Phase I/II study of carboplatin/nab-paclitaxel and pembrolizumab for patients with advanced non-small cell lung cancer (NSCLC)

Hoosier Cancer Research Network: LUN13-175

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Phase I/II study of carboplatin/nab-paclitaxel and pembrolizumab for patients with advanced non-small cell lung cancer (NSCLC)

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I confirm I have read this protocol, I understand it, and I will work according to this protocol and to the ethical principles stated in the latest version of the Declaration of Helsinki, the applicable guidelines for good clinical practices, or the applicable laws and regulations of the country of the study site for which I am responsible, whichever provides the greater protection of the individual. I will accept the monitor's overseeing of the study. I will promptly submit the protocol to applicable ethical review board(s).

Instructions to the investigator: Please **SIGN** and **DATE** this signature page. **PRINT** your name and title, the name and location of the facility in which the study will be conducted, and the expected IRB approval date. Scan and email the completed form to Hoosier Cancer Research Network and keep a copy for your files.

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Signature of Investigator Date

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Investigator Name (printed)

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Investigator Title

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Synopsis

TITLE	Phase I/II study of carboplatin/nab-paclitaxel and pembrolizumab for advanced non-small cell lung cancer (NSCLC)
SHORT TITLE	Phase I/II carboplatin/nab-paclitaxel and pembrolizumab in NSCLC
PHASE	I/II
OBJECTIVES	Primary Objective: Phase I: To determine the recommended Phase II dose schedule (RP2DS) and evaluate the safety and tolerability of the combination of pembrolizumab with carboplatin/nab-paclitaxel for the first line treatment of subjects with advanced NSCLC. Phase II: To evaluate progression-free survival (PFS) and objective response rate for subjects receiving carboplatin/nab-paclitaxel and pembrolizumab for the first line treatment of advanced NSCLC. Secondary Objectives: Phase I: 1. To describe the following for subjects receiving carboplatin/nab-paclitaxel and pembrolizumab: a) Progression-free survival (PFS) b) Objective response c) Anti-tumor activity using change in tumor measurements d) Overall survival (OS) 2. To evaluate the association of PD-L1 expression on PFS for subjects receiving pembrolizumab. Phase II: 1. To evaluate the following for subjects receiving carboplatin/nab-paclitaxel and pembrolizumab: a) Overall survival (OS) b) Anti-tumor activity using change in tumor measurements c) Safety and tolerability 2. To evaluate the association of PD-L1 expression on PFS for subjects receiving pembrolizumab.
TREATMENT SUMMARY	**Phase I:** Cohort 1 Carboplatin AUC 6 IV, Day 1 nab-paclitaxel 100 mg/m2 IV, Days 1, 8, 15 pembrolizumab 2 mg/kg IV, Day 1 Cycle length: 21 days

	Number of cycles: 4 Maintenance pembrolizumab 2 mg/kg IV continues every 21 days after Cycle 4 for up to 2 years. <u>Cohort 2 (if necessary)</u> Carboplatin AUC 6 IV, Day 1 nab-paclitaxel 100 mg/m2 IV, Days 1, 8, 15 pembrolizumab 2 mg/kg IV, Day 1 (cycle 2-4 only) Cycle length: 21 days Number of cycles: 4 Maintenance pembrolizumab 2 mg/kg IV continues every 21 days after Cycle 4 for up to 2 years. **Phase II:** Carboplatin AUC 6 IV, Day 1 nab-paclitaxel 100 mg/m2 IV, Days 1, 8, 15 pembrolizumab 200 mg IV, Day 1 Cycle length: 21 days Number of cycles: 4 Maintenance pembrolizumab 200 mg IV continues every 21 days after Cycle 4 for up to 2 years.
ELIGIBILITY CRITERIA	**Inclusion Criteria** 1. Subjects must be ≥ 18 years of age. 2. Individuals with stage IIIB or IV, unresectable non-small cell lung cancer (NSCLC) who have not received prior chemotherapy for Stage IIIB or IV disease, and who are not candidates for curative surgery or radiation therapy. 3. ECOG performance status (PS) 0-1 4. Measurable disease by RECIST v1.1 criteria 5. Prior to registration, all subjects must have either adequate archival tissue identified or available PD-L1 testing results using the Dako 22C3 antibody. If the patient has not had prior PD-L1 testing and no acceptable archival tissue is available, subjects must be willing to consent to providing a pre-treatment biopsy for PD-L1 testing. Regardless of PD-L1 testing status, archival tissue will be requested for research testing if available. PD-L1 status is required but does not need to be positive to be eligible for study. 6. Phase II subjects must be willing to consent to providing a post-treatment core biopsy for research if clinically feasible.

	7. Women are eligible to participate if they are of non-childbearing potential or have documentation of a negative pregnancy test (serum or urine β-hCG) within 3 days of registration. Sexually active pre-menopausal women of childbearing potential must agree to use adequate, highly effective contraceptive measures, starting with the first dose of study drug through 120 days after the last dose of the last study drug. 8. Male subjects should agree to use an adequate method of contraception starting with the first dose of study drug through 120 days after the last dose of the last study drug. **Exclusion Criteria** 1. Individuals with the presence of symptomatic CNS metastases requiring radiation treatment, surgery, or ongoing use of corticosteroids. 2. Untreated or brain metastasis causing any symptoms. Treated brain metastases must be stable for 4 weeks prior to first dose of study drug and not requiring steroids for at least 7 days prior to study treatment. 3. History of solid organ or stem cell transplant requiring immunosuppressive medications. 4. Any prior adjuvant cytotoxic chemotherapy within the last 12 months. Subjects who received chemotherapy for earlier stage disease more than 12 months prior to study registration are eligible for this trial. 5. Has received prior therapy with an anti-PD-1, anti-PD-L1, anti-PD-L2, anti-CD137, or anti-Cytotoxic T-lymphocyte-associated antigen-4 (CTLA-4) antibody (including ipilimumab or any other antibody or drug specifically targeting T-cell co-stimulation or checkpoint pathways). 6. Any radiotherapy within 2 weeks prior to registration (4 weeks for brain radiotherapy as noted above) 7. Is currently participating in or has participated in a study of an investigational agent or using an investigational device within 4 weeks of the first dose of study drug.

	8. History of other invasive malignancy that is currently active and/or has been treated within 12 months prior to registration (Notable exceptions include; basal cell carcinoma, squamous cell carcinoma of the skin, localized prostate cancer, in situ carcinomas of the cervix and breast, and superficial bladder cancers [non- muscle-invasive]). 9. Has known history of Human Immunodeficiency Virus (HIV) (HIV 1/2 antibodies). 10. Active autoimmune disease that has required systemic treatment in past 2 years (i.e. with use of disease modifying agents, corticosteroids or immunosuppressive drugs). Replacement therapy (e.g., thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency, etc.) is not considered a form of systemic treatment 11. Pulmonary conditions such as sarcoidosis, silicosis, idiopathic pulmonary fibrosis, or hypersensitivity pneumonitis. 12. Has a history of pneumonitis that required steroids or current pneumonitis. 13. Pre-existing peripheral neuropathy ≥ Grade 2 by CTCAE v4 criteria. 14. Known significant liver disease including viral, alcoholic, active hepatitis B or C, and/or cirrhosis. 15. Abnormal liver or renal function. 16. Abnormal baseline hematologic or coagulation parameters. 17. Has received a live vaccine within 30 days of first dose of study drug. 18. Known activating EGFR mutation or ALK translocation. Testing is not required but should be performed if clinically indicated; results are not required prior to enrollment.
STATISTICAL CONSIDERATIONS	**<u>Phase I:</u>** **Analytic plan for primary objective:** Cohort 1 All subjects who receive treatment will be evaluated for toxicity. Toxicities by type and grade will be summarized overall and by

	dose level. During the phase I portion of the study, there will be weekly teleconferences to review toxicities for all subjects on study. If at any point more than 4 subjects experience a DLT, enrollment to the current cohort will end. These ongoing assessments will occur throughout phase I for both cohort 1 and cohort 2 (if necessary). For example, if all 5 of the first 5 subjects enrolled have a DLT, no more subjects will be enrolled to that Phase I cohort or treated. If this occurs during cohort 2, the trial will end. After 12 subjects in Cohort 1 are treated, if the rates of unacceptable toxicity after 2 cycles of pembrolizumab, defined in Section 5.2.1.1 Definition of DLT, are ≤ 33% of subjects (≤ 4 of 12), the study will advance to the Phase II with pembrolizumab dose at 200 mg. If unacceptable toxicity occurs in > 33% of subjects (≥ 5 of 12), a second cohort of subjects will be enrolled. Cohort 2 (if necessary) Twelve subjects will be treated with delayed initiation of pembrolizumab 2 mg/kg. Pembrolizumab will be omitted for Cycle 1 and start on Day 1 of Cycle 2. If ≤ 33% of subjects have unacceptable toxicity (as defined above) at this dose level, 2 mg/kg starting Cycle 2, Day 1 will be the RP2D and schedule and the study will proceed to the Phase II part of the study. If > 33% of subjects (≥ 5 of 12) have unacceptable toxicity at this level, the study will be discontinued due to unacceptable toxicity of this drug combination. **Analytic plan for secondary objectives:** Median PFS and median OS outcomes will be described using KM method and two-sided 80% confidence intervals will be calculated. Response will be reported as a percentage of subjects registered to the study. PD-L1 expression will be categorized as positive or negative from pre-treatment biopsies. Positive PD-L1 expression rates are estimated to be 70%, based on preliminary data from pembrolizumab PN 001. The distribution of PFS will be summarized by PD-L1 expression using Kaplan-Meier method and PFS will be compared using one-sided logrank test. Nominal p-values will be reported to measure the strength of the

	differences tested. Anti-tumor activity will be reported as a percentage change in the sum of the dimensions of all measurable lesions as defined by RECIST 1.1 criteria. The baseline imaging before treatment will be compared to each subsequent imaging assessment. The maximum anti-tumor activity will be reported using the assessment with the smallest sum of dimensions (maximum response). **Phase II:** **Analytic plan for primary objective:** Recruitment of 43 subjects will last approximately 12 months and subjects will be followed until 39 PFS events occur or a maximum of 2 years from enrollment of the last subject. The estimated study duration is 3 years. Two co-primary outcomes are chosen –PFS based on mechanism of action and RR based on acknowledgement of 'traditional' single arm studies. For the first co-primary outcome, PFS, assumptions are that the addition of pembrolizumab will increase PFS by 50% to 9.0 months compared to historical control of 6.0 months. After completion of the study, or when 39 or more subjects have experienced a PFS event, the distribution of PFS will be summarized using Kaplain-Meier method, and median PFS will be reported. A one-sided 5% type I error, 20% type II error and exponential distribution of PFS were assumed. Success will be defined as a lower 95% one sided confidence limit for the median (Brookmeyer, R. and Crowley, J. (1982), "A Confidence Interval for the Median Survival Time," *Biometrics,* 38, 29-41.) being greater than 6 months. For the second co-primary outcome, response rate, a single stage, single arm design will assume a historical control response rate of 31% and a hypothesized study rate of 50%. This effect size may be detected with 80% power, a one-sided 5% type I error rate and 20% type II error rate. Success will be defined as the number of responses being greater than or equal to 19 out of 43. The analysis of both co-primary outcomes will use the intention-to-treat approach from the time of registration. **Analytic plan for secondary objectives:** OS outcomes will be summarized using KM method. Safety and tolerability will be reported as rates of Grade 1-5 toxicity by CTCAE v4 criteria for all events with a frequency of ≥ 1. Anti-tumor activity will be reported as a percentage change in the sum

	of the dimensions of all measurable lesions as defined by RECIST 1.1 criteria. The baseline imaging before treatment will be compared to each subsequent imaging assessment. The maximum anti-tumor activity will be reported using the assessment with the smallest sum of dimensions (maximum response). PD-L1 expression will be categorized as positive (≥ 1% expression) or negative (< 1% expression) from pre-treatment and post-treatment biopsies. Positive PD-L1 expression rates are estimated to be 70%, based on preliminary data from pembrolizumab PN 001. The distribution of PFS will be summarized by PD-L1 expression using Kaplan-Meier method and PFS will be compared using one-sided logrank test.
TOTAL NUMBER OF SUBJECTS	Phase I: 12 to 24 Phase II: 43
ESTIMATED STUDY DURATION	Estimated 36 months utilizing Northwestern University as lead institution with additional Hoosier Cancer Research Network sites

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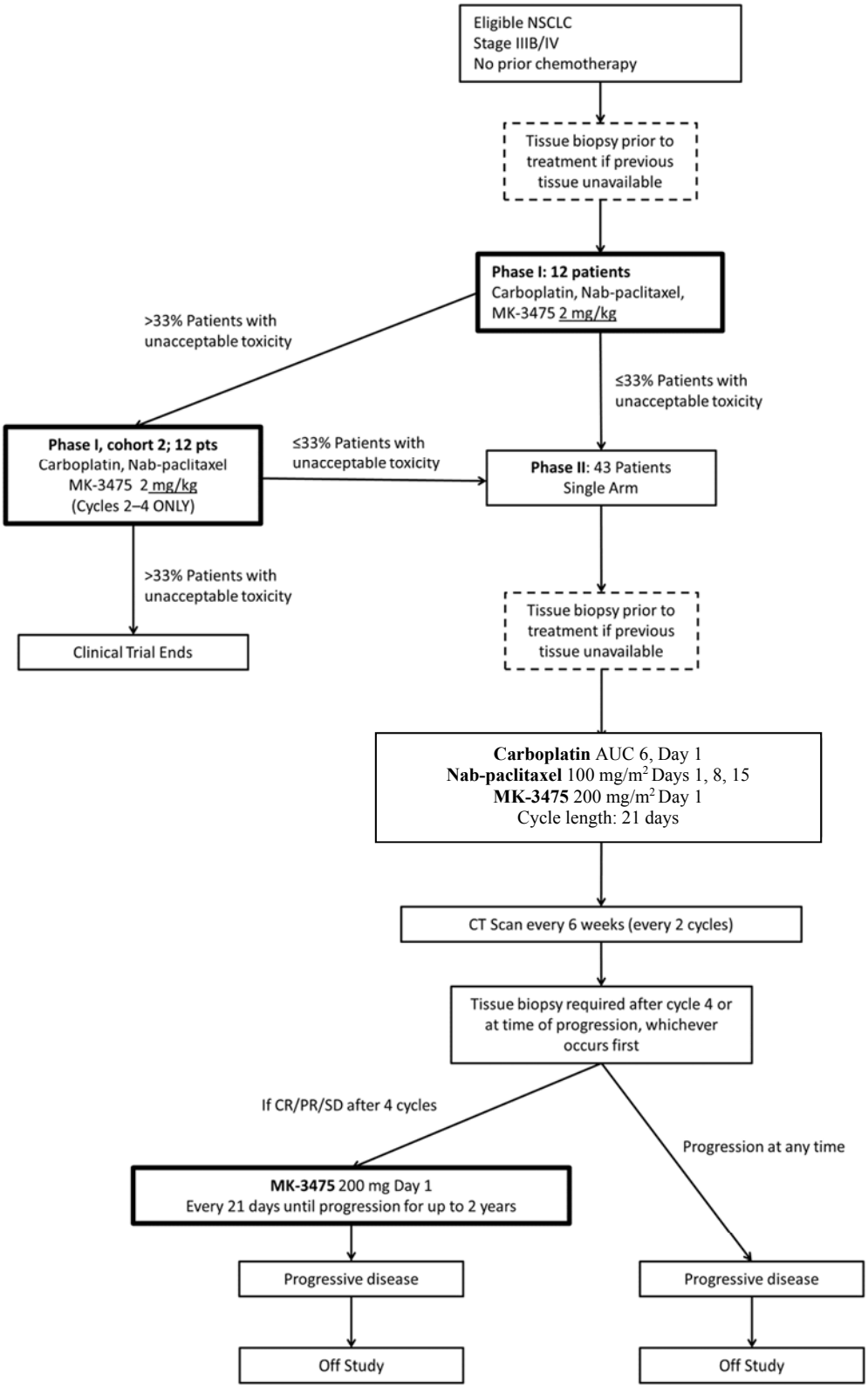
Eligible NSCLC
Stage IIIB/IV
No prior chemotherapy
Tissue biopsy prior to treatment if previous tissue unavailable
Phase I: 12 patients
Carboplatin, Nab-paclitaxel,
MK-3475 2 mg/kg
>33% Patients with unacceptable toxicity
≤33% Patients with unacceptable toxicity
Phase I, cohort 2; 12 pts
Carboplatin, Nab-paclitaxel
MK-3475 2 mg/kg
(Cycles 2–4 ONLY)
≤33% Patients with unacceptable toxicity
Phase II: 43 Patients
Single Arm
>33% Patients with unacceptable toxicity
Clinical Trial Ends
Tissue biopsy prior to treatment if previous tissue unavailable
Carboplatin AUC 6, Day 1
Nab-paclitaxel 100 mg/m2 Days 1, 8, 15
MK-3475 200 mg/m2 Day 1
Cycle length: 21 days
CT Scan every 6 weeks (every 2 cycles)
Tissue biopsy required after cycle 4 or at time of progression, whichever occurs first
If CR/PR/SD after 4 cycles
Progression at any time
MK-3475 200 mg Day 1
Every 21 days until progression for up to 2 years
Progressive disease
Progressive disease
Off Study
Off Study

1. BACKGROUND AND RATIONALE

The hypothesis of this study is that the addition of pembrolizumab, an anti-PD-1 antibody to carboplatin/nab-paclitaxel for the first-line treatment of patients with advanced non-small cell lung cancer (NSCLC) will improve the median progression-free survival (PFS) by 4 months (from 6 months to 10 months) when compared to historical controls of patients treated with carboplatin/nab-paclitaxel alone.

1.1 Non-Small Cell Lung Cancer

Lung cancer is the most commonly diagnosed cancer worldwide and accounts for nearly 1.4 million deaths annually [1]. In the United States, over 228,000 new cases of lung cancer are diagnosed each year, and it is the leading cause of cancer mortality, resulting in more deaths than breast, prostate, and colon cancer combined [2]. The most common type of lung cancer, comprising nearly 7 of 8 cases, is NSCLC. Over 50% of patients are diagnosed with advanced stage disease, and only 18% of all patients with NSCLC are alive five years after diagnosis [3]. Platinum-based double chemotherapy has been the standard treatment for patients with good performance status (PS) and advanced stage (stage IIIB/IV) NSCLC. A large cooperative group study compared 4 platinum doublets, cisplatin-paclitaxel, cisplatin-gemcitabine, cisplatin-docetaxel, and carboplatin-paclitaxel, and found no differences in outcomes, including overall survival (OS), between these regimens [4].

1.2 Maintenance Therapy

Although some studies have shown that extending chemotherapy beyond four to six cycles of platinum-based doublet chemotherapy can improve outcomes in individual patients, early studies that continued platinum-based doublets beyond four or six cycles were largely negative due to minimal improvements in overall survival and additional toxicity and deterioration of quality of life [5]. In 2006, the Eastern Cooperative Oncology Group (ECOG) 4599 study, demonstrated an improved overall survival with the addition of bevacizumab, a monoclonal antibody targeting VEGF, to carboplatin-paclitaxel chemotherapy. In this study, bevacizumab was continued past induction therapy until progression of disease or unacceptable toxicity. With the results of this study and development of other better-tolerated therapies with activity in lung cancer, there has been renewed interest in maintenance therapy. One of the first notable studies to show that maintenance chemotherapy was a viable strategy was conducted by Fidias, et al [6]. In this randomized, phase III study, patients who received early docetaxel after induction chemotherapy had a 3-month improvement in progression-free survival (PFS) and 2.6-month improvement in OS when compared to patients who received second-line docetaxel at the time of progression. The OS improvement did not reach statistical significance, but the study was not powered for OS. Continuation of pemetrexed after cisplatin-pemetrexed induction has been shown to improve OS by nearly three months to 13.9 months from randomization in the PARAMOUNT trial [7]. Similarly, maintenance pemetrexed after other platinum-based doublet chemotherapy and maintenance therapy with erlotinib, a tyrosine kinase with anti-EGFR activity, have been shown to improve OS [8, 9]. Other maintenance strategies have resulted in significant improvement in PFS as well [9-12]. In PointBreak, a trial that randomized 939 patients to two commonly used chemotherapy and maintenance strategies, median overall survival from initiation of first line treatment was 12.6 months and 13.4 months in the two arms. There was no statistically significant difference between the two arms [12]

1.3 Nab-Paclitaxel

Paclitaxel is an anti-microtubule agent with broad-spectrum activity against human cancers. Paclitaxel is dissolved in a proprietary solvent of Cremophor and ethanol in its formulation, known as Taxol (Bristol-Myers Squibb, New York, New York). ABI-007 (nab-paclitaxel, Abraxane, Celgene) is a proprietary solvent-free, protein-stabilized formulation of paclitaxel comprised of paclitaxel and human albumin in a non-crystalline amorphous state. Nab-paclitaxel has been developed to improve the therapeutic index of paclitaxel and reducing the toxicities associated with Taxol. Nab-paclitaxel has linear pharmacokinetic (PK) characteristics and based on its PK properties, the dose and short infusion time, and increase in maximum concentration (C_{max}) of free paclitaxel up to 10-fold greater than with soluble paclitaxel has been reported in the literature [13]. In vitro studies demonstrated that the transport of paclitaxel across the endothelium is enhanced through albumin receptor mediated transcytosis, and the delivery of paclitaxel to tumors may be enhanced by binding of the albumin-bound paclitaxel to interstitial albumin binding proteins, such as secreted protein acidic and rich in cysteine (SPARC) [14]. Nab-paclitaxel conferred the ability to achieve a higher maximum tolerated dose (MTD) based on every 3-weeks dosing: 300 mg/m^2 versus 175 mg/m^2 of soluble paclitaxel. Nab-paclitaxel can also be given in a shorter timeframe of 30 minutes compared to 3 hours with soluble paclitaxel. Nab-paclitaxel is given without steroid and anti-histamine pre-medication, which is required for soluble paclitaxel to prevent solvent-related hypersensitivity reactions.

1.4 Nab-paclitaxel and Lung Cancer

Nanoparticle albumin-bound paclitaxel (nab-paclitaxel) is approved for the treatment of NSCLC based on the results of a Phase III study that compared nab-paclitaxel 100 mg/m^2 (weekly) and carboplatin with soluble paclitaxel (200 mg/m^2) and carboplatin [15]. This large non-inferiority study randomized 1,052 patients to one of the two arms. Those receiving nab-paclitaxel had a higher overall response rate (ORR) (33% vs. 25%, p=0.005). The median duration of response was similar in both arms; 9.6 months in the nab-paclitaxel/carboplatin arm and 9.5 months in the paclitaxel/carboplatin arm (p=0.551). The nab-paclitaxel arm demonstrated equal efficacy compared to the control arm, with significantly less severe peripheral neuropathy, arthralgia, and myalgia.

1.5 Immune Checkpoints

T-cells are responsible for cellular immunity and are activated when antigen-presenting cells (APC) present an antigen to the T-cell receptor (TCR) in the presence of a costimulatory molecule, B7. After activation of the T-cell, cytotoxic T-lymphocyte antigen 4 (CTLA-4), a receptor on the T-cell is upregulated and binds to B7 on APCs, which acts as a negative regulator of T-cell activation. Programmed cell death 1 receptor (PD-1), is another receptor on the T-cell surface that acts as a negative regulator. Its normal role is to down-modulate excessive immune responses, such as autoimmune reactions. This receptor interacts its ligand (PD-L1 and PD-L2), which is often present on tumor or host cells, and when activated, will also downregulate antigen receptor signaling [16, 17]. The mechanism by which PD-1 down modulates T-cell responses is similar to, but distinct from, that of CTLA-4, as both molecules regulate an overlapping set of signaling proteins [18, 19]. Binding of either PD-L1 or PD-L2 to PD-1 inhibits T-cell activation triggered through the T-cell receptor. PD-L1 is expressed at low levels on various non-hematopoietic tissues, most notably on vascular endothelium; whereas PD-L2 is only detectably expressed on antigen-presenting cells found in lymphoid tissue or chronic inflammatory

environments. PD-L2 is thought to control immune T-cell activation in lymphoid organs, whereas PD-L1 serves to dampen unwarranted T-cell function in peripheral tissues [19].

1.6 PD-1 Pathway and Cancer

The importance of intact functions of immune surveillance in controlling neoplastic transformation of cells is well recognized [20]. The presence of T-cell infiltration of tumors, such as the presence of CD8+ T cells and the ratio of CD8+ effector T-cells / FoxP3+ regulatory T-cells (T regs), have been shown to correlate with improved prognosis and survival in multiple solid malignancies. PD-L1 expression by tumors has been linked to the development of immunoresistance in cancer cells mediated by its interaction with T-cell PD-1 [21]. Although healthy organs express little (if any) PD-L1, a variety of cancers were demonstrated to express abundant levels of this T-cell inhibitor. High expression of PD-L1 on tumor cells has been found to correlate with poor prognosis and survival in multiple solid tumors [22-25]. PD-1 has also been suggested to regulate tumor-specific T-cell expansion in patients with melanoma [26]. The observed correlation of clinical prognosis with PD-L1 expression in multiple cancers suggests that the PD-1/PD-L1 pathway plays a critical role in tumor immune evasion and is an attractive target for therapeutic intervention.

1.7 Corticosteroids and Immune Response

Corticosteroids are known to have anti-inflammatory and immunosuppressive effects and are an effective therapy for inflammatory disorders, such as autoimmune disease, asthma, and allergies [27]. Several molecular mechanisms have been proposed for corticosteroids' impact on the downregulation of T-cell activation, including modulation of activation-induced cell death and the inhibition of recruitment of neutrophils and monocytes to inflammatory sites [28]. In vitro studies have shown that dexamethasone leads to inactivation of T-cells through downregulation of the IL-2 receptors [27]. Glucocorticoids have also been shown to lead to expansion of regulatory T-cells mediated by production of TGF-β [29]. It is unclear whether steroid use impacts T-cell immune response to tumor cells in patients with cancer. Due to the downregulation of T-cell activation, concomitant corticosteroids could potentially blunt a desired immune response to anti PD-1 immunotherapy. Corticosteroids have been successfully used for the treatment adverse effects of immunotherapy, such as autoimmune colitis and pneumonitis.

1.8 Clinical Activity of Immune Checkpoint Inhibitors

Two phase III studies of ipilimumab, an anti-CTLA4 monoclonal antibody, have shown significant improvements in overall survival in patients with metastatic melanoma [30, 31]. Blocking the PD-1/PD-L1 interaction with anti-PD-1 or anti-PD-L1 antibodies can also increase T-cell response to malignancy and lead to tumor cell death in patients with solid tumor malignancies, including lung cancer [32-36]. Nivolumab (BMS-936558), a monoclonal antibody against PD-1, showed an overall response rate of approximately 28% and 27% in patients with advanced melanoma and renal cell carcinoma, respectively [33]. An objective response rate of nearly 20% in patients with NSCLC has been observed by targeting PD-1 [33, 37]. Pembrolizumab has shown an overall response rate of over 40% in patients with melanoma and over 20% in patients with NSCLC (Merck pembrolizumab Investigator Brochure).

1.9 Pembrolizumab

Pembrolizumab is a highly selective humanized mAb designed to block the interaction between PD-1 and its ligands, PD-L1 and PD-L2. Pembrolizumab is an IgG4/kappa isotype with a stabilizing sequence alteration in the Fc region. Pembrolizumab potently blocks binding to both ligands with half maximal inhibitory concentration (IC50) values below1 nM. Pembrolizumab enhances T cell responses in human donor blood cell cultures with an EC50 of ~0.1 to 0.3 nM. Pembrolizumab binds to cynomolgus PD-1 with similar affinity, blocking activity, and demonstrates equivalent enhancement of cynomolgus T cell responses. It does not cross-react with rodent PD-1 (Merck, Inc. pembrolizumab Investigator Brochure).

Pembrolizumab strongly enhances T lymphocyte immune responses in cultured blood cells from healthy human donors, cancer patients, and primates. The antibody potentiates existing immune responses only in the presence of antigen-receptor stimulation and does not nonspecifically activate all T cells. Using an anti-mouse PD-1 analog antibody, PD-1 blockade is demonstrated to significantly inhibit tumor growth in a variety of syngeneic murine tumor models. In experiments in mice, anti-PD-1 therapy is synergistic with chemotherapeutic agents such as gemcitabine and 5-FU and combination therapy results in increased efficacy and increased complete regression rates in vivo. In addition, there has been significant clinical experience with pembrolizumab (Merck, Inc. pembrolizumab Investigator Brochure).

1.10 Pembrolizumab Dose Selection Rationale

The dose regimen of 200 mg Q3W of pembrolizumab is planned for all cancer trials. Available PK results in subjects with melanoma, NSCLC, and other solid tumor types support a lack of meaningful difference in PK exposures obtained at a given dose among tumor types. An open-label Phase 1 trial (PN001) in melanoma subjects is being conducted to evaluate the safety and clinical activity of single agent pembrolizumab. The dose escalation portion of this trial evaluated three dose levels, 1 mg/kg, 3 mg/kg, and 10 mg/kg, administered every 2 weeks (Q2W) in subjects with advanced solid tumors. All three dose levels were well tolerated and no dose-limiting toxicities were observed. This first in human study of pembrolizumab showed evidence of target engagement and objective evidence of tumor size reduction at all dose levels (1 mg/kg, 3 mg/kg and 10 mg/kg Q2W). No maximum tolerated dose (MTD) has been identified.

In KEYNOTE-001, two randomized cohort evaluations of melanoma subjects receiving pembrolizumab at a dose of 2 mg/kg versus 10 mg/kg Q3W have been completed. The clinical efficacy and safety data demonstrate a lack of clinically important differences in efficacy response or safety profile at these doses. For example, in Cohort B2, advanced melanoma subjects who had received prior ipilimumab therapy were randomized to receive pembrolizumab at 2 mg/kg versus 10 mg/kg Q3W. The overall response rate (ORR) was 26% (21/81) in the 2mg/kg group and 26% (25/79) in the 10 mg/kg group (full analysis set (FAS)). The proportion of subjects with drug-related adverse events (AEs), grade 3-5 drug-related AEs, serious drug-related AEs, death or discontinuation due to an AE was comparable between groups or lower in the 10 mg/kg group.

Available pharmacokinetic results in subjects with melanoma, NSCLC, and other solid tumor types support a lack of meaningful difference in pharmacokinetic exposures obtained at a given dose among tumor types. Population PK analysis has been performed and has confirmed the expectation that intrinsic factors do not affect exposure to pembrolizumab to a clinically meaningful extent. Taken together, these data support the use of lower doses (with similar exposure to 2 mg/kg Q3W) in all solid tumor indications. 2 mg/kg Q3W is being evaluated in NSCLC in PN001, Cohort F30 and PN010, and 200 mg Q3W is being evaluated in head and neck cancer in PN012, which are expected to provide additional data supporting the dose selection.

Selection of 200 mg as the appropriate dose for a switch to fixed dosing is based on simulation results indicating that 200 mg will provide exposures that are reasonably consistent with those obtained with 2 mg/kg dose and importantly will maintain individual patient exposures within the exposure range established in melanoma as associated with maximal clinical response. A population PK model, which characterized the influence of body weight and other patient covariates on exposure, has been developed using available data from 476 subjects from PN001. The distribution of exposures from the 200 mg fixed dose are predicted to considerably overlap those obtained with the 2 mg/kg dose, with some tendency for individual values to range slightly higher with the 200 mg fixed dose. The slight increase in PK variability predicted for the fixed dose relative to weight-based dosing is not expected to be clinically important given that the range of individual exposures is well contained within the range of exposures shown in the melanoma studies of 2 and 10 mg/kg to provide similar efficacy and safety. The population PK evaluation revealed that there was no significant impact of tumor burden on exposure. In addition, exposure was similar between the NSCLC and melanoma indications. Therefore, there are no anticipated changes in exposure between different tumor types and indication settings.

1.11 Study Rationale

Checkpoint inhibitors, specifically those targeting PD-1, have demonstrated striking efficacy in multiple solid tumors, including lung cancer. These agents are particularly promising due to the potential of inducing prolonged responses in a disease that traditionally has very short progression-free intervals. Pembrolizumab is a novel PD-1 inhibitor with demonstrated activity in lung cancer in the phase I setting. Due to the potential of prolonged response, starting pembrolizumab in the first line setting combined with standard chemotherapy may maximize the potential benefit from this drug.

Corticosteroids, often at high doses, are frequently administered in conjunction with cytotoxic chemotherapeutics, such as paclitaxel, as anti-emetic therapy or to prevent hypersensitivity. Unfortunately, corticosteroids are known to decrease T-cell mediated inflammation, and high doses of corticosteroids could lead to decreased efficacy of concomitant immunotherapy. Nab-paclitaxel combined with carboplatin, unlike paclitaxel, does not require additional corticosteroid premedication that is required with paclitaxel.

Nab-paclitaxel may have additional benefits when paired with immunotherapy beyond the ability to omit corticosteroid use. Secreted protein acidic and rich in cysteine (SPARC) is responsible for maintaining extracellular matrix [38], has a high affinity for albumin, has been shown to be over-expressed in NSCLC, and may correlate with prognosis [39]. The recognition of SPARC

over-expression in NSCLC is important when targeting an immune response because the density and organization of the extracellular matrix may control migration of T cells to tumors [40]. Nab-paclitaxel, due to its albumin-bound properties, may be better able to disrupt the extracellular matrix where SPARC is over-expressed and allow for better PD-1 inactivated T-cell migration to the tumor targets. In this phase II study, we propose the addition of pembrolizumab to standard induction chemotherapy with carboplatin and nab-paclitaxel without the use of corticosteroids for patients with advanced NSCLC.

This Phase I/II trial will study the effects of pembrolizumab in combination with carboplatin /nab-paclitaxel for the first-line treatment of patients with advanced NSCLC**.**

2. OBJECTIVES

2.1 Primary Objectives

2.1.1 Phase I

To determine the recommended Phase II dose (RP2D) and evaluate the safety and tolerability of the combination of pembrolizumab with carboplatin/nab-paclitaxel for the first line treatment of subjects with advanced NSCLC.

2.1.2 Phase II

To evaluate progression-free survival (PFS) and objective response for subjects receiving pembrolizumab and carboplatin/nab-paclitaxel for the first line treatment of advanced NSCLC.

2.2 Secondary Objectives

2.2.1 Phase I

To describe the following for subjects receiving pembrolizumab and carboplatin/nab-paclitaxel:

- Progression-free survival (PFS)
- Objective response
- Anti-tumor activity
- Overall survival (OS)
- To evaluate the association of PD-L1 expression on PFS for subjects receiving pembrolizumab

2.2.2 Phase II

- To evaluate the following for subjects receiving pembrolizumab and carboplatin/nab-paclitaxel:
    - Overall survival (OS)
    - Anti-tumor activity
    - Safety and tolerability
- To evaluate the association of PD-L1 expression on PFS for subjects receiving pembrolizumab

3 SELECTION OF SUBJECTS

Accrual will take place at Northwestern University (NU) and other sites in the Hoosier Cancer Research Network (HCRN). The study will enroll 12 to 24 subjects in the Phase I part and 43 subjects in the phase II part for a total of 55 to 67 subjects. It is estimated that 25 potentially eligible subjects may be evaluated per month, and approximately 6 will be enrolled per month. It is estimated that accrual will be completed in one year and the total study duration will be 3 years.

3.1 Inclusion Criteria

1. Subjects must be willing and able to provide written informed consent for the trial and HIPAA authorization for release of protected health information.
   NOTE: HIPAA authorization may be included in the informed consent or obtained separately.
2. Subjects must be ≥ 18 years of age.
3. Individuals with stage IIIB or IV, unresectable non-small cell lung cancer (NSCLC) who have not received prior chemotherapy for Stage IIIB or IV disease, and who are not candidates for curative surgery or radiation therapy.
4. ECOG performance status (PS) 0-1
5. Measurable disease by RECIST v1.1 criteria
6. Prior to registration, all subjects should have archival tissue available. For subjects who have no archival tissue, but have PD-L1 testing results using the Dako 22C3 antibody, subjects will be permitted to enroll without submitting tissue. If the patient has not had prior testing and no acceptable archival tissue is available, subjects must be willing to consent to providing a pre-treatment biopsy for PD-L1 testing. Regardless of PD-L1 testing status, archival tissue will be requested for research testing if available. PD-L1 status is required but does not need to be positive to be eligible for study.
7. Phase II subjects must be willing to consent to providing a mandatory post-treatment core biopsy for research if clinically feasible.
8. Women are eligible to participate if they are of non-childbearing potential or have documentation of a negative pregnancy test (serum or urine β-hCG) within 3 days of registration. Sexually active pre-menopausal women of childbearing potential must agree to use adequate, highly effective contraceptive measures, starting with the first dose of study drug and for 120 days after the last dose of last study drug. Effective birth control includes (a) intrauterine device (IUD) plus one barrier method; (b) oral, implantable, or injectable contraceptives plus one barrier method; or (c) 2 barrier methods. Effective barrier methods are male or female condoms, diaphragms, and spermicides (creams or gels that contain a chemical to kill sperm). Women of childbearing potential are those who have not been surgically sterilized or have not been free from menses for ≥ 1 year.
10. Male subjects should agree to use an adequate method of contraception starting with the first dose of study drug through 120 days after the last dose of last study drug.

3.2 Exclusion Criteria

1. Individuals with the presence of symptomatic CNS metastases requiring radiation treatment, surgery, or ongoing use of corticosteroids.
2. Untreated or brain metastasis causing any symptoms, such as neurologic deficits or headache. Individuals with previously treated brain metastases may participate provided they are stable (without evidence of progression by imaging for at least four weeks prior to the first dose of study drug and any neurologic symptoms have returned to baseline and whole brain radiation or stereotactic radiosurgery completed over 4 weeks prior to registration), have no evidence of new or enlarging brain metastases, and are not using steroids for at least 7 days prior to study treatment.
3. History of solid organ or stem cell transplant requiring immunosuppressive medications.
4. Any prior adjuvant cytotoxic chemotherapy within 12 months of registration. Subjects who received chemotherapy for earlier stage disease more than 12 months prior to study registration are eligible for this trial.
5. Has received prior therapy with an anti-PD-1, anti-PD-L1, anti-PD-L2, anti-CD137, or anti-Cytotoxic T-lymphocyte-associated antigen-4 (CTLA-4) antibody (including ipilimumab or any other antibody or drug specifically targeting T-cell co-stimulation or checkpoint pathways).
6. Any radiotherapy within 2 weeks prior to registration (4 weeks for brain radiotherapy as noted above).
7. Is currently participating in or has participated in a study of an investigational agent or using an investigational device within 4 weeks of the first dose of treatment.
8. History of other invasive malignancy that is currently active and/or has been treated within 12 months of registration. (Notable exceptions include: basal cell carcinoma, squamous cell carcinoma of the skin, localized prostate cancer, in situ carcinomas of the cervix and breast, and superficial bladder cancers [non-muscle-invasive]).
9. Has known history of Human Immunodeficiency Virus (HIV) (HIV 1/2 antibodies).
10. Active autoimmune disease that has required systemic treatment in past 2 years (i.e. with use of disease modifying agents, corticosteroids or immunosuppressive drugs). Replacement therapy (e.g., thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency, etc.) is not considered a form of systemic treatment.
11. Pulmonary conditions such as sarcoidosis, silicosis, idiopathic pulmonary fibrosis, or hypersensitivity pneumonitis.
12. Has a history of pneumonitis that required steroids or current pneumonitis.
13. Pre-existing peripheral neuropathy that is ≥ Grade 2 by CTCAE v 4 criteria.
14. Known significant liver disease including viral, alcoholic, active hepatitis B or C, and/or cirrhosis.
15. Abnormal liver or renal function as defined as:
    - Bilirubin ≥ 1.5 mg/dL
    - AST or ALT ≥ 2.5 x the ULN
    - Alkaline phosphatase > 2.5 x the ULN, there is no upper limit if bone metastasis is present in the absence of liver metastasis
    - Creatinine > 1.5 mg/dl

16. Abnormal baseline hematologic or coagulation parameters as defined as:
    - Absolute neutrophil count (ANC) <1.5 x 10^9/L
    - Hemoglobin < 9.0 g/dL; subjects may not be transfused to meet enrollment criteria
    - Platelets < 100 x 10^9/L
    - International Normalized Ratio (INR) of Prothrombin Time (PT) ≥1.5 x ULN unless subjects is receiving anticoagulant therapy as long as PT or PTT is within therapeutic range of intended use of anticoagulants
    - Activated Partial Thromboplastin Time (aPTT) ≥ 1.5 x ULN unless subjects is receiving anticoagulant therapy as long as PT or PTT is within therapeutic range of intended use of anticoagulants
17. Has received a live vaccine within 30 days prior to the first dose of study drug.
18. Known activating EGFR mutation or ALK translocation. Testing is not required but should be performed if clinically indicated; results are not required prior to enrollment.
19. Is pregnant or breastfeeding, or expecting to conceive or father children within the projected duration of the trial, starting with the pre-screening or screening visit through 120 days after the last dose of pembrolizumab.

4 SUBJECT REGISTRATION

All subjects must be registered through the Hoosier Cancer Research Network (HCRN) electronic data capture (EDC) system. A subject will be considered registered when they are given an "on study" date in the EDC system. Subjects must be registered prior to starting protocol therapy and begin therapy **within five business days** of registration.

5 TREATMENT PLAN

5.1 Administration

All subjects in both phases of this study will be treated in cycles lasting 21 days (3 weeks). The drugs being used in this study include carboplatin, nab-paclitaxel, and pembrolizumab. All subjects in both phases of the study will receive carboplatin/nab-paclitaxel and pembrolizumab as induction therapy. Induction will continue for no more than 4 cycles of study treatment. Maintenance pembrolizumab will be continued for subjects without progression (complete response [CR], partial response [PR], or stable disease [SD] as defined by RECIST v1.1 criteria) after completion of 4 cycles of study treatment until the time of progression, unacceptable toxicity, or up to 2 years maximum from C1D1 (see Table 1).

After completion of Phase I, the Phase II part of the study will begin with pembrolizumab at a dose of 200 mg in combination with chemotherapy.

Table 1: Treatment Schedules

	Induction Therapy	Maintenance if CR/PR/SD
Phase I, Cohort 1	1. carboplatin AUC 6 IV, Day 1 2. nab-paclitaxel 100 mg/m^2 IV, Days 1, 8, 15 3. pembrolizumab 2* mg/kg IV, Day 1 Cycle length: 21 days Duration: maximum 4 cycles	pembrolizumab 2* mg/kg, Day 1 Cycle length: 21 days Duration: until progressive disease, unacceptable toxicity, or up to 2 years maximum
Phase I, Cohort 2 (if necessary)	1. carboplatin AUC 6 IV, Day 1 2. nab-paclitaxel 100 mg/m^2 IV, Days 1, 8, 15 3. pembrolizumab 2* mg/kg IV, Day 1 (Cycle 2-4 only) Cycle length: 21 days Duration: maximum 4 cycles	pembrolizumab 2* mg/kg, Day 1 Cycle length: 21 days Duration: until progressive disease, unacceptable toxicity, or up to 2 years maximum
Phase II	1. carboplatin AUC 6 IV, Day 1 2. nab-paclitaxel 100 mg/m^2 IV, Days 1, 8, 15 3. pembrolizumab 200 mg IV Day 1 of each cycle Cycle length: 21 days Duration: maximum 4 cycles of study treatment	pembrolizumab 200 mg, Day 1 of Cycle 5 and beyond. Cycle length: 21 days Duration: until progressive disease, unacceptable toxicity or a maximum of 2 years from C1D1.

Abbreviations: IV-intravenous; mg-milligrams; kg-kilograms; m^2-per meter squared
*As additional data from ongoing trials becomes available, the dose of pembrolizumab may be adjusted. See section 5.1.2.1 below.

5.1.1 Treatment Schedules

5.1.1.1 Phase I, Cohort 1

Induction Therapy

12 subjects will be enrolled to Cohort 1 and treated with carboplatin AUC 6 given IV on Day 1, nab-paclitaxel 100 mg/m^2 given IV on Days 1, 8, and 15, and pembrolizumab 2* mg/kg IV on Day 1. Treatment will continue for a maximum duration of 4 cycles.

Maintenance Therapy

For subjects who have confirmed CR, PR, or SD (non-progression) after 4 cycles study treatment, maintenance therapy with pembrolizumab 2* mg/kg will continue on Day 1 of each 21-day cycle. Treatment will continue until progression of disease, unacceptable toxicity, or for a maximum of 2 years from Cycle 1, Day 1. Subjects who complete 24 months of treatment with pembrolizumab may be eligible for up to one year of additional study treatment if they progress after stopping study treatment provided they meet the requirements detailed in Section 3.1 Inclusion Criteria.

*As additional data from ongoing trials becomes available, the dose of pembrolizumab may be adjusted. See section 5.1.2.1 below.

5.1.1.2 Phase I, Cohort 2

Induction Therapy

If unacceptable toxicity is seen in Phase I, Cohort 1, 12 additional subjects will be enrolled in Phase I, Cohort 2. Subjects will be treated with carboplatin AUC 6 given IV on Day 1 and nab-paclitaxel 100 mg/m^2 given IV on Days 1, 8, and 15. Pembrolizumab 2* mg/kg IV will be given on Day 1 starting in cycle 2. Treatment will continue for a maximum duration of 4 cycles (pembrolizumab given Cycles 2 to 4 only).

Maintenance Therapy

For subjects who have confirmed CR, PR, or SD (non-progression) after 4 cycles of induction therapy, maintenance therapy with pembrolizumab 2* mg/kg will continue on Day 1 of each 21-day cycle. Treatment will continue until progression of disease, unacceptable toxicity, or for a maximum of 2 years from Cycle 2, Day 1. Subjects who complete 24 months of treatment with pembrolizumab may be eligible for up to one year of additional study treatment if they progress after stopping study treatment provided they meet the requirements detailed in Section 3.1 Inclusion Criteria.

*As additional data from ongoing trials becomes available, the dose of pembrolizumab may be adjusted. See section 5.1.2.1 below.

5.1.1.3 Phase II

Induction Therapy Cycles 1-4

Subjects will be treated with carboplatin AUC 6 given IV on Day 1, nab-paclitaxel 100 mg/m^2 given IV on Days 1, 8, and 15, and pembrolizumab 200 mg IV on Day 1. Treatment will continue for a maximum duration of 4 cycles of study treatment. Each cycle starts when all the criteria to start a new cycle are met. A cycle is defined only when you can give all 3 drugs on Day 1, and it coincides with pembrolizumab. Pembrolizumab should be given with carboplatin and nab-paclitaxel on day 1 of the cycle. Chemotherapies may be withheld for six weeks, while pembrolizumab can be withheld for 12-weeks. If there is a pembrolizumab-specific toxicity requiring pembrolizumab to be held, chemotherapy should be resumed without pembrolizumab within 6 weeks if it is felt that chemotherapy is safe by the site investigator. Delays in chemotherapy beyond 6 weeks require withdrawal from the study treatment.

Maintenance Therapy

For subjects who have confirmed CR, PR, or SD (non-progression) after 4 cycles of induction therapy, maintenance therapy with pembrolizumab 200 mg will continue on Day 1 of each 21-day cycle. Treatment will continue until progression of disease, unacceptable toxicity, or for a maximum of 2 years from Cycle 1 Day 1. Subjects who complete 24 months of treatment with pembrolizumab may be eligible for up to one year of additional study treatment if they progress after stopping study treatment provided they meet the requirements detailed in Section 3.1 Inclusion Criteria.

*As additional data from ongoing trials becomes available, the dose of pembrolizumab may be adjusted. See section 5.1.2.1 below.

5.1.2 Dosing and route of administration

5.1.2.1 Pembrolizumab

Pembrolizumab 200 mg will be administered as a 30 minute IV infusion on Day 1 of each cycle. Pembrolizumab, when given on the same day as chemotherapy, will be administered prior to other chemotherapy agents. The dose of pembrolizumab used in the study may be adjusted based on emerging data provided by Merck.

Sites should make every effort to target infusion timing to be as close to 30 minutes as possible. However, given the variability of infusion pumps from site to site, a window of -five minutes and +10 minutes is permitted (i.e., infusion time is 30 minutes: -5 min/+10 min).

5.1.2.2 Nab-paclitaxel

Nab-paclitaxel will be dosed at 100 mg/m^2 and be administered as an intravenous (IV) infusion of reconstituted solution over 30 minutes. The solution has a concentration of 5 mg/mL. The total volume infused can be calculated as 20 mL/m^2 based on body surface area (BSA) calculations for height and weight on Day 1 of each cycle. Nab-paclitaxel dose should be completely administered before initiating carboplatin dose.

5.1.2.3 Carboplatin

Carboplatin will be dosed at an AUC of 6 and given as an IV infusion in 250 mL of D5W or NS over 30 minutes.

5.1.2.4 Dose Calculations

Body Surface Area (BSA)

BSA calculations will be used for dosing of nab-paclitaxel. BSA should be calculated on Day 1 of each cycle based on the subject's current height and weight using institutional standards. Dose modifications of all drugs should occur when the subject's weight changes >5% from baseline.

Area Under the Curve (AUC)

Dosing of carboplatin will be calculated using the Calvert formula, using the target AUC and glomerular filtration rate (GFR) on Day 1 of each cycle. This formula is as follows: mg = AUC x (GFR +25). GFR should be calculated using the Cockroft & Gault method using the subject's actual body weight. For the dosing calculation, the maximum GFR should be capped at 125 mL/min.

5.2 Dose Modifications

All toxicities should be graded according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE), version 4, which can be located on the CTEP website at http://ctep.cancer.gov.

All dose reductions of chemotherapy are considered permanent. Once a dose of chemotherapy is reduced, it will not be increased to previous level, even if toxicity has resolved. Subjects who miss a treatment of chemotherapy and/or pembrolizumab for a **reason unrelated to toxicity** need to resume therapy ≤ 7 days of the originally planned treatment. If a delay of more than 7 days occurs, the subject will be taken off treatment.

5.2.1 Dosing Levels and Toxicity Management

Table 2 should be used for all dosing adjustments based on the toxicities described in this section.

Table 2: Dose Levels for carboplatin, nab-paclitaxel and Pembrolizumab

	Carboplatin	Nab-paclitaxel	Pembrolizumab
Original Dose	AUC 6	100 mg/m^2	See below
1st Dose Reduction	AUC 4.5	75 mg/m^2	See below
2nd Dose Reduction	AUC 3	50 mg/m^2	See below

5.2.1.1 Definition of Dose-limiting Toxicity (DLT)

The occurrence of any of the following toxicities, which may be observed within the first 2 cycles of treatment, will be considered a DLT, if judged by the site investigator to be possibly, probably or definitely related to pembrolizumab or the combination of pembrolizumab plus the cytotoxic chemotherapy regimen:

- More than one missed dose of pembrolizumab (i.e., pembrolizumab not given during 2 or more cycles for any reason). **NOTE:** a 1 week delay in starting a cycle for any hematologic toxicity (see section 5.2.1.3) does not count as a missed dose.
- Any ≥ Grade 2 uveitis or eye pain that does not respond to topical therapy and does not improve to Grade 1 severity within the re-treatment period (≤ 6 weeks and/or prior to next pembrolizumab dose) OR requires systemic treatment.
- Any ≥ Grade 2 pneumonitis or interstitial lung disease that does not resolve with dose delay and systemic steroids. The management algorithm for pneumonitis or pulmonary toxicity can be found in the current pembrolizumab Investigator Brochure.
- Any ≥ Grade 3 febrile neutropenia.
- Any Grade 3 non-skin, non-laboratory adverse event lasting ≥ 3 days despite optimal supportive care. Any ≥ Grade 4 adverse event including laboratory abnormalities, except Grade 4 leukopenia or neutropenia lasting < 7 days and not accompanied by fever.
- Any liver function test (LFT) abnormality that meets the following criteria:
    - AST or ALT > 5 to 8 x ULN and/or total bilirubin > 3x ULN for > 2 weeks.
    - AST or ALT > 8 x ULN.
    - Total bilirubin > 5 x ULN.
    - ALT/AST > 3 x ULN and total bilirubin > 2 x ULN with alkaline phosphatase activity < 2 x ULN and no other reason can be found to explain the combination of elevations.
- Grade 3 thrombocytopenia associated with bleeding.

For the purposes of pembrolizumab dose decision-making, DLTs will be evaluated for the first 2 cycles of pembrolizumab treatment. Any AE with the potential to become a DLT based on the duration should be followed appropriately to accurately determine the duration of the event. Subjects should delay/interrupt or discontinue treatment if they experience any adverse event, laboratory abnormality or intercurrent illness (regardless of causality) which, in the opinion of the site investigator, presents a substantial clinical risk to the subject with continued dosing. Such delay/interruption or discontinuation, however, will not be considered a DLT unless it meets at least one of the DLT criteria defined above or if deemed dose-limiting by the DRC.

5.2.1.2 Dose modifications specifically for pembrolizumab

Subjects with evidence of PD by RECIST 1.1 criteria may continue to receive pembrolizumab beyond progression until confirmation scan is completed if they meet the following criteria:

- Absence of clinical significant symptoms and signs (including worsening of laboratory values) indicating PD.
- No decline in ECOG performance status (Appendix 16.2).
- Absence of rapid progression of disease or progressive tumor at critical anatomical sites (e.g., cord compression) requiring urgent alternative medical intervention.

In this scenario, pembrolizumab may continue for another 2 cycles for a repeat response assessment at 6 weeks later to evaluate response. If progression is confirmed, the subject will discontinue treatment.

If a dose of pembrolizumab is withheld for toxicity, then subjects may resume dosing with pembrolizumab if that is appropriate at their next scheduled appointment or when toxicity has improved as described below.

Pembrolizumab will be withheld for drug-related Grade 4 hematologic toxicities, non-hematological toxicity ≥ Grade 3 including laboratory abnormalities, and severe or life-threatening AEs as per Table 3 below. Table 16.3 Chemotherapy Dose Modification and Toxicity Management Guidelines for Immune-related AEs Associated with Pembrolizumab should be utilized as appropriate.

In the case that toxicity does not resolve to Grade 0-1 within 12 weeks after last infusion, study therapy should be discontinued after consultation with the sponsor-investigator (**NOTE:** this only applies to subjects on maintenance pembrolizumab alone. For delays ≥ 3 weeks from a scheduled Day 1 carboplatin dose (i.e., 6 weeks from last carboplatin dose), all treatments will be discontinued. Subjects who require corticosteroids to manage pembrolizumab-related AEs must be at an equivalent dose of ≤ 10 mg per day of prednisone to resume dosing with pembrolizumab. Furthermore, an inability to reduce the corticosteroid dose for managing a drug-related adverse event to the equivalent of ≤ 10 mg prednisone per day within 12 weeks of the last pembrolizumab dose should prompt discussion between the site investigator and sponsor-investigator regarding the subject's ability to continue on treatment in the study. With site investigator and sponsor-investigator agreement, subjects with a laboratory adverse event still at Grade 2 after 12 weeks may continue treatment in the study only if asymptomatic and controlled.

In subjects who continue on pembrolizumab having experienced a Grade 3, Grade 4, or persistent (> 4 weeks) Grade 2 pembrolizumab-related AE, dosing should be held until the AE resolves to Grade 0-1 or baseline and dosing should be resumed at 2 mg/kg every 3 weeks for Phase I subjects and 200 mg every 3 weeks for Phase II subjects.

However, in subjects who experience Grade 3 or 4 pneumonitis, or recurrent persistent (> 4 weeks) Grade 2 drug-related pneumonitis after re-challenge from a prior episode of persistent (> 4 weeks) Grade 2 drug-related pneumonitis, pembrolizumab must be permanently discontinued.

Table 3 Dose Modification Guidelines for Pembrolizumab Drug-Related Adverse Events

Toxicity	Hold Treatment For Grade	Timing for Restarting Treatment	Treatment Discontinuation
Diarrhea/Colitis	2-3	Toxicity resolves to Grade 0-1.	Toxicity does not resolve within 6 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 6 weeks.
	4	Permanently discontinue	Permanently discontinue
AST, ALT, or Increased Bilirubin	2	Toxicity resolves to Grade 0-1	Toxicity does not resolve within 6 weeks of last dose.
	3-4	Permanently discontinue (see exception below)[1]	Permanently discontinue
Type 1 diabetes mellitus (if new onset) or Hyperglycemia	T1DM or 3-4	Hold pembrolizumab for new onset Type 1 diabetes mellitus or Grade 3-4 hyperglycemia associated with evidence of beta cell failure.	Resume pembrolizumab when subjects are clinically and metabolically stable.
Hypophysitis	2-4	Toxicity resolves to Grade 0-1. Therapy with pembrolizumab can be continued while endocrine replacement therapy is instituted	Toxicity does not resolve within 6 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 6 weeks.
Hyperthyroidism	3	Toxicity resolves to Grade 0-1	Toxicity does not resolve within 6 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 6 weeks.
	4	Permanently discontinue	Permanently discontinue
Hypothyroidism		Therapy with pembrolizumab can be continued while thyroid replacement therapy is instituted	Therapy with pembrolizumab can be continued while thyroid replacement therapy is instituted.
Infusion Reaction	3-4	Permanently discontinue	Permanently discontinue
Pneumonitis	2	Toxicity resolves to Grade 0-1	Toxicity does not resolve within 6 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 6 weeks.
	3-4	Permanently discontinue	Permanently discontinue

Renal Failure or Nephritis	2	Toxicity resolves to Grade 0-1	Toxicity does not resolve within 6 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 6 weeks.
	3-4	Permanently discontinue	Permanently discontinue
All Other Drug-Related Toxicity[2]	3 or Severe	Toxicity resolves to Grade 0-1	Toxicity does not resolve within 6 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 6 weeks.
	4	Permanently discontinue	Permanently discontinue

Note: Permanently discontinue for any severe or Grade 3 drug-related AE that recurs or any life-threatening event.

[1] For subjects with liver metastasis who begin treatment with Grade 2 AST or ALT, if AST or ALT increases by greater than or equal to 50% relative to baseline and lasts for at least 1 week then subjects should be discontinued.

[2] Subjects with intolerable or persistent Grade 2 drug-related AE may hold study medication at physician discretion. Permanently discontinue study drug for persistent Grade 2 adverse reactions for which treatment with study drug has been held, that do not recover to Grade 0-1 within 6 weeks of the last dose.

5.2.1.3 Dose Modifications for Hematologic Toxicity

A CBC with differential will be obtained on Day 1 of each cycle and each day the subject receives nab-paclitaxel. Day 1 carboplatin and nab-paclitaxel may only be given if the platelets count $\geq 100 \times 10^9$/L and ANC $\geq 1.5 \times 10^9$/L. A CBC with differential will also be obtained on Day 8 and Day 15 prior to nab-paclitaxel dosing. Filgrastim support per FDA labeled guidelines may be utilized Cycle 2 or subsequent Cycles if warranted by neutropenic fever or neutrophil count causing delay or dose reduction in chemotherapy.

Hematologic toxicities *requiring* dose modification of carboplatin and nab-paclitaxel are as follows (see also 5.2.1.1). These are considered a DLT if occurring during the first 2 cycles:

- Grade 4 hematologic toxicity:
  - Lasting ≥ 7 days OR
- Febrile neutropenia Grade 3 or Grade 4:
  - Grade 3 is defined as ANC < 1000/mm^3 with a single temperature of > 38.3 degrees C (101° F) or a sustained temperature of ≥ 38 degrees C (100.4° degrees F) for > 1 hour.
  - Grade 4 is defined as ANC < 1000/mm^3 with a single temperature of > 38.3 degrees C (101° F) or a sustained temperature of ≥ 38 degrees C (100.4° F) for more > 1 hour, with life-threatening consequences and urgent intervention indicated
- Grade 3 or Grade 4 thrombocytopenia if associated with:
  - A bleeding event which does not result in hemodynamic instability but requires an elective platelet transfusion, or
  - A life-threatening bleeding event which results in urgent intervention and admission to an Intensive Care Unit

All other hematologic toxicities that do not meet the above specifications are not considered a DLT.

For Day 1 hematologic toxicities occurring for cycles 1-4, the current cycle should be delayed by 1 week. A cycle is defined only when you can give all 3 drugs on Day 1, and it coincides with pembrolizumab. A CBC with differential should be checked at least once a week if carboplatin, nab-paclitaxel, or pembrolizumab is not given on Day 1. Study treatment may be resumed after a 1 week delay if the platelet count is $\geq 100 \times 10^9$/L and ANC is $\geq 1.5 \times 10^9$/L. Continuation at the same dose or at a reduced dose is based on investigator discretion unless the above criteria requiring dose reduction is met. If chemotherapy is delayed more than 1 week, dose reductions should occur. Refer to nab-paclitaxel product label for guidance.

- If platelets remain $< 100 \times 10^9$/L and/or ANC $< 1.5 \times 10^9$/L and chemotherapy cannot resume within 6 weeks of last chemotherapy, all treatments should be discontinued.

Special consideration for weekly nab-paclitaxel dosing on Day 8 and Day 15:

- For hematologic toxicities occurring on Day 8 or 15 of the cycle, treatment can be held or dose reduced based on site investigator discretion. If there is concern regarding ability to dose on Day 8 or Day 15, labs may be obtained locally within 48 hours prior to the dose of nab-paclitaxel for subject convenience. If the subject does not receive dosing on Day 8 or Day 15, due to counts or for other reasons, an AE assessment should be done via telephone call by research staff. If clinical concerns arise regarding AEs, the patient should be seen in a clinic for further AE assessment and treatment as clinically indicated. If the criteria requiring dose reductions for hematologic toxicities listed above are not met, a dose reduction is not required, but is permissible based on site investigator discretion. Refer to nab-paclitaxel product label for guidance. If a dose reduction is indicated, permanently reduce nab-paclitaxel and carboplatin doses as specified in Table 4.

Table 4: Dose Reductions for Hematologic Toxicity

	Carboplatin	Nab-paclitaxel	Pembrolizumab
1st episode*	Dose reduce to AUC 4.5	Dose reduce to 75 mg/m^2	No adjustments
2nd episode	Dose reduce to AUC 3	Dose reduce to 50 mg/m^2	No adjustments
3rd episode	Discontinue	Discontinue	Discontinue
Anemia	No adjustments	No adjustments	No adjustments

*Episodes = febrile neutropenia, severe neutropenia, or platelet nadir $< 25 \times 10^9$/L

5.2.1.4 Dose Modifications for Renal Toxicity

Glomerular filtration rate (GFR) as calculated by the standard Cockcroft and Gault formula must be used to calculate creatinine clearance (CrCl) prior to each dose of carboplatin on Day 1 of each cycle. Only subjects with a CrCl of ≥ 30 mL/min will be treated.

- If CrCl < 30 mL/min, carboplatin, nab-paclitaxel, and pembrolizumab should be held.

- If a Grade 3 or Grade 4 toxicity (Table 5) occurs, carboplatin and pembrolizumab should be held.

Table 5: CTCAE Grading of Renal Toxicity

	Grade 1	Grade 2	Grade 3	Grade 4
Creatinine increased	> 1 - 1.5 x baseline; > ULN - 1.5 x ULN	> 1.5 - 3.0 x baseline; > 1.5 - 3.0 x ULN	> 3.0 x baseline; > 3.0 - 6.0 x ULN	> 6.0 x ULN

Abbreviations: ULN, upper limit of normal

If medications are held, a serum chemistry should be checked and CrCl calculated at least once a week. Carboplatin may be resumed at one dose level lower (See Table 2) once the CrCl returns to ≥ 30 mL/min or returns to Grade 1 toxicity level. Pembrolizumab can be resumed at standard dose.

- If CrCl remains < 30 mL/min or > Grade 1 toxicity for ≥ 3 weeks after last dose of carboplatin or pembrolizumab, all treatments should be discontinued and the subject will come off study.

5.2.1.5 Dose Modifications for Hepatic Toxicity

Hepatic function labs should be assessed on Day 1 of each cycle. Laboratory criteria for dose reductions are detailed in Table 6. If any medications are required to be held, hepatic function labs should be repeated once a week. Treatment can be resumed once liver function tests return to acceptable levels.

- If liver function tests remain elevated (AST > 10 x ULN and Alk Phos > 10 x ULN or Bilirubin > 5 x ULN) for ≥ 3 weeks after last dose of nab-paclitaxel or pembrolizumab, all treatments should be discontinued.

Table 6: Dose Reductions for Hepatic Toxicity

AST/ALT		Alkaline phosphatase		Bilirubin	Nab-paclitaxel	Pembrolizumab
< 10 x ULN	and	< 5 x ULN	and	> ULN-1.25 x ULN	100%	100%
< 10 x ULN	and	< 5 x ULN	or	> 1.25-2 x ULN	Reduce to 75 mg/m^2	100%
< 10 x ULN	and	< 10 x ULN	or	> 2-5 x ULN	Reduce to 50 mg/m^2	Discontinue*
> 10 x ULN	or	> 10 x ULN	or	> 5 x ULN	Discontinue	Discontinue

*See specific recommendations for immune-related hepatic toxicity.

5.2.1.6 Dose Modifications for Sensory Peripheral Neuropathy Toxicity

Sensory peripheral neuropathy assessment will be conducted at screening by history and graded by CTCAE v4. Withhold nab-paclitaxel and carboplatin for Grade 3-4 sensory peripheral neuropathy. Resume nab-paclitaxel and carboplatin at reduced doses (see Table 7 below) when sensory peripheral neuropathy improves to Grade 1 or completely resolves.

Table 7: Dose Reductions for Sensory Peripheral Neuropathy

	Occurrence	Nab-paclitaxel	Carboplatin
Sensory Neuropathy Grades 3-4	First	Dose reduce to 75 mg/m^2	Dose reduce to AUC 4.5
	Second	Dose reduce to 50 mg/m^2	Dose reduce to AUC 3
	Third	Discontinue	Discontinue

5.3 Rescue Medications and Supportive Care

5.3.1 Nausea/vomiting

Nausea and vomiting should be treated aggressively, and consideration should be given in subsequent cycles to the administration of prophylactic antiemetic therapy according to standard institutional practice. Subjects should be strongly encouraged to maintain liberal oral fluid intake.

5.3.1.1 Carboplatin and nab-paclitaxel

Steroids should be avoided as premedication for chemotherapy, especially in subjects receiving pembrolizumab. Suggested anti-emetic prophylaxis for carboplatin and nab-paclitaxel is as follows:

- Palonosetron 0.25 mg IV Day 1 only
    - OR: ondansetron 16-24 mg PO or 8-16 mg IV followed by ondansetron 8 mg PO or IV every 8-12 hours through Day 3
- Aprepitant 125 mg PO Day 1 and 80 mg PO daily for Days 2-3
    - OR: fosaprepitant 150 mg IV Day 1
- As needed:
    - Ondansetron 8 mg PO or IV every 8 hours (starting Day 4 for subjects who receive palonosetron on Day 1)
    - Prochlorperazine 10 mg PO or IV every 6 hours
    - Lorazepam 0.5-2 mg PO or IV every 4-6 hours

5.3.1.1.1 Nab-paclitaxel alone

When receiving nab-paclitaxel alone, NCCN guidelines for low emetic risk intravenous chemotherapy can be followed, which may include:

- Metoclopramide 10-40 mg PO or IV
- Prochlorperazine 10 mg PO or IV
- Ondansetron 8 mg PO or IV
- As needed medications as described above

5.3.1.2 Pembrolizumab alone

No anti-emetic prophylaxis required

5.3.2 Anemia
Transfusions and/or erythropoietin may be utilized as clinically indicated for the treatment of anemia, but should be clearly noted as concurrent medications. Consider a potential immunologic etiology.

5.3.3 Neutropenia
Prophylactic use of colony-stimulating factors including Granulocyte Colony-Stimulating Factor (G-CSF), pegylated G-CSF or Granulocyte Macrophage Colony-Stimulating Factor GM CSF is not allowed in this study. Therapeutic use of G-CSF is allowed in subjects with Grade 3-4 febrile neutropenia. Consider a potential immunologic etiology.

5.3.4 Thrombocytopenia
Transfusion of platelets may be used if clinically indicated. Idiopathic Thrombocytopenic Purpura (ITP) should be ruled out before initiation of platelet transfusion.

5.3.5 Anti-infective
Subjects with a documented infectious complication should receive oral or IV antibiotics or other anti-infective agents as considered appropriate by the site investigator for a given infectious condition, according to standard institutional practice.

5.3.6 Pneumonitis
- For **Grade 2 events**, treat with systemic corticosteroids. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks.
- For **Grade 3-4 events**, immediately treat with intravenous steroids. Administer additional anti-inflammatory measures, as needed.
- Add prophylactic antibiotics for opportunistic infections in the case of prolonged steroid administration.

5.3.7 Diarrhea/Colitis
Subjects should be carefully monitored for signs and symptoms of enterocolitis (such as diarrhea, abdominal pain, blood or mucus in stool, with or without fever) and of bowel perforation (such as peritoneal signs and ileus).
- All subjects who experience diarrhea/colitis should be advised to drink liberal quantities of clear fluids. If sufficient oral fluid intake is not feasible, fluid and electrolytes should be substituted via IV infusion. For Grade 2 or higher diarrhea, consider GI consultation and endoscopy to confirm or rule out colitis.
- For **Grade 2 diarrhea/colitis** that persists greater than 3 days, administer oral corticosteroids.
- For **Grade 3 or 4 diarrhea/colitis** that persists > 1 week, treat with intravenous steroids followed by high dose oral steroids.
- When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks.

5.3.8 Type 1 diabetes mellitus (if new onset, including diabetic ketoacidosis [DKA]) or ≥ Grade 3 Hyperglycemia, if associated with ketosis (ketonuria) or metabolic acidosis (DKA)

- For **T1DM** or **Grade 3-4** Hyperglycemia
  - Insulin replacement therapy is recommended for Type I diabetes mellitus and for Grade 3-4 hyperglycemia associated with metabolic acidosis or ketonuria.
  - Evaluate subjects with serum glucose and a metabolic panel, urine ketones, glycosylated hemoglobin, and C-peptide.

5.3.9 Hypophysitis

- For **Grade 2** events, treat with corticosteroids. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks. Replacement of appropriate hormones may be required as the steroid dose is tapered. For **Grade 3-4** events, treat with an initial dose of IV corticosteroids followed by oral corticosteroids. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks. Replacement of appropriate hormones may be required as the steroid dose is tapered.

5.3.10 Hyperthyroidism or Hypothyroidism

Thyroid disorders can occur at any time during treatment. Monitor subjects for changes in thyroid function (at the start of treatment, periodically during treatment, and as indicated based on clinical evaluation) and for clinical signs and symptoms of thyroid disorders.

- **Grade 2** hyperthyroidism events (and **Grade 2-4** hypothyroidism):
  - In hyperthyroidism, non-selective beta-blockers (e.g. propranolol) are suggested as initial therapy.
  - In hypothyroidism, thyroid hormone replacement therapy, with levothyroxine or liothyroinine, is indicated per standard of care.
- **Grade 3-4** hyperthyroidism
  - Treat with an initial dose of IV corticosteroid followed by oral corticosteroids. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks. Replacement of appropriate hormones may be required as the steroid dose is tapered.

5.3.11 Hepatic

- For **Grade 2** events, monitor liver function tests more frequently until returned to baseline values (consider weekly).
  - Treat with IV or oral corticosteroids
- For **Grade 3-4** events, treat with intravenous corticosteroids for 24 to 48 hours.
- When symptoms improve to Grade 1 or less, a steroid taper should be started and continued over no less than 4 weeks.

5.3.12 Renal Failure or Nephritis

- For **Grade 2** events, treat with corticosteroids.
- For **Grade 3-4** events, treat with systemic corticosteroids.
- When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks.

5.3.13 Management of Infusion Reactions

Signs and symptoms usually develop during or shortly after drug infusion and generally resolve completely within 24 hours of completion of infusion. Table 9 below shows treatment guidelines for subjects who experience an infusion reaction associated with administration of pembrolizumab (MK-3475).

Table 9 Infusion Reaction Treatment Guidelines

NCI CTCAE Grade	Treatment	Premedication at subsequent dosing
Grade 1 Mild reaction; infusion interruption not indicated; intervention not indicated	Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator.	None
Grade 2 Requires infusion interruption but responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDS, narcotics, IV fluids); prophylactic medications indicated for < =24 hrs	**Stop Infusion.** Additional appropriate medical therapy may include but is not limited to: IV fluids Antihistamines NSAIDS Acetaminophen Narcotics Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator. If symptoms resolve within one hour of stopping drug infusion, the infusion may be restarted at 50% of the original infusion rate (e.g. from 100 mL/hr to 50 mL/hr). Otherwise dosing will be held until symptoms resolve and the subject should be premedicated for the next scheduled dose. **Subjects who develop Grade 2 toxicity despite adequate premedication should be permanently discontinued from further trial treatment administration.**	Subject may be premedicated 1.5h (± 30 minutes) prior to infusion of pembrolizumab with: Diphenhydramine 50 mg p.o. (or equivalent dose of antihistamine). Acetaminophen 500-1000 mg p.o. (or equivalent dose of antipyretic).
Grades 3 or 4 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 ventilatory support indicated	**Stop Infusion.** Additional appropriate medical therapy may include but is not limited to: IV fluids Antihistamines NSAIDS Acetaminophen Narcotics Oxygen Pressors Corticosteroids Epinephrine Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator. Hospitalization may be indicated. **Subject is permanently discontinued from further trial treatment administration.**	No subsequent dosing

NCI CTCAE Grade	Treatment	Premedication at subsequent dosing
Appropriate resuscitation equipment should be available in the room and a physician readily available during the period of drug administration. For Further information, please refer to the Common Terminology Criteria for Adverse Events v4.0 (CTCAE) at http://ctep.cancer.gov		

5.3.14 Other toxicities

For all Grade 3 or Grade 4 clinically significant toxicities, all drugs should be held. Medications should be delayed until resolution to ≤ Grade 1 or baseline grade at the time of registration, before proceeding. Use of supportive therapies is encouraged (i.e., anti-emetics for nausea/vomiting, anti-diarrheal medications for diarrhea). Upon resolution, carboplatin or nab-paclitaxel should be resumed at 1 dose level lower (Table 2) if toxicity is felt to be related to either of these medications. If toxicity is felt to be related to pembrolizumab, it should be restarted at the same dose level.

5.4 Duration of Therapy

Therapy with pembrolizumab will continue until disease progression by RECIST v1.1 criteria, unacceptable toxicity, or for a maximum of 2 years. Subjects who complete 24 months of treatment with pembrolizumab may be eligible for up to one year of additional study treatment if they progress after stopping study treatment provided they meet the requirements detailed in Section 3.1 Inclusion Criteria.

5.4.1 Reasons for withdrawal from treatment

- Any clinically significant Grade 3 or 4 non-hematologic toxicity that persists for ≥ 3 weeks
- 3rd episode of hematologic toxicity after appropriate dose reductions. Hematologic toxicity defined as:
    - Febrile neutropenia (Grade 3)
        - neutrophil count < 1.0 x 109/L and
        - a single oral temperature of > 38.3°C (101°F) or a temperature of ≥ 38.0°C (100.4°F) sustained for > 1 hour
    - Severe neutropenia
        - Neutrophil count < 0.50 x 10^9/L ≥ 1 week
- Creatinine clearance < 30 ml/min for ≥ 3 weeks
- AST/ALT and Alk Phos > 10 x ULN for ≥ 3 weeks
- Bilirubin > 5 x ULN for ≥ 3 weeks
- Grade ≥ 3 pneumonitis or second episode of Grade ≥ 2 pneumonitis
- Pneumonitis that persists for ≥ 12 weeks
- Grade 3 or Grade 4 AE that requires 10 mg of prednisone equivalent or > 12 weeks from time of onset
- In case a grade 3 or grade 4 toxicity does not resolve to Grade 0-1 within 12 weeks after last infusion, study therapy should be discontinued after consultation with the sponsor-investigator. In cases of laboratory grade 2 toxicity only, subjects may be permitted to continue on study with sponsor-investigator approval.
- Palliative RT involving target lesions is required. Of note, palliative RT to non-target lesions in the absence of progression by RECIST v1.1 criteria is permitted.

- Subject withdraws consent
- Subject becomes pregnant or is unwilling to use appropriate birth control techniques as outlined in inclusion criteria (Section 3.1 Inclusion Criteria)
- Serious illness that prevents safe continuation of therapy, for example mechanical ventilation, septic shock requiring treatment in the intensive care unit, or ECOG performance status 4 for > 2 weeks.
- Two years of uninterrupted delivery of pembrolizumab every 3 weeks and no documented progression of disease. **NOTE:** 24 months of study medication is calculated from the date of first dose. Subjects who stop pembrolizumab after 24 months may be eligible for up to one year of additional study treatment if they progress after stopping study treatment provided they meet the requirements detailed in Section 3.1 Inclusion Criteria.

6 RESPONSE ASSESSMENT

6.1 Timing of Response Assessment

A baseline CT scan of the chest and upper abdomen (must include liver and adrenals) with IV contrast and an MRI brain are required prior to enrollment on study. Response by CT of measurable disease will be assessed after every 2 chemotherapy cycles. If there are treatment delays, the scans will be adjusted to coincide with completion of 2 cycles of chemotherapy each time for all subjects on study. Subjects may have other imaging performed at other intervals for other reasons, such as the evaluation of new symptoms, and the results of these tests should be documented and may be used to determine progression of disease (see Section 6.2.4 Response Criteria).

After documented progression by RECIST v1.1 criteria, if subjects are clinically stable, treatment with pembrolizumab may continue for another 2 cycles for a repeat response assessment at 6 weeks later to evaluate response as delayed response has been previously described in Section 5.2.1.2.

6.2 Methods of Response Assessment

Response and progression will be evaluated in this study using the new international criteria proposed by the revised 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 v1.1 criteria.

6.2.1 Definitions

Evaluable for toxicity

All subjects will be evaluable for toxicity from the time of their first treatment on Cycle 1 Day 1.

Evaluable for objective response

Only those subjects 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 response. These subjects will have their response classified according to the definitions stated

below. (Note: Subjects who exhibit objective disease progression prior to the end of cycle 1 will also be considered evaluable.)

Evaluable Non-Target Disease Response
Subjects who have lesions present at baseline that are evaluable but do not meet the definitions of measurable disease, have received at least one cycle of therapy, and have had their disease re-evaluated will be considered evaluable for non-target disease. The response assessment is based on the presence, absence, or unequivocal progression of the lesions.

6.2.2 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, MRI, or calipers by clinical exam. All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters).

NOTE: Tumor lesions that are situated in a previously irradiated area might be considered measurable if disease progression has been previously documented.

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, and abdominal masses (not followed by CT or MRI), are considered as 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 subject, these are preferred for selection as target lesions.

Target lesions
All measurable lesions up to a maximum of 2 lesions per organ and up to 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 that 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.

6.2.3 Response Criteria

6.2.3.1 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 progression).

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

6.2.3.2 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 subject 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 sponsor-investigator).

6.2.3.3 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 subject's best response assignment will depend on the achievement of both measurement and confirmation criteria.

Table 10: RECIST v1.1 Criteria for Evaluation of Subjects with Measurable 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 v1.1 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: Subjects 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.

6.2.4 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).

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.

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.

6.2.5 Progression-Free Survival
PFS is defined as the duration of time from date of registration to time of progression or death, whichever occurs first.

6.2.6 Overall Survival
Overall survival is defined as the duration of time from date of registration to the time of death.

7. STUDY PARAMETERS

		Induction Phase							Maintenance Phase	
Examination	Screening -28 days	C1D1	C1-C4 Day8 ±1 day	C1-C4 Day 15 ±1 day	C2D1 ±1 day	C3D1 ±1 day	C4D1 ±1 day	C5+D1 (odd # cycles)	C6+D1 (even # cycles)	EOT[14] 30 days (±7) from last dose
REQUIRED ASSESSMENTS										
Informed consent and eligibility confirmation	X									
Pathology Review[1]	X									
Tumor Biopsy[2]	X							X		
Medical History including smoking history	X									
Physical exam, Vitals, ECOG PS[3]	X	X	X[16]	X[16]	X	X	X	X	X	X
Review Adverse Events, ECIs and con meds		X	X[16]	X[16]	X	X	X	X	X	X
Sensory neuropathy test	X									
LABORATORY ASSESSMENTS										
CBC with differential[4]	X[11]	X	X[16]	X[16]	X	X	X	X	X	X
Chemistry panel (and liver function)[5]	X[11]	X	BMP[16]	BMP[16]	X	X	X	X	X	X
Thyroid Function[6]	X[11]				X		X		X	X
Pregnancy test[7]	X									
PT/INR, PTT	X[11]							X		
DISEASE ASSESSMENT										
CT Chest	X[12]					X[13]		X[13]	X[13]	
CT Abd	X[12]					X[13]		X[13]	X[13]	
MRI Brain	X[12]					X[13]		X[13]	X[13]	
Other Imaging[8]	X					X[13]		X[13]	X[13]	
TREATMENT EXPOSURE										
Carboplatin[9]		X			X	X	X			
Nab-paclitaxel[9]		X	X[16]	X[16]	X	X	X			
Pembrolizumab		X[10]			X	X	X	X[10]	X[10]	
FOLLOW UP										
Follow-up[15]										X[15]

Footnotes:

1: A pathology report confirming diagnosis of advanced stage NSCLC is required. For subjects with early stage disease that later developed metastatic disease, a biopsy confirmation of the metastatic disease is required.

2: Adequate archival tissue or available PD-L1 testing results using the Dako 22C3 antibody are required for enrollment. If the patient has not had prior testing and no acceptable archival tissue is available, subjects must be willing to consent to providing a pre-treatment biopsy for PD-L1 testing. This biopsy is to be obtained within 28 days prior to registration. Phase II subjects are required to provide a post-treatment tumor biopsy after completion of 4 cycles of study treatment or at progression. The progression biopsy should be performed once confirmed by second scan unless unequivocal progression that requires the subject come off study treatment prior to confirmation scan. In the event that a subject has had a complete response or there is no disease feasible to biopsy, no biopsy will be obtained at that time. In this case, the subject will have the option to undergo a biopsy at progression. Window for tumor biopsies ±10 days to allow for scheduling conflicts (weekends/holidays). Acceptable biopsies will be obtained via transcutaneous core needle biopsies or surgical biopsies. At least 3 cores of tissue will be required. FNAs are NOT acceptable. See CLM (Correlative Laboratory Manual) for details regarding collection and shipping of sample.

3: Subjects are assessed for physical examination (includes height and weight), vital signs and ECOG PS.

4: CBC with differential is checked at screening and prior to chemotherapy on Day 1 of each cycle. Repeat CBC on Days 8 & 15 of C1-C4. CBC is required prior to post-treatment biopsy for Phase II subjects.

5: Comprehensive chemistry (including liver function) checked at screening and prior to chemo on Day 1 of each cycle. Repeat basic chemistry (include electrolytes & creatinine) on Days 8 & 15 of C1-C4.

6: Thyroid function assessment includes TSH, T3, and free T4. This test will be done at screening, Cycle 2, and every other cycle thereafter).

7: Women of childbearing potential must have a negative serum or urine β-hCG pregnancy test obtained within 3 days of registration.

8: Not required; other imaging may be done at physician discretion prior to registration to identify other areas of known or expected disease based on subject symptoms.

9: Induction Cycles 1-4: Subjects will be treated with carboplatin AUC 6 given IV on Day 1, nab-paclitaxel 100 mg/m2 given IV on Days 1, 8 and 15.

10: Induction: Phase I Cohort 1 will begin Pembrolizumab on C1D1. Phase II treatment; Induction: pembrolizumab will be administered Day 1 of each cycle. Maintenance: pembrolizumab will be given on Day 1 of Cycles 5+ for a maximum duration of 2 years from Cycle 1 Day 1. Cycle 5 will begin once all 4 cycles of chemotherapy are complete.

11: Tests must be obtained within 10 days of registration.

12: Tests must be obtained within 4 weeks of registration. A CT scan with IV contrast of the chest and upper abdomen to include liver and adrenals is required. A CT abdomen may be completed as a separate study or as part of the CT chest study as long as the liver and bilateral adrenal glands are included per institutional standards. Oral contrast is not necessary. CT Pelvis should be obtained if clinically indicated or if there is known disease in the pelvis.

13: Initial post treatment scans will be done after completion of 2 cycles of chemotherapy. The next set of scans will be performed after completion of 4 cycles of chemotherapy (need to be complete prior to Cycle 5 Day 1). Thereafter, scans will be every 6 weeks beginning with Cycle 7. The method of radiology imaging should remain the same throughout the treatment process. If new symptoms have developed, additional radiology imaging should be performed as clinically indicated per the investigator's discretion. MRI of the brain is to be done at screening per Footnote 12 for all patients. For those subjects with documented brain involvement, an MRI of the brain should be performed at a minimum of every 3 months. Brain imaging may be repeated when clinically indicated if there is a concern for brain metastasis. A ± 7-day window may be applied to all scans.

14: End of treatment visit to include; physical exam, vital signs, ECOG PS, AEs and concomitant medications, CBC, CMP, TSH. Imaging if clinically indicated.

15: Subjects who discontinue treatment without evidence of progression will have repeat imaging every 6 weeks the first year off treatment (± 7 days), every 9 weeks the second year after treatment (± 14 days). After the second year of treatment, radiology imaging should be completed at regular intervals (every 3-6 months suggested; ± 12 weeks) at the investigator's discretion. Subjects will be followed for survival once progression is confirmed or another anti-cancer treatment is initiated. The subject will be followed for survival once progression is confirmed or another anti-cancer treatment is initiated. Follow up for survival will occur every three months and may be accomplished via email, phone or other means as appropriate.

16: Circumstances may occur based on laboratory/clinical trends where the ability to dose nab-paclitaxel on Day 8 or Day 15 is in question. In these circumstances, labs may be obtained locally within 48 hours prior to the dose of nab-paclitaxel to lessen the burden on the subject. If the subject does not receive dosing on Day 8 or Day 15, due to counts or for other reasons, an AE assessment should be done via telephone call by research staff. If treatment is not administered, physical exam, vital signs and ECOG status are not required. If clinical concerns arise regarding AEs, the patient should be seen in a clinic for further AE assessment and treatment as clinically indicated.

7.1 Screening Assessments

A signed informed consent will be obtained before any screening procedures are performed. Subjects who are considered for eligibility but do not meet all criteria will be considered screening failures. Reasons for screen failures will be documented for those subjects who do not meet inclusion/exclusion criteria. Clinical data collected on these subjects will be entered into the database.

7.1.1 Within 28 days of registration

- Collect signed and dated informed consent statement (ICS).
- Pathologic confirmation of NSCLC diagnosis (see Section 14.1 Pathology Requirements for Enrollment)
- Document relevant medical history including history of their lung cancer and prior treatments, other past medical and surgical histories, current medications, allergies, social history including smoking history, and family history.
- Physical exam (includes height and weight), vital signs (oral temperature, blood pressure, heart rate, respiratory rate and pulse oximetry) and ECOG PS (Appendix 16.2)
- Sensory neuropathy assessment by history and graded by CTCAE v4.
- Collect unstained slides from an archived tumor tissue. Note: if adequate tissue is unavailable, a pre-treatment biopsy for research purposes is required.
- Baseline scans including; CT scan with IV contrast of the chest and upper abdomen to include liver and adrenals is required unless medically contraindicated and MRI of the brain. Note: Additional other imaging may be used at the discretion of the treating physician to assess other areas based on previously known disease or suspicion of new areas of involvement due to the subject's complaints. These baseline tests will be used to determine the location(s) of baseline disease that may be used for responses assessment (see Section 6.0 Response Assessment).

7.1.2 Within 28 days of registration

- Adequate archival tissue or available PD-L1 testing results using the Dako 22C3 antibody are required for enrollment. If the patient has not had prior testing and no acceptable archival tissue is available, subjects must be willing to consent to providing a pre-treatment biopsy for PD-L1 testing. This biopsy is to be obtained within 28 days prior to registration. Acceptable biopsies will be obtained via transcutaneous core needle biopsies or surgical biopsies. At least 3 cores of tissue will be required. FNAs are NOT acceptable. See CLM (Correlative Laboratory Manual) for details regarding collection and shipping of sample. Window for tumor biopsies ±10 days to allow for scheduling conflicts (weekends/holidays).

7.1.3 Within 10 days of registration

- CBC with differential
- Comprehensive chemistry panel
- Liver function tests (AST, ALT, Alkaline phosphatase, bilirubin)
- Thyroid function test including; TSH, T3 and free T4
- PT/INR, PTT (± 5 days)

7.1.4 Within 3 days of registration

- Collect serum or urine β-hCG pregnancy test (within 3 days of registration) for pre-menopausal women (i.e., last menstrual period ≤ 12 months ago) and women < 1 years after onset of menopause. Menopause is defined as the time at which fertility ceases, where a woman has had no menstruation for > 12 months.

7.2 On Treatment Assessments

The following assessments will be completed prior to chemotherapy treatment. Lab values will be recorded and checked for toxicity that would necessitate a dose reduction (most notably white blood count and differential to calculate absolute neutrophil count (ANC), platelet count, creatinine, AST, ALT, Alk Phos, and bilirubin). Grading of all toxicities will be according to CTCAE v4. Dosing of carboplatin, nab-paclitaxel, and pembrolizumab will be based on height and weight on the day of treatment (see Section 5.1.2.4 Dose Calculations).

7.2.1 Day 1 of each cycle (± 1 day) unless otherwise specified

- Physical exam (includes weight), vital signs (oral temperature, blood pressure, heart rate, respiratory rate and pulse oximetry) and ECOG PS (Appendix 16.2)
- AE assessment including ECIs and concomitant medications
- CBC with differential and platelet count
- Comprehensive chemistry panel
- Liver function tests (AST, ALT, Alkaline phosphatase, bilirubin)
- Thyroid function test including; TSH, T3 and free T4 (Cycle 2 and every other cycle thereafter)
- A CT scan with IV contrast of the chest and upper abdomen to include liver and adrenals is required unless medically contraindicated (Cycle 3 and odd number cycles thereafter). Repeat all other imaging studies at these same intervals if disease was identified at baseline. Additional imaging studies may be obtained at these intervals or at any time if clinically indicated and at site investigator discretion. Results from all imaging, whether at the scheduled interval or otherwise, should be recorded and used for response assessments (see Section 6.0 Response Assessment). Window of ± 7 days.
  Phase II subjects are required to provide a post-treatment tumor biopsy after completion of 4 cycles of study treatment (or at progression, whichever comes first). In the event that a subject has had a complete response and there is no evidence of disease feasible to biopsy, no post-treatment biopsy will be obtained. Window for tumor biopsies ±10 days to allow for scheduling conflicts (weekends/holidays). Acceptable biopsies will be obtained via transcutaneous core needle biopsies or surgical biopsies. At least 3 cores of tissue will be required. FNAs are NOT acceptable. See CLM (Correlative Laboratory Manual) for details regarding collection and shipping of sample.

7.2.2 Days 8 & 15 Cycles 1-4 (±1 day)

- Physical exam (includes weight), vital signs (oral temperature, blood pressure, heart rate, respiratory rate and pulse oximetry) and ECOG PS (Appendix 16.2)
- AE assessment including ECIs and concomitant medications
- CBC with differential and platelet count
- Basic chemistry panel including electrolytes and creatinine

- Circumstances may occur based on laboratory/clinical trends where the ability to dose Nab-paclitaxel on Day 8 or Day 15 is in question. In these circumstances, labs may be obtained locally within 48 hours prior to the dose of nab-paclitaxel to lessen the burden on the subject. If the subject does not receive dosing on Day 8 or Day 15, due to counts or for other reasons, an AE assessment should be done via telephone call by research staff. If treatment is not administered, physical exam, vital signs and ECOG status are not required. If clinical concerns arise regarding AEs, the subject should be seen in a clinic for further AE assessment and treatment as clinically indicated.

7.3 Off Treatment Assessments

7.3.1 End of treatment (30 days from last dose of study treatment ± 7 days)

- Physical exam (includes weight), vital signs (oral temperature, blood pressure, heart rate, respiratory rate and pulse oximetry) and ECOG PS (Appendix 16.2)
- AE assessment including ECIs and concomitant medications
- CBC with differential and platelet count
- Basic chemistry panel including electrolytes and creatinine
- TSH
- Repeat imaging if clinically indicated and at the discretion of the site investigator

7.3.2 Follow-up

- Subjects who discontinue treatment without evidence of progression will have repeat imaging every 6 weeks the first year off treatment, then every 3 months thereafter.
- The subject will be followed for survival once progression is confirmed or another anti-cancer treatment is initiated. Follow up for survival will occur every three months and may be accomplished via email, phone or other means as appropriate.

7.4 Tumor Biopsy parameters

Adequate archival tissue or available PD-L1 testing results using the Dako 22C3 antibody are required for enrollment. If the patient has not had prior testing and no acceptable archival tissue is available, subjects must be willing to consent to providing a pre-treatment biopsy for PD-L1 testing. This biopsy is to be obtained within 28 days prior to registration. Phase II subjects are required to provide a post-treatment tumor biopsy after completion of 4 cycles of study treatment or at progression. The progression biopsy should be performed once confirmed by second scan unless unequivocal progression that requires the subject come off study treatment prior to confirmation scan. In the event that a subject has had a complete response or there is no disease feasible to biopsy, no biopsy will be obtained at that time. In this case, the subject will have the option to undergo a biopsy at progression. Window for tumor biopsies ±10 days to allow for scheduling conflicts (weekends/holidays). Acceptable biopsies will be obtained via transcutaneous core needle biopsies or surgical biopsies. At least 3 cores of tissue will be required. FNAs are NOT acceptable. See CLM (Correlative Laboratory Manual) for details regarding collection and shipping of sample.

7.4.1 Pre-treatment biopsy (- 28 days)

The pre-treatment biopsy is required only if adequate tissue is not available prior to registration (at least 5 unstained slides). Prior to the biopsy, baseline complete blood count (CBC) and PT/PTT will be reviewed to confirm the safety of this invasive procedure. The treating physician, in consultation with an interventional radiologist and/or surgeon, will determine the most accessible tumor for biopsy. The best candidate lesions for biopsy are those that are measurable and identified as target lesions (see Section 6.2.2 Disease Parameters) whenever possible. Lymph nodes measuring less than 2 cm diameter and bone lesions should not be selected as candidate lesions for biopsy. The location that is selected for biopsy will be documented. Acceptable biopsies will be obtained via transcutaneous core needle biopsies, surgical biopsies. At least 3 cores of tissue will be required. If a tumor biopsy was obtained of a target lesion during eligibility assessment, it is preferred to obtain a new baseline scan. The tissue sample should have proper size to enable multiple planned biomarker analyses, but not artificially decrease the longest diameter of the lesion. Biopsy of lesions on study should be limited to non-target lesions or new lesions if their pathologic etiology is ambiguous.

7.4.2 Post-treatment biopsy ± 10 days (Phase II only)

Phase II subjects are required to provide a post-treatment tumor biopsy after completion of 4 cycles of study treatment or at progression. The progression biopsy should be performed once confirmed by second scan unless unequivocal progression that requires the subject come off study treatment prior to confirmation scan. Window for tumor biopsies ±10 days to allow for scheduling conflicts (weekends/holidays). Acceptable biopsies will be obtained via transcutaneous core needle biopsies or surgical biopsies. At least 3 cores of tissue will be required. FNAs are NOT acceptable. A CBC and PT/PTT is required before the biopsy to confirm the safety of this invasive procedure. The same procedure and requirements for biopsy will be used. Whenever possible, the same lesion that was biopsied pre-treatment should be biopsied post-treatment. Target lesions should not be biopsied as that would compromise the ability to monitor and measure them effectively. Only non-target lesions should be biopsied. If the subject has had a complete response in that particular lesion, another similar lesion should be biopsied, preferably one that has had a partial response.

In the event that a subject has had a complete response or disease is not feasible to biopsy per site investigator discretion, no post-treatment biopsy will be obtained at that time. In this case, the subject will have the option to undergo a biopsy at progression. Acceptable biopsies will be obtained via transcutaneous core needle biopsies or surgical biopsies. At least 3 cores of tissue will be required. Fine-needle aspirate biopsies are NOT acceptable. See CLM for collection, labeling and shipping instructions.

7.4.3 Tumor biopsy analysis

Pre-treatment and post-treatment biopsies will be processed by the local study site pathology department and paraffin embedded. PD-L1 expression in pre-treatment and post-treatment tumor biopsies will be analyzed at a central lab using a Merck-specified assay. See CLM for collection, labeling and shipping instructions.

7.5 Laboratory Tests parameters

7.5.1 Labs prior to tumor biopsies

Subjects undergoing tumor biopsies are required to have a CBC and PT/INR, and PTT prior to tumor biopsies. Subjects with platelets $< 50 \times 10^9$ or an INR > 1.5 will not be permitted to undergo biopsies. Platelets and/or fresh frozen plasma (FFP) should be transfused to correct the underlying abnormality at the treating physician's discretion in order to decrease the risk of bleeding complications during the tumor biopsy.

7.6 Imaging Tests parameters (window of ± 7 days)

7.6.1 Baseline imaging

All subjects will have baseline imaging including, but not limited to, a CT of the Chest and upper abdomen to include liver and bilateral adrenal glands with IV contrast, and an MRI of the brain. Additional imaging tests may be used at the discretion of the treating physician to image other areas based on previously known disease or suspicion of new areas of involvement due to subject complaints. These baseline tests will be used to determine the location(s) of baseline disease that may be used for response assessment (see Section 6.0 Response Assessment).

7.6.2 Response assessment imaging

A CT of the Chest/upper abdomen to include liver and bilateral adrenal glands with IV contrast is repeated on Day 1 (±3 days) of Cycle 3 and the odd numbered cycles thereafter. Any other baseline imaging studies that identified areas of disease should also be repeated at these same time intervals for the entire duration the subject remains on study. Additional studies may be obtained at these intervals or at any time if new areas of disease are suspected at the site investigator's discretion. Results from all imaging, whether at the scheduled time interval or otherwise, should be recorded and used for response assessments using RECIST v1.1 criteria (see Section 6.0 Response Assessment).

7.6.3 Post-progression imaging

This study will use RECIST 1.1 to capture all outcomes. However, the study will allow patients to receive treatment beyond progression at the discretion of the site investigator given the unique tumor response seen in this class of therapeutics.

After the first documentation of progression per RECIST 1.1, if the subject is clinically stable, confirmatory scans should be performed 6 weeks later. It is at the discretion of the site investigator to keep a clinically stable subject on study therapy or to stop study therapy until repeat imaging performed.

Clinical Stability is defined as:

1) Absence of symptoms and signs indicating clinical significant progression of disease (including worsening of laboratory values) indicating disease progression.
2) No decline in ECOG performance status (Appendix 16.2).
3) Absence of rapid progression of disease or progressive tumor at critical anatomical sites (e.g., cord compression) requiring urgent alternative medical intervention.

Subjects that are deemed clinically unstable are not required to have repeat imaging for confirmation.

If progression is confirmed, then the subject will be discontinued from study therapy. If progression is not confirmed, then the subject should resume/continue study therapy and continue scans every 6 weeks. The previous response assessments based on RECIST 1.1 for these patients will not be re-categorized for purposes of the study endpoints. For patients that continue on study drug treatment, all aspects of the protocol will continue to be followed.

When feasible, subjects should not be discontinued until progression is confirmed.

7.6.4 Confirmation of response for CR and PR

After the first documentation of CR or PR per RECIST 1.1, confirmatory scans will be obtained at the next regularly scheduled assessment on the odd number cycles (6 weeks). Repeat assessment for progression will continue every 6 weeks thereafter.

8. DRUG FORMULATION AND PROCUREMENT

8.1 Carboplatin

Please see product package insert for complete details regarding Carboplatin.

8.1.1 Availability

Carboplatin is commercially available

8.1.2 Chemical Name

Carboplatin (carboplatin for injection or platinum diamine [1,1-cyclobutane- decarbozxylate (2—0,0')-,(SP-4-2)]) is a platinum compound used as a chemotherapeutic agent. It will be supplied commercially.

8.1.3 Formulation

Carboplatin is available as a sterile lyophilized powder in single-dose vials containing 50 mg, 150 mg, or 450 mg of carboplatin. Each vial contains equal parts by weight of carboplatin and mannitol. Commercial supplies of carboplatin will be used in this study.

8.1.4 Preparation

Immediately before use, the contents of a carboplatin vial must be reconstituted with either sterile water for injection, USP, 5% dextrose in water, or 0.9% sodium chloride injection, USP. The following shows the proper diluent volumes to be used to obtain a carboplatin concentration of 10 mg/mL. Carboplatin solution can be further diluted to concentrations as low as 0.5 mg/mL with D5W or 0.9% normal saline. Carboplatin reacts with aluminum to form a precipitate and cause a loss of potency. Therefore, needles or intravenous sets containing aluminum parts that may come in contact with the drug must not be used for the preparation or administration of carboplatin.

8.1.5 Storage and Stability

Intact vials of carboplatin are stable for the period indicated on the package when stored at room temperature (15-30°C or 59-86°F) and protected from light. When prepared as described above, carboplatin solutions are stable for 8 hours at room temperature if protected from light. The solution should be discarded after 8 hours since no antibacterial preservative is contained in the formulation.

8.1.6 Adverse Events Associated with Carboplatin

Incidence rates of adverse events associated with carboplatin are provided in the product package insert. Some of the adverse events expected with Carboplatin treatment are listed below.

Hematologic: Myelosuppression is the major dose-limiting toxicity. Thrombocytopenia, neutropenia, leukopenia, and anemia are common, but typically resolve by Day 28 when carboplatin is given as a single agent.

Allergic Reactions: Hypersensitivity to carboplatin has been reported in 2% of subjects receiving the drug. Symptoms include rash, urticaria, erythema, pruritus, and rarely bronchospasm and hypotension. The reactions can be successfully managed with standard epinephrine, corticosteroid, and antihistamine therapy.

Neurologic: Peripheral neuropathies have been observed in 4% of subjects receiving carboplatin with mild paresthesia being the most common.

Gastrointestinal: Nausea and vomiting are the most common GI events; both usually resolve within 24 hours and respond to antiemetics. Other GI events include diarrhea, weight loss, constipation, and gastrointestinal pain.

Hepatic Toxicity: Elevated alkaline phosphatase, total bilirubin, and SGOT have been observed.

Other: Pain and asthenia are the most common miscellaneous adverse events. Alopecia has been reported in 3% of the subjects taking carboplatin.

8.2 nab-Paclitaxel

Please see product package insert for complete details regarding nab-Paclitaxel.

8.2.1 Availability

Nab-paclitaxel is commercially available.

8.2.2 Chemical Name

The chemical name for paclitaxel is 5β,20-Epoxy-1,2α,4,7β,10β,13α-hexahydroxytax-11-en-9-one 4,10-diacetate 2-benzoate 13-ester with (2*R*,3*S*)-*N*-benzoyl-3-phenylisoserine.

8.2.3 Formulation

Nab-paclitaxel is supplied as a white to yellow, sterile, lyophilized powder for reconstitution with 20 mL of 0.9% Sodium Chloride Injection, USP prior to intravenous infusion. Each single-use vial contains 100 mg of paclitaxel (bound to human albumin) and approximately 900 mg of

human albumin (containing sodium caprylate and sodium acetyltryptophanate). Each milliliter (mL) of reconstituted suspension contains 5 mg paclitaxel. nab-paclitaxel is free of solvents.

8.2.4 Preparation and Administration Precautions

Nab-paclitaxel is a cytotoxic drug and, as with other potentially toxic paclitaxel compounds, caution should be exercised in handling nab-paclitaxel. The use of gloves is recommended. If nab-paclitaxel (lyophilized cake or reconstituted suspension) contacts the skin, wash the skin immediately and thoroughly with soap and water. Following topical exposure to paclitaxel, events may include tingling, burning and redness. If nab-paclitaxel contacts mucous membranes, the membranes should be flushed thoroughly with water.

Given the possibility of extravasation, it is advisable to closely monitor the infusion site for possible infiltration during drug administration. Limiting the infusion of nab-paclitaxel to 30 minutes, as directed, reduces the likelihood of infusion-related reactions.

Premedication to prevent hypersensitivity reactions is generally not needed prior to the administration of nab-paclitaxel. Premedication may be needed in subjects who have had prior hypersensitivity reactions to nab-paclitaxel. Subjects who experience a severe hypersensitivity reaction to nab-paclitaxel should not be re-challenged with this drug.

8.2.5 Preparation for Intravenous Administration

Nab-paclitaxel is supplied as a sterile lyophilized powder for reconstitution before use. **Avoid errors, read entire preparation instructions prior to reconstitution.**

1. Aseptically, reconstitute each vial by injecting 20 mL of 0.9% Sodium Chloride Injection, USP.
2. Slowly inject the 20 mL of 0.9% Sodium Chloride Injection, USP, over a minimum of 1 minute, using the sterile syringe to direct the solution flow onto the INSIDE WALL OF THE VIAL.
3. DO NOT INJECT the 0.9% Sodium Chloride Injection, USP, directly onto the lyophilized cake as this will result in foaming.
4. Once the injection is complete, allow the vial to sit for a minimum of 5 minutes to ensure proper wetting of the lyophilized cake/powder.
5. Gently swirl and/or invert the vial slowly for at least 2 minutes until complete dissolution of any cake/powder occurs. Avoid generation of foam.
6. If foaming or clumping occurs, stand solution for at least 15 minutes until foam subsides.

8.2.6 How Supplied

Product No.: 103450
NDC No.: 68817-134-50 100 mg of paclitaxel in a single-use vial, individually packaged in a carton.

8.2.7 Storage

Store the vials in original cartons at 20ºC to 25ºC (68º F to 77ºF). Retain in the original package to protect from bright light.

8.2.8 Handling and Disposal

Procedures for proper handling and disposal of anticancer drugs should be considered. Several guidelines on this subject have been published. There is no general agreement that all of the procedures recommended in the guidelines are necessary or appropriate.

8.2.9 Adverse Events Associated with nab-Paclitaxel

Please see product package insert for complete details regarding adverse events associated with nab-Paclitaxel.

Hematologic Disorders

Neutropenia was dose dependent and reversible. Among subjects with metastatic breast cancer in the randomized trial, neutrophil counts declined below 500 cells/mm3 (Grade 4) in 9% of the subjects treated with a dose of 260 mg/m2 compared to 22% in subjects receiving paclitaxel injection at a dose of 175 mg/m2. Pancytopenia has been observed in clinical trials.

Infections

Infectious episodes were reported in 24% of the subjects treated with nab-paclitaxel. Oral candidiasis, respiratory tract infections and pneumonia were the most frequently reported infectious complications**.**

Hypersensitivity Reactions (HSRs)

Grade 1 or 2 HSRs occurred on the day of nab-paclitaxel administration and consisted of dyspnea (1%) and flushing, hypotension, chest pain, and arrhythmia (all <1%). The use of nab-paclitaxel in subjects previously exhibiting hypersensitivity to paclitaxel injection or human albumin has not been studied.

Cardiovascular

Hypotension, during the 30-minute infusion, occurred in 5% of subjects. Bradycardia, during the 30-minute infusion, occurred in <1% of subjects. These vital sign changes most often caused no symptoms and required neither specific therapy nor treatment discontinuation.

Severe cardiovascular events possibly related to single-agent nab-paclitaxel occurred in approximately 3% of subjects. These events included cardiac ischemia/infarction, chest pain, cardiac arrest, supraventricular tachycardia, edema, thrombosis, pulmonary thromboembolism, pulmonary emboli, and hypertension. Cases of cerebrovascular attacks (strokes) and transient ischemic attacks have been reported.

Electrocardiogram (ECG) abnormalities were common among subjects at baseline. ECG abnormalities on study did not usually result in symptoms, were not dose-limiting, and required no intervention. ECG abnormalities were noted in 60% of subjects. Among subjects with a normal ECG prior to study entry, 35% of all subjects developed an abnormal tracing while on study. The most frequently reported ECG modifications were non-specific repolarization abnormalities, sinus bradycardia, and sinus tachycardia.

Respiratory

Dyspnea (12%), cough (7%), and pneumothorax (<1%) were reported after treatment with nab-paclitaxel.

Neurologic
The frequency and severity of sensory neuropathy increased with cumulative dose. Sensory neuropathy was the cause of nab-paclitaxel discontinuation in 7/229 (3%) subjects. Twenty-four subjects (10%) treated with nab-paclitaxel developed Grade 3 peripheral neuropathy; of these subjects, 14 had documented improvement after a median of 22 days; 10 subjects resumed treatment at a reduced dose of nab-paclitaxel and 2 discontinued due to peripheral neuropathy. Of the 10 subjects without documented improvement, 4 discontinued the study due to peripheral neuropathy.

No Grade 4 sensory neuropathies were reported. Only one incident of motor neuropathy (Grade 2) was observed in either arm of the controlled trial.

Vision Disorders
Ocular/visual disturbances occurred in 13% of all subjects (n=366) treated with nab-paclitaxel and 1% were severe. The severe cases (keratitis and blurred vision) were reported in subjects who received higher doses than those recommended (300 or 375 mg/m2). These effects generally have been reversible.

Arthralgia/Myalgia
The symptoms were usually transient, occurred two or three days after nab-paclitaxel administration, and resolved within a few days.

8.3 Pembrolizumab
Please see Investigator's Brochure for detailed information regarding Pembrolizumab

8.3.1 Availability
Pembrolizumab is an investigational drug in this setting and not available outside of a clinical trial.

The site investigator shall take responsibility for and shall take all steps to maintain appropriate records and ensure appropriate supply, storage, handling, distribution and usage of investigational product in accordance with the protocol and any applicable laws and regulations.

8.3.2 Chemical Properties
Pembrolizumab is a humanized anti-PD-1 mAb of the IgG4/kappa isotype with a stabilizing S228P sequence alteration in the fragment crystallizable (Fc) region. Pembrolizumab binds to human PD-1 and blocks the interaction between PD-1 and its ligands.

8.3.3 Product Descriptions
Clinical Supplies will be provided by Merck as summarized in Table 11.

Table 11 Product Descriptions

Product Name & Potency	Dosage Form
Pembrolizumab 50 mg	Lyophilized Powder for Injection
Pembrolizumab 100 mg/ 4mL	Solution for Injection

8.3.4 Packaging and Labeling Information
Clinical supplies will be affixed with a clinical label in accordance with regulatory requirements.

8.3.5 Clinical Supplies Disclosure
This study is open-label; therefore, the subject, the study site personnel, the site investigator and/or designee are not blinded to treatment. Drug identity (name, strength) is included in the label text; random code/disclosure envelopes or lists are not provided.

8.3.6 Adverse Events
Please see Investigator's Brochure for complete details regarding adverse events related to Pembrolizumab.

Pembrolizumab is generally well tolerated and demonstrates a favorable safety profile in comparison to chemotherapy. Pembrolizumab is an immunomodulatory agent, and based on this mechanism of action, immune mediated adverse events are of primary concern. Important identified risks for pembrolizumab are of an immune mediate nature, including: pneumonitis, colitis, hypophysitis (including hypothyroidism or hyperthyroidism), hepatitis, Type I diabetes mellitus, uveitis, and nephritis, myositis, Guillain-Barre syndrome, pancreatitis, and severe skin reaction toxic epidermal necrolysis (TEN), some with fatal outcome. A new important risk of myocarditis has been identified; cases with fatal outcome have been reported.

The majority of immune-mediated adverse events were mild to moderate in severity, were manageable with appropriate care, and rarely required discontinuation of therapy. In addition to the previously noted identified risks, infusion-related reactions are a risk but are not considered immune mediated; these are also further described in the current IB.

9. STATISTICAL CONSIDERATIONS

9.1 Study Design
This is a Phase I/II study for previously untreated subjects with advanced NSCLC. The study will take place in two phases. First, a cohort of twelve subjects will be enrolled in the Phase I part and will be treated with carboplatin, nab-paclitaxel, and pembrolizumab. A cohort of twelve subjects will be evaluated for safety and tolerability after 2 cycles of therapy. All subjects who receive either nab-paclitaxel or pembrolizumab will be evaluable. If 33% of subjects or less have unacceptable toxicity in the first cohort or any subsequent cohort (if necessary), the study will proceed to the Phase II part. If more than 33% have unacceptable toxicity, 12 additional subjects will be enrolled in a second cohort, if necessary. If unacceptable toxicity is seen in more than 33% in Cohort 2, the study will end due to unacceptable toxicity of this drug combination.

During the phase I portion of the study, there will be weekly teleconferences to review toxicities for all subjects on study. If at any point more than 4 subjects experience a DLT, enrollment to the current cohort will end. These ongoing assessments will occur throughout phase I for both cohort 1 and cohort 2 (if necessary). For example, if all 5 of the first 5 subjects enrolled have a DLT, no more subjects will be enrolled to that Phase I cohort or treated. If this occurs during cohort 2, the trial will end.

The Phase II part of the study is a single arm study. All subjects will be treated with carboplatin, nab-paclitaxel, and pembrolizumab in 21-day cycles for up to 4 cycles.

Mandatory pre-treatment tumor biopsies will be obtained prior to initiating treatment for all subjects (only if adequate archived samples are unavailable). Mandatory tumor biopsies will be obtained in the Phase II part of the study after 4 cycles of study treatment or at the time of progression, whichever comes first.

For subjects without progression of disease after Cycle 4, pembrolizumab will continue every 3 weeks for up to 2 years or until unacceptable toxicity.

9.2 Phase I

9.2.1 Definition of primary outcomes/endpoints

Recommended Phase II dose (RP2D)

RP2DS is defined as the dosing schedule of pembrolizumab resulting in less than 33% toxicity rate as assessed after completion of 2 cycles. Unacceptable toxicity will be defined as any non-hematologic toxicity Grade ≥ 3 or any hematologic toxicity Grade ≥ 4 as defined in greater detail in section 5.2.1.1. Toxicities are graded according to CTCAE v4.

Safety and Tolerability

Safety and tolerability is defined as rates of Grade 1-5 toxicity according to CTCAE v4.

9.2.2 Definition of secondary outcomes/endpoints

PFS

PFS is defined as the time from registration to progressive disease according to RECIST v1.1 criteria or death from any cause.

Response

Response is defined as partial response [PR] or complete response [CR] according to RECIST v1.1 criteria.

OS

OS is defined as the time from registration until death from any cause.

PD-L1 expression

PD-L1 expression is defined as positive if ≥ 1% of tissue stains positive for PD-L1 by IHC.

Anti-tumor activity

Defined as the change in the sum of the dimensions of all measurable lesions as defined by RECIST 1.1 criteria.

9.2.3 Analytic plan for primary objective

Cohort 1
All subjects who receive treatment will be evaluated for toxicity. Toxicities by type and grade will be summarized overall and by dose level. During the phase I portion of the study, there will be weekly teleconferences to review toxicities for all subjects on study. If at any point more than 4 subjects experience a DLT, we stop accrual to Cohort 1. For example, if all 5 of the first 5 subjects enrolled have a DLT, no more subjects will be enrolled to that Phase I cohort or treated. The same process will apply for cohort 2 (below). After 12 subjects in Cohort 1 are treated, if the rates of unacceptable toxicity after 2 cycles of pembrolizumab, defined as Grade ≥ 3 non-hematologic or Grade ≥ 4 hematologic toxicity, are ≤ 33% of subjects (≤ 4 of 12), the recommended Phase II dose (RP2D) of pembrolizumab will be 2 mg/kg and the study will advance to the Phase II part of study. If unacceptable toxicity occurs in > 33% of subjects (≥ 5 of 12), a second cohort of subjects will be enrolled.

Cohort 2 (if necessary)
Twelve subjects will be treated with delayed initiation of pembrolizumab 2 mg/kg. **Pembrolizumab will be omitted for Cycle 1 and start on Day 1 of Cycle 2.** Ongoing assessments will occur as described above in cohort 1. At any point that 5 subjects have unacceptable toxicity, the trial will end. Presuming all 12 subjects are treated in the cohort, if ≤ 33% of subjects have unacceptable toxicity (as defined above) at this dose level, 2 mg/kg starting Cycle 2, Day 1 will be the RP2D and schedule and the study will proceed to the Phase II part of the study. If > 33% of subjects (≥ 5 of 12) have unacceptable toxicity at this level, the study will be discontinued due to unacceptable toxicity of this drug combination.

9.2.4 Analytic plan for secondary objectives

Median PFS and median OS outcomes will be described using KM method and two-sided 80% confidence intervals will be calculated.

Response will be reported as a percentage of subjects registered to the study.

PD-L1 expression will be categorized as positive (≥ 1% expression) or negative (< 1% expression) from pre-treatment biopsies. Positive PD-L1 expression rates are estimated to be 70% based on preliminary data from pembrolizumab PN 001. The distribution of PFS will be summarized by PD-L1 expression using Kaplan-Meier method and PFS will be compared using one-sided logrank test. Nominal p-values will be reported to measure the strength of the differences tested.

Anti-tumor activity will be reported as a percentage change in the sum of the dimensions of all measurable lesions as defined by RECIST 1.1 criteria. The baseline imaging before treatment will be compared to each subsequent imaging assessment. The maximum anti-tumor activity will be reported using the assessment with the smallest sum of dimensions (maximum response).

9.2.5 Sample size justification

Table 12 indicates the probability of a dose proceeding to Phase II (observe ≤ 4 of 12 unacceptable toxicities) for a range of true unacceptable toxicity rates; there is a high probability (72%) if there is truly a 30% rate of unacceptable toxicity, and a low probability (19%) if there is truly a 50% rate of unacceptable toxicity.

Table 12: Probability of dose proceeding to Phase II

	True Probability of Unacceptable toxicity at Current Dose						
	0.10	0.20	0.30	0.40	0.50	0.60	0.70
Probability that dose proceeds to Phase II	0.99	0.93	0.72	0.44	0.19	0.06	0.01

9.3 Phase 2

9.3.1 Definition of primary outcomes/endpoints

Progression-free survival (PFS)

PFS is defined as the time from registration until progression of disease, as defined by RECIST v1.1 criteria, or death from any cause.

Response (PR or CR)

PR or CR is defined according to RECIST v1.1 criteria.

9.3.2 Definition of secondary outcomes/endpoints

OS

OS is defined as the time from registration until death from any cause.

Safety and Tolerability

Safety and tolerability is defined as rates of Grade 1-5 toxicity according to CTCAE v4.

PD-L1 expression

PD-L1 expression is defined as positive if ≥ 1% of tissue stains positive for PD-L1 by IHC.

Anti-tumor activity

Defined as the change in the sum of the dimensions of all measurable lesions as defined by RECIST 1.1 criteria.

9.3.3 Analytic plan for primary objective

Recruitment of 43 subjects will last approximately 12 months and subjects will be followed until 39 PFS events occur or a maximum of 2 years from registration of the last subject. The estimated study duration is 3 years. Two co-primary outcomes are chosen – PFS based on mechanism of action, and RR based on acknowledgement of 'traditional' single arm studies.

For the first co-primary outcome, PFS, assumptions are that the addition of pembrolizumab will increase PFS by 50% to 9.0 months compared to historical control of 6.0 months. After completion of the study, or when 39 or more subjects have experienced a PFS event, the distribution of PFS will be summarized using Kaplain-Meier method, and median PFS will be

reported. A one-sided 5% type I error, 20% type II error and exponential distribution of PFS were assumed. Success will be defined as a lower 95% one sided confidence limit for the median (Brookmeyer, R. and Crowley, J. (1982), "A Confidence Interval for the Median Survival Time," *Biometrics*, 38, 29–41.) being greater than 6 months.

For the second co-primary outcome, response rate, a single stage single arm design will assume a historical control response rate of 31% and a hypothesized study rate of 50%. This effect size may be detected with 80% power, a one-sided 5% type I error rate and a 20% type II error rate. Success will be defined as the number of responses being greater than or equal to 19 out of 43.

The analysis of both co-primary outcomes will use the intention-to-treat approach from the time of registration.

9.3.4 Analytic plan for secondary objectives

- OS outcomes will be summarized using KM method.
- Safety and tolerability will be reported as rates of Grade 1-5 toxicity by CTCAE v4 criteria for all events with a frequency of ≥ 1%.
- PD-L1 expression will be categorized as positive or negative from pre-treatment and post-treatment biopsies. Positive PD-L1 expression rates are estimated to be 70%, based on preliminary data from pembrolizumab PN 001. The distribution of PFS will be summarized by PD-L1 expression using Kaplan-Meier method and PFS will be compared using one-sided logrank test. Nominal p-values will be reported to measure the strength of the differences tested.
- Anti-tumor activity will be reported as a percentage change in the sum of dimensions of all measurable lesions as defined by RECIST 1.1 criteria. The baseline imaging before treatment will be compared to each subsequent imaging assessment. The maximum anti-tumor activity will be reported using the assessment with the smallest sum of dimensions (maximum response).

9.3.5 Sample size justification

As described above, sample size calculations indicated that 43 subjects were needed to meet the co-primary endpoint PFS goal of 9.0 months compared to a retrospective cohort with a median PFS of 6.0 months. This sample size would also have 80% power to meet the co-primary endpoint of a 50% response rate versus an historic control rate of 31%. An alpha of 0.05 and beta of 0.20 were used for each primary endpoint, resulting in an overall type I error rate of 0.10.

9.3.6 Subject Accrual

Twenty-five potentially eligible subjects are expected to be identified per month and 6 subjects per month registered to the study. It is estimated it will take approximately 12 months to register 43 subjects. Subjects will be followed until 39 PFS events occur or a maximum of 2 years from registration of the last subject.

9.3.7 Reporting and Exclusions

9.3.7.1 Evaluation of toxicity
All subjects will be evaluable for toxicity from the time of their first treatment on study.

9.3.7.2 Evaluation of Response
All subjects included in the study must be assessed for response to treatment, even if there are major protocol treatment deviations or if they are ineligible. Each subject will be assigned one of the following categories: 1) complete response, 2) partial response, 3) stable disease, 4) progressive disease, 5) early death from malignant disease, 6) early death from toxicity, 7) early death because of other cause, or 9) unknown (not assessable, insufficient data). [Note: By arbitrary convention, category 9 usually designates the "unknown" status of any type of data in a clinical database.]

All of the subjects who met the eligibility criteria should be included in the main analysis of the response rate. An incorrect treatment schedule or drug administration does not result in exclusion from the analysis of the response rate.

All conclusions will be based on all eligible subjects. Sub-analyses may then be performed on the basis of a subset of subjects, excluding those for whom major protocol deviations have been identified (e.g., early death due to other reasons, early discontinuation of treatment, major protocol violations, etc.). However, these sub-analyses may not serve as the basis for drawing conclusions concerning treatment efficacy, and the reasons for excluding subjects from the analysis should be clearly reported.

10. ADVERSE EVENT REQUIREMENTS
The descriptions and grading scales found in the NCI CTCAE v4 will be utilized for AE assessment. A copy of the CTCAE v4 can be downloaded from the CTEP website at http://ctep.cancer.gov.

10.1 Definitions

10.1.1 Adverse Event (AE)
An adverse event (AE) is any unfavorable and unintended sign (including an abnormal laboratory finding), symptom or disease temporally associated with the administration, at any dose, or a medicinal or therapeutic product whether or not considered related to that product. All abnormal laboratory values or diagnostic test results during the phase I portion constitute adverse events and will be reported during the Phase I portion of the study. During the Phase II portion, abnormal laboratory values or diagnostic test results constitute adverse events only if they induce clinical signs or symptoms or require treatment or further diagnostic tests.

10.1.2 Serious Adverse Event (SAE)
A serious adverse event (SAE) is any adverse event occurring at any dose or during study therapy that:

- Death. **NOTE:** Death due to disease progression should not be reported as a SAE, unless it is attributable by the site investigator to the study therapy

- Is life-threatening (defined as an event in which the subject 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 for >24 hours or prolongation of existing hospitalization. **NOTE**: Hospitalization for anticipated or protocol specified procedures such as administration of chemotherapy, central line insertion, metastasis interventional therapy, resection of primary tumor, or elective surgery, will not be considered serious adverse events.
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly or 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 (e.g., 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 not resulting in hospitalization; or the development of drug dependency or drug abuse.
- Is a new cancer
- Overdose; see 10.3
- Pregnancy; see 10.4

10.1.3 Expectedness

Expected adverse event

Expected AE are those events that have been previously identified as resulting from administration of the agent. For the purposes of this study, an AE is considered expected when it appears in the current AE list, the Investigator's Brochure (IB), the package insert or is included in the informed consent document as a potential risk.

Unexpected adverse event

For the purposes of this study, an AE is considered unexpected when it varies in nature, intensity or frequency from information provided in the current AE list, the IB, the package insert or when it is not included in the informed consent document as a potential risk.

10.1.4 Attribution

Attribution is the relationship between an AE or SAE and the study treatment. Attribution will be assigned as follows:

- 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.
- Unrelated – The AE is clearly NOT related to the study treatment.

10.2 Reporting

10.2.1 Adverse Events

- Adverse events should be recorded from the start of treatment through a minimum of 30 days post-operative (or in unresected subjects 30 days past the date of the restaging scan or the attempted surgery).
- AEs will be recorded regardless of whether or not they are considered related to the study drug.
- AEs considered related to study drug will be followed until resolution to ≤ Grade 1 or baseline, deemed clinically insignificant, and/or until a new anti-cancer treatment starts, whichever is earlier.
- After initiation of neoadjuvant treatment, all adverse events will be reported according to the guidelines in the following sections. Throughout the study, site investigators should report any deaths, serious adverse events, or other adverse events of concern that are believed to be related to the investigational intervention.

10.2.2 Site Requirements for Reporting SAEs

PLEASE NOTE: Robert H. Lurie Comprehensive Cancer Center at Northwestern University has specific reporting instructions to Celgene. Please see Section 10.2.3.2.

Site investigators will assess the occurrence of SAEs at all subject evaluation time points during the study.

Site investigators and other site personnel must report any SAE both related and unrelated occurring from the time of informed consent signature to 90 days following cessation of treatment or 30 days following cessation of treatment if the subject initiate new anticancer therapy, whichever is earlier. The SAE should be reported on the SAE/ECI Submission Form **within 24 hours** of discovery of the event.

Additionally, any serious adverse event, considered by a site investigator who is a qualified physician to be related to Merck product that is brought to the attention of the site investigator at any time outside of the time period specified in the previous paragraph also must be reported to HCRN.

The completed SAE/ECI Submission Form must be sent electronically to Hoosier Cancer Research Network at **safety@hoosiercancer.org**. The site investigator is responsible for informing the IRB of the SAE per local requirements. The original copy of the SAE/ECI Submission Form and the fax confirmation sheet must be kept at the study site.

Recurrent episodes, complications, or progression of the initial SAE must be reported as follow-up to the original episode **within one business day** of the site investigator receiving the follow-up information.

Follow-up information will be sent electronically to HCRN at safety@hoosiercancer.org using the SAE/ECI Submission Form stating that this is a follow-up to a previously reported SAE. The follow-up information should describe whether the event has resolved or continues, if and how it was treated, and whether the subject continued or withdrew from study participation.

All AEs and SAEs whether reported by the subject, discovered during questioning, directly observed or detected by physical examination, laboratory test or other means, will be recorded in the subject's medical record and on the appropriate study specific eCRF forms within the EDC system.

10.2.3 Reporting requirements

The study must be conducted in compliance with FDA regulations, local safety reporting requirements and reporting requirements of the sponsor-investigator. Progress reports and notifications of serious unexpected adverse drug reactions will be provided to the IRB according to local regulations and guidelines. These reports will be reviewed by the sponsor-investigator and those considered unexpected and possibly related to study drug plus all deaths within 90 days of discontinuing treatment will be forwarded to participating sites for submission to their Institutional Review Boards per their guidelines. All other events will be held and submitted to the sites for continuing review.

10.2.4 Hoosier Cancer Research Network Requirements for Reporting SAEs

10.2.4.1 Reporting to Merck

HCRN will report any serious adverse event, or follow up to a serious adverse event whether or not related to Merck product that occurs to any subject from the time the consent is signed through 90 days following cessation of treatment or 30 days following cessation of treatment if the subject initiate new anticancer therapy, whichever is earlier. The SAE/ECI Submission Form should be sent to Merck **within one business day** of receipt from the site. HCRN will provide follow-up information as reasonably requested.

Hoosier Cancer Research Network will fax the SAE/ECI Submission Form and any other relevant safety information to Merck GS at +1-215-993-1220.

10.2.4.2 Reporting to Celgene

Robert H. Lurie Comprehensive Cancer Center at Northwestern University will report to Celgene and HCRN concurrently in writing using a Celgene SAE form any SAE **within 24 hours** of becoming aware of the event. SAEs received from other participating sites will be sent to HCRN and HCRN will report to Celgene by **within 24 hours** of HCRN becoming aware of the event. HCRN will report to Celgene using a MEDWATCH 3500A form. Celgene will communicate directly with HCRN regarding SAE follow up questions and HCRN will respond to those questions within **5 days**.

The initial report will be as complete as possible, including an assessment of the causal relationship between the event and the investigational product(s), if available. Information not available at the time of the initial report (e.g., an end date for the adverse event or laboratory values received after the report) will be documented on a follow-up report. A final report to

document resolution of the SAE is required. The Celgene tracking number (AX-CL-NSCLC-PI-004076) and the institutional protocol number should be included on SAE reports (or on the fax cover letter) sent to Celgene. A copy of the fax transmission confirmation of the SAE report to Celgene should be attached to the SAE and retained with the study records.

Celgene Drug Safety Contact Information:
Celgene Corporation
Global Drug Safety and Risk Management
Connell Corporate Park
300 Connell Dr. Suite 6000
Berkeley Heights, NJ 07922
Fax: (908) 673-9115
E-mail:drugsafety@celgene.com

10.2.4.3 Reporting to the Northwestern QAM

All SAEs, including deaths must be reported to the assigned Northwestern QAM. The completed SAE Submission Form must be emailed to croqualityassurance@northwestern.edu **within one business day** of discovery of the event. See Section 11 for additional reporting information.

10.2.4.4 Reporting to the Food and Drug Administration (FDA)

This study was determined to be exempt by the FDA on 1.28.15. HCRN will continue to facilitate compliance of applicable requirements for the sponsor-investigator in relation to this study. This includes but is not limited to 21 CFR 50.20 informed consent, 21 CFR Part 56 IRB, and pertinent sections of the Public Health Service Act and FDAAA.

10.3 Definition of an Overdose

For purposes of this trial, an overdose of pembrolizumab will be defined as any dose of 1,000 mg or greater (≥5 times the indicated dose). No specific information is available on the treatment of overdose of pembrolizumab. Appropriate supportive treatment should be provided if clinically indicated. In the event of overdose, the subject should be observed closely for signs of toxicity.

If an adverse event(s) is associated with ("results from") the overdose of a Merck product, the adverse event(s) is reported as a serious adverse event, even if no other seriousness criteria are met.

If a dose of Merck's product meeting the protocol definition of overdose is taken without any associated clinical symptoms or abnormal laboratory results, the overdose is reported as a non-serious Event of Clinical Interest (ECI), using the terminology "accidental or intentional overdose without adverse effect."

All reports of overdose with and without an adverse event must be reported.

10.4 Reporting of Pregnancy and Lactation

Although pregnancy and lactation are not considered adverse events, it is the responsibility of investigators or their designees to report any pregnancy or lactation in a subject (spontaneously reported to them) that occurs during the trial.

Pregnancies and lactations that occur after the consent form is signed but before treatment allocation/randomization must be reported by the investigator if they cause the subject to be excluded from the trial, or are the result of a protocol-specified intervention, including but not limited to washout or discontinuation of usual therapy, diet, placebo treatment or a procedure.

Pregnancies and lactations that occur from the time of treatment allocation/randomization through 120 days following cessation of the study drugs, or 30 days following cessation of treatment if the subject initiates new anticancer therapy, whichever is earlier, must be reported by the investigator. All reported pregnancies must be followed to the completion/termination of the pregnancy. Pregnancy outcomes of spontaneous abortion, missed abortion, benign hydatidiform mole, blighted ovum, fetal death, intrauterine death, miscarriage and stillbirth must be reported as serious events (Important Medical Events). If the pregnancy continues to term, the outcome (health of infant) must also be reported.

10.5 Events of Clinical Interest (ECI)

Selected non-serious and serious adverse events are also known as Events of Clinical Interest (ECI) and must be recorded as such on the SAE/ECI Submission Form. ECIs (both non-serious and serious adverse events) identified from the date of first dose through 90 days following cessation of treatment, or 30 days after the initiation of a new anticancer therapy, whichever is earlier, will be reported from the site to HCRN **within one business day**. HCRN will report to Merck **within one business day**.

Events of clinical interest for this trial include:

1. an overdose of Pembrolizumab, as defined in Section 10.3 - Definition of an Overdose and Reporting Guidelines, that is not associated with clinical symptoms or abnormal laboratory results.

2. an elevated AST or ALT lab value that is greater than or equal to 3X the upper limit of normal and an elevated total bilirubin lab value that is greater than or equal to 2X the upper limit of normal and, at the same time, an alkaline phosphatase lab value that is less than 2X the upper limit of normal, as determined by way of protocol-specified laboratory testing or unscheduled laboratory testing.*

***NOTE:** These criteria are based upon available regulatory guidance documents. The purpose of the criteria is to specify a threshold of abnormal hepatic tests that may require an additional evaluation for an underlying etiology. The trial site guidance for assessment and follow up of these criteria can be found in the Investigator Trial Master File (or equivalent).

11. TRIAL MANAGEMENT

The Robert H. Lurie Comprehensive Cancer Center's Data Monitoring Committee (DMC) will provide study oversight activities as outlined in Section 11.2. This study will be conducted with guidance from the Data and Safety Monitoring Plan of the Robert H. Lurie Comprehensive Cancer Center, a copy of which can be found at:
https://www.cancer.northwestern.edu/research/clinical-trials-office/research-oversight.html

11.1 HCRN oversight activities include

- Review and processing of all adverse events requiring expedited reporting as defined in the protocol
- Provide trial accrual progress, safety information and data summary reports to the sponsor-investigator
- Submit data summary reports to the lead institution DMC and attend DMC reviews:
    - during the Phase I portion of the study, semi-monthly to present safety summary reports
    - during the Phase II portion of the study, as applicable: following any reports of protocol deviations or SAEs; and overall study data delinquency that exceeds 10% incomplete forms or sites with data delinquency that are not responding sufficiently to the HCRN data delinquency escalation process
    - throughout the study, semi-annual comprehensive DMC review
- During the Phase I portion of the study there will be weekly Phase I safety calls with all participating institutions

11.2 Robert H. Lurie Comprehensive Cancer Center's Data Monitoring Committee (DMC)

HCRN will provide the following for the Robert H. Lurie Comprehensive Cancer Center's DMC to review:

- Adverse event summary report
- Monitoring reports
- Audit results if applicable
- Study accrual patterns
- Data delinquency
- Protocol deviations

The Robert H. Lurie Comprehensive Cancer Center's DMC will conduct a comprehensive study review semi-annually. Documentation of DMC reviews will be provided to sponsor-investigator and HCRN. Issues of immediate concern by the DMC will be brought to the attention of the sponsor-investigator and other regulatory bodies as appropriate. The sponsor-investigator will work with HCRN to address the DMC's concerns.

11.3 Data Quality Oversight Activities

11.3.1 Onsite Monitoring

Monitoring visits to the trial sites may be made periodically during the trial to ensure key aspects of the protocol are followed. For cause visits may occur as necessary. Selected source documents will be reviewed for verification of agreement with data entered into the EDC system. It is important for the site investigator and their relevant personnel to be available for a sufficient amount of time during the monitoring visits or audit, if applicable. The site investigator and institution guarantee access to source documents by HCRN or its designee.

The trial site may also be subject to quality assurance audit by Merck or Celgene or its designee as well as inspection by appropriate regulatory agencies.

11.3.2 Remote Data Validation

Remote validation of the EDC system data will be completed on a continual basis throughout the life cycle of the study. The data entry completion status of each participating site will be reviewed on a weekly basis to ensure timeliness of data entry. Electronic Case Report Form (eCRF) constraints will be utilized to prevent data entry errors and ensure complete data entry. Automated bi-weekly edit check programs will check for errors in accuracy, validity, and consistency in the data. Listings from the edit check programs will be used to generate queries in the EDC system. Corrections will be made in a timely manner by the study site personnel.

11.4 Compliance with Trial Registration and Results Posting Requirements

Under the terms of the Food and Drug Administration Modernization Act (FDAMA) and the Food and Drug Administration Amendments Act (FDAAA), the sponsor-investigator of the trial is solely responsible for determining whether the trial and its results are subject to the requirements for submission to the Clinical Trials Data Bank, http://www.clinicaltrials.gov. All results of primary and secondary objectives must be posted to CT.gov within a year of completion. The sponsor-investigator has delegated responsibility to HCRN for registering the trial and posting the results on clinicaltrials.gov. Information posted will allow subjects to identify potentially appropriate trials for their disease conditions and pursue participation by calling a central contact number for further information on appropriate trial locations and study site contact information.

12. DATA HANDLING AND RECORD KEEPING

12.1 Data Management

HCRN will serve as the Clinical Research Organization for this trial. Data will be collected through a web based electronic data capture system (EDC), a system compliant with Good Clinical Practices and Federal Rules and Regulations. HCRN personnel will coordinate and manage data for quality and integrity. All data will be collected and entered into EDC system by study site personnel from participating institutions.

12.2 Case Report Forms and Submission

Generally, clinical data will be electronically captured in the EDC system and correlative results will be captured in EDC system or other secure database(s). If procedures on the study calendar are performed for standard of care, at minimum, that data will be captured in the source document. Select standard of care data will also be captured in EDC system, according to study-specific objectives.

The completed dataset is the sole property of the sponsor-investigator's institution and should not be exported to third parties, except for authorized representatives of appropriate Health/Regulatory Authorities, without permission from the sponsor-investigator and HCRN.

12.3 Record Retention

To enable evaluations and/or audits from Health Authorities/HCRN, the site investigator agrees to keep records, including the identity of all subjects (sufficient information to link records; e.g., hospital records), all original signed informed consent forms, copies of all source documents, and detailed records of drug disposition. All source documents are to remain in the subject's file and

retained by the site investigator in compliance with the site contract with HCRN. No records will be destroyed until HCRN confirms destruction is permitted.

12.4 Confidentiality

There is a slight risk of loss of confidentiality of subject information. All records identifying the subjects will be kept confidential and, to the extent permitted by the applicable laws and/or regulations, will not be made publicly available. Information collected will be maintained on secure, password protected electronic systems. Paper files that contain personal information will be kept in locked and secure locations only accessible to the study site personnel.

Subjects will be informed in writing that some organizations including the sponsor-investigator and his/her research associates, HCRN, Merck, Celgene, IRB, or government agencies, like the FDA, may inspect their medical records to verify the information collected, and that all personal information made available for inspection will be handled in strictest confidence and in accordance with local data protection laws.

If the results of the study are published, the subject's identity will remain confidential.

13. ETHICS

13.1 Ethics Review

The final study protocol, including the final version of the Informed Consent Form, must be approved by an IRB. The site investigator must submit written approval to HCRN before he/she can register any subject to the study.

The site investigator is responsible for informing the IRB of any amendment to the protocol in accordance with local requirements. In addition, the IRB must approve all advertising used to recruit subjects for the study. The protocol must be re-approved by the IRB annually, as local regulations require.

13.2 Ethical Conduct of the Study

The study will be performed in accordance with ethical principles originating from the Declaration of Helsinki, which are consistent with ICH/Good Clinical Practice, and applicable regulatory requirements.

13.3 Informed Consent

The site investigator will ensure the subjects is given full and adequate oral and written information about the nature, purpose, possible risks and benefits of the study. Subjects must also be notified they are free to discontinue from the study at any time. The subject should be given the opportunity to ask questions and allowed time to consider the information provided. The subject's signed and dated informed consent must be obtained before conducting any procedure specifically for the study. The site investigator must store all original, signed Informed Consent Forms. A copy of the signed Informed Consent Form must be given to the subject.

14. PATHOLOGY REQUIREMENTS

14.1 Pathology Requirements for Enrollment

14.1.1 Source of specimen

A pathology report confirming the diagnosis of advanced stage non-small cell lung cancer (NSCLC) must be available at the time of enrollment on study. For subjects with locally advanced or metastatic disease at the time of diagnosis, the original pathology from this diagnosis is sufficient. For subjects with early stage disease who later developed metastatic disease, biopsy confirmation of the metastatic disease is required. All biopsies done at other institutions should be reviewed and confirmed by a pathologist at the local study site.

14.1.2 Adequacy of available specimen

For all subjects, unstained slides from an archived tumor block must be available prior to registration, with the exception for subjects who have had prior PD-L1 testing using the Dako 22C3 antibody and insufficient tissue for additional studies. Adequacy of tissue samples will be determined by the Merck & Co. laboratory responsible for doing correlative studies. If adequate tissue samples are not available, additional biopsy will be required. Acceptable biopsies will be obtained via transcutaneous core needle biopsies or surgical biopsies. At least 3 cores of tissue will be required.

14.1.3 Histology

The following histology is eligible

- Adenocarcinoma
- Large cell carcinoma
- Poorly differentiated carcinoma
- NSCLC, not otherwise specified
- Squamous Cell Carcinoma

14.2 Pathology Requirements for Study Biopsies

14.2.1 Subject selection for biopsies

Adequate archival tissue or available PD-L1 testing results using the Dako 22C3 antibody are required for enrollment. If the patient has not had prior testing and no acceptable archival tissue is available, subjects must be willing to consent to providing a pre-treatment biopsy for PD-L1 testing. This biopsy is to be obtained within 28 days prior to registration. Phase II subjects are required to provide a post-treatment tumor biopsy after completion of 4 cycles of study treatment or at progression. The progression biopsy should be performed once confirmed by second scan unless unequivocal progression that requires the subject come off study treatment prior to confirmation scan. In the event that a subject has had a complete response or there is no disease feasible to biopsy, no biopsy will be obtained at that time. In this case, the subject will have the option to undergo a biopsy at progression. Window for tumor biopsies ±10 days to allow for scheduling conflicts (weekends/holidays). Acceptable biopsies will be obtained via transcutaneous core needle biopsies or surgical biopsies. At least 3 cores of tissue will be required. FNAs are NOT acceptable. See CLM (Correlative Laboratory Manual) for details regarding collection and shipping of sample.

14.2.2 Preparation and shipment of specimen

All biopsies, whether obtained in Interventional Radiology, or in the operating room, should be processed by the local study site's pathology lab. See CLM for collection, labeling and shipping of samples.

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16. APPENDICES

16.1 Robert H. Lurie CCC DSMP

This study will be conducted in accordance with the Data and Safety Monitoring Plan of the Robert H. Lurie Comprehensive Cancer Center, a copy of which can be found at: http://cancer.northwestern.edu/cro/library.cfm#CPSRMS

16.2 ECOG Performance status

Table 13: ECOG Performance Status

Grade	Description
Grade 0	Fully active, able to carry on all pre-disease performance without restriction
Grade 1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
Grade 2	Ambulatory and capable of all self care but unable to carry out any work activities. Up and about more than 50% of waking hours
Grade 3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours
Grade 4	Completely disabled. Cannot carry on any self care. Totally confined to bed or chair

Table 16.3 Dose Modification and Toxicity Management Guidelines for Immune-related AEs Associated with Pembrolizumab

General instructions:

1. Corticosteroid taper should be initiated upon AE improving to Grade 1 or less and continue to taper over at least 4 weeks.
2. For situations where pembrolizumab has been withheld, pembrolizumab can be resumed after AE has been reduced to Grade 1 or 0 and corticosteroid has been tapered. Pembrolizumab should be permanently discontinued if AE does not resolve within 12 weeks of last dose or corticosteroids cannot be reduced to ≤10 mg prednisone or equivalent per day within 12 weeks.
3. For severe and life-threatening irAEs, IV corticosteroid should be initiated first followed by oral steroid. Other immunosuppressive treatment should be initiated if irAEs cannot be controlled by corticosteroids.

Immune-related AEs	Toxicity grade or conditions (CTCAEv4.0)	Action taken to pembrolizumab	irAE management with corticosteroid and/or other therapies	Monitor and follow-up
Pneumonitis	Grade 2	Withhold	• Administer corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper	• Monitor participants for signs and symptoms of pneumonitis • Evaluate participants with suspected pneumonitis with radiographic imaging and initiate corticosteroid treatment • Add prophylactic antibiotics for opportunistic infections
	Grade 3 or 4, or recurrent Grade 2	Permanently discontinue		
Diarrhea / Colitis	Grade 2 or 3	Withhold	• Administer corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper	• Monitor participants for signs and symptoms of enterocolitis (ie, diarrhea, abdominal pain, blood or mucus in stool with or without fever) and of bowel perforation (ie, peritoneal signs and ileus). • Participants with ≥ Grade 2 diarrhea suspecting colitis should consider GI consultation and performing endoscopy to rule out colitis. • Participants with diarrhea/colitis should be advised to drink liberal quantities of clear fluids. If sufficient oral fluid intake is not
	Grade 4	Permanently discontinue		

				feasible, fluid and electrolytes should be substituted via IV infusion.
AST / ALT elevation or Increased bilirubin	Grade 2	Withhold	• Administer corticosteroids (initial dose of 0.5- 1 mg/kg prednisone or equivalent) followed by taper	• Monitor with liver function tests (consider weekly or more frequently until liver enzyme value returned to baseline or is stable
	Grade 3 or 4	Permanently discontinue	• Administer corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper	
Type 1 diabetes mellitus (T1DM) or Hyperglycemia	Newly onset T1DM or Grade 3 or 4 hyperglycemia associated with evidence of β-cell failure	Withhold	• Initiate insulin replacement therapy for participants with T1DM • Administer anti-hyperglycemic in participants with hyperglycemia	• Monitor participants for hyperglycemia or other signs and symptoms of diabetes.
Hypophysitis	Grade 2	Withhold	• Administer corticosteroids and initiate hormonal replacements as clinically indicated.	• Monitor for signs and symptoms of hypophysitis (including hypopituitarism and adrenal insufficiency)
	Grade 3 or 4	Withhold or permanently discontinue[1]		
Hyperthyroidism	Grade 2	Continue	• Treat with non-selective beta-blockers (eg, propranolol) or thionamides as appropriate	• Monitor for signs and symptoms of thyroid disorders.
	Grade 3 or 4	Withhold or permanently discontinue[1]		
Hypothyroidism	Grade 2-4	Continue	• Initiate thyroid replacement hormones (eg, levothyroxine or liothyroinine) per standard of care	• Monitor for signs and symptoms of thyroid disorders.
Nephritis and Renal dysfunction	Grade 2	Withhold	• Administer corticosteroids (prednisone 1-2 mg/kg or equivalent) followed by taper.	• Monitor changes of renal function
	Grade 3 or 4	Permanently discontinue		
Myocarditis	Grade 1 or 2	Withhold	• Based on severity of AE administer corticosteroids	

	Grade 3 or 4	Permanently discontinue		• Ensure adequate evaluation to confirm etiology and/or exclude other causes
All other immune-related AEs	Intolerable/ persistent Grade 2	Withhold	• Based on type and severity of AE administer corticosteroids	• Ensure adequate evaluation to confirm etiology and/or exclude other causes
	Grade 3	Withhold or discontinue based on the type of event. Events that require discontinuation include and not limited to: Gullain-Barre Syndrome, encephalitis		
	Grade 4 or recurrent Grade 3	Permanently discontinue		

1. Withhold or permanently discontinue pembrolizumab is at the discretion of the investigator or treating physician.

NOTE:
For participants with Grade 3 or 4 immune-related endocrinopathy where withhold of pembrolizumab is required, pembrolizumab may be resumed when AE resolves to ≤ Grade 2 and is controlled with hormonal replacement therapy or achieved metabolic control (in case of T1DM).