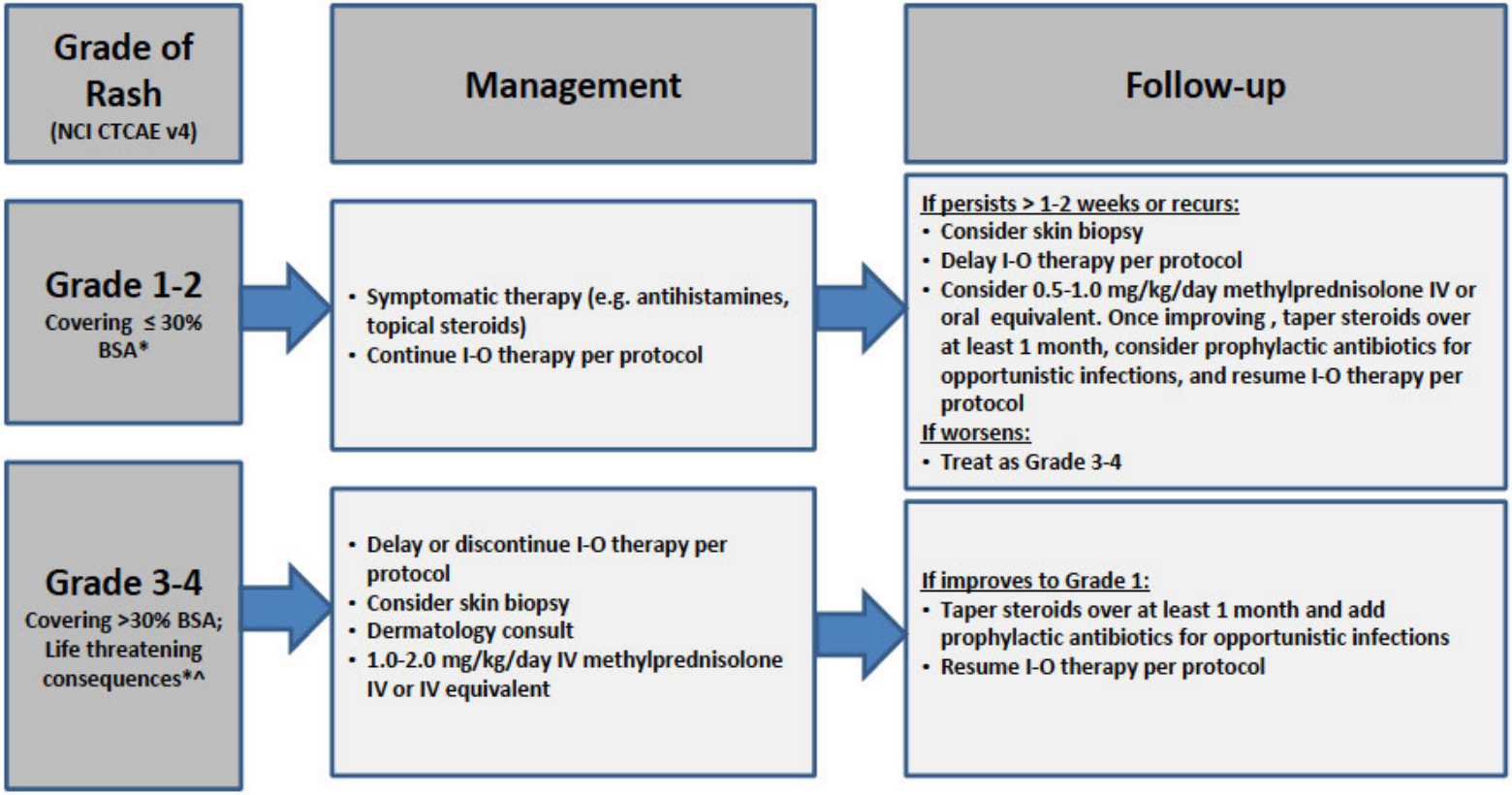


Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of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

Updated 05-Jul-2016

Skin Adverse Event Management Algorithm

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



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

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Neurological Adverse Event Management Algorithm

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

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

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

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