PROTOCOL AMENDMENT #4

LCCC 1516: A Phase II Trial of Sequential Consolidation with Pembrolizumab followed by Nab-paclitaxel after Standard First-Line Induction Chemotherapy in Advanced NSCLC

AMENDMENT INCORPORATES (check all that apply):
_ Editorial, administrative changes
X Scientific changes (IRB approval)
X Therapy changes (IRB approval)
X Eligibility Changes (IRB approval)

Rationale for Amendment: Study design is changed from an open-label three arm, non-comparative randomized phase II study to an open-label single arm phase II study due to accrual rate lower than initially anticipated. All enrolled patients will receive 4 cycles of pembrolizumab monotherapy followed by 4 cycles of nab-paclitaxel monotherapy, according to the time and events schedule for Arm A of the original study design.

Amendment Summary

Scientific changes

1. Updated total accrual goal to 35 subjects in Section 1.1.
2. Removed the option for subjects to co-enroll in LCCC1108, a tissue procurement protocol, in section 1.8.
3. Removed the Section 4.2 "Randomization" due to change in the study design to a single arm.
4. Updated Section 4.9, Study Withdrawal, to be consistent with the latest LCCC protocol template.
5. Updated Section 7.3.3 on SAE reporting to be consistent with the UNC IRB policy.

Therapy changes

1. Updated study schema to reflect changes in the study design to a single arm study of pembrolizumab followed by nab-paclitaxel in Section 4.1.
2. Updated section 5.1 to include more detail on pembrolizumab preparation and handling.

Eligibility changes

1. Updated Section 3.1.5 by adding necitumumab as a recently approved agent used as a standard of care.

2. Updated Section 3.1.8 in Inclusion Criteria by removing the statement "exceptions to these criteria may be allowed at the discretion of the UNC PI for toxicities that are not expected to be exacerbated by pembrolizumab or nab-paclitaxel" to be consistent with the latest UNC IRB policy.
3. Updated section 9.5.2 to state that eligibility single subject exceptions are not permitted for Lineberger Comprehensive Cancer Center Investigator Initiated Trials.

THE ATTACHED VERSION DATED 23 MAY 2018 INCORPORATES THE ABOVE REVISIONS

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LCCC 1516: A Randomized, Non-comparative Three Arm Phase II Trial of Sequential

PROTOCOL AMENDMENT #3

Consolidation with Pembrolizumab followed by Nab-paclitaxel, Sequential Consolidation with Nab-paclitaxel followed by Pembrolizumab and Concurrent Consolidation with Nab-paclitaxel and Pembrolizumab after Standard First-Line Induction Chemotherapy in Advanced NSCLC

AMENDMENT INCORPORATES (check all that apply):

X Editorial, administrative changes
Scientific changes (IRB approval)
X_ Therapy changes (IRB approval)
_ Eligibility Changes (IRB approval)

The protocol is revised to include adverse event management language provided in a Dear Investigator Letter issued on 10 February 2017 by Merck and Co., Inc. regarding cases of Stevens-Johnson syndrome, Toxic Epidermal Necrolysis and Immune-mediated myocarditis with pembrolizumab.

Editorial

1. Corrected footnotes in Time and Events tables to state that a pregnancy test must be completed within 72 hours of Day 1 of study treatment (footnote #10 in sections 6.1 and 6.2 and footnote #9 in section 6.3).

Scientific

2. Section 4.5.4 was revised to include supportive care guidelines for Steven's Johnson Syndrome, Toxic Epidermal Necrolysis and Immune-mediated myocarditis that was provided in the Dear Investigator letter.
3. Added SJS, TEN and myocarditis to adverse events associated with pembrolizumab in section 5.1.6

THE ATTACHED VERSION DATED 19 APRIL 2017 INCORPORATES THE ABOVE REVISIONS

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PROTOCOL AMENDMENT #2

LCCC 1516: A Randomized, Non-comparative Three Arm Phase II Trial of Sequential Consolidation with Pembrolizumab followed by Nab-paclitaxel, Sequential Consolidation with Nab-paclitaxel followed by Pembrolizumab and Concurrent Consolidation with Nab-paclitaxel and Pembrolizumab after Standard First-Line Induction Chemotherapy in Advanced NSCLC

AMENDMENT INCORPORATES (check all that apply):

Editorial, administrative changes
X Scientific changes (IRB approval)
__ Therapy changes (IRB approval)
X_ Eligibility Changes (IRB approval)

Amendment Summary

1. Modified 3.2.8 criterion to exclude subjects with a history of non-infectious pneumonitis that required steroids because pneumonitis is an identified risk of pembrolizumab therapy. Subjects with current non-infectious pneumonitis are also excluded from study participation.
2. Checks for respiratory signs/symptoms + respiratory history were added to Evaluations and Assessments in section 6.0 of the protocol. These changes are now noted in Time and Events tables 6.1, 6.2, 6.3 and accompanying footnotes added to account for these assessments. Ongoing patients are to be evaluated for active pneumonitis. Patients with a history of pneumonitis should be re-consented for this trial to consider if they should continue pembrolizumab or discontinue treatment based on the risk of fatal pneumonitis reported in recent safety findings.
   In addition, assessments of respiratory signs/symptoms are now included in sections 6.4, 6.5.1, 6.5.2, 6.6.4, 6.6.5, 6.7.1, 6.7.3, and 6.8 of the protocol.
3. Noted that the optional biopsy only applies to patients enrolled at UNC in sections 6.5.3 and 6.11.2
4. Corrected the study schema to remove language about the preconsent in section 4.1.
5. Updated the following sections of the protocol to align with the most recent dose modification and guidelines recommended for Merck protocols: Inclusion criteria 3.1.11 and 3.1.12; Added section 5.1.8 – Contraception which provides details on acceptable methods of birth control for WOCBP and males on the study; also updated sections 4.5.3, 4.5.4, 4.6.1, 4.6.2, 5.1.11, 7.1.1, 7.1.4, and 7.3.3. Section 7.1.5 was deleted.
6. Updated 6.13.2 to ensure irRC data is analyzed based on unidimensional measurements (sum of the longest diameters)

THE ATTACHED VERSION DATED September 8, 2016 INCORPORATES THE ABOVE REVISIONS

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PROTOCOL AMENDMENT #1

LCCC 1516: A Randomized, Non-comparative Three Arm Phase II Trial of Sequential Consolidation with Pembrolizumab followed by Nab-paclitaxel, Sequential Consolidation with Nab-paclitaxel followed by Pembrolizumab and Concurrent Consolidation with Nab-paclitaxel and Pembrolizumab after Standard First-Line Induction Chemotherapy in Advanced NSCLC

AMENDMENT INCORPORATES (check all that apply):

X Editorial, administrative changes
X Scientific changes (IRB approval)
___ Therapy changes (IRB approval)
___ Eligibility Changes (IRB approval)

Amendment Summary

3. Clarified in Section 1.8 that subjects at UNC in LCCC1516 trial will be given the option to co-enroll in LCCC1108, a tissue procurement protocol.
4. Removed reference to CRA and replaced with Study Coordinator in Section 4.2 Randomization
5. Noted that Abraxane will be provided by Celgene corporation at no cost to the patient in Section 5.2.1
6. Noted that blood/serum samples will be collected for biocorrelative studies in the Time and Events tables in Sections 6.1, 6.2. 6.3 and relevant footnotes clarified to state that 5mLs of blood will be collected into SST tube for serum collection
7. Revised study assessment visits to reflect blood/serum samples to be collected in Study Assessment Sections 6.6.1, 6.5.1, 6.5.4, 6.6.1, 6.6.4, 6.7.1, 6.8, 6.9, and 6.11.3. We will collect 8.5 mLs of blood per ACD tube (acid citrate dextrose = yellow top; 3 tubes in total) + 5 mLs of blood into SST tube for serum collection for biocorrelative studies; additional information provided in laboratory manual).
8. Removed weight as a clinical assessment on D8 of nab-paclitaxel therapy (Sections 6.5.6, 6.6.3 and 6.7.2)
9. Clarified that quality of life assessments will be performed at the end of treatment in relevant footnotes in the Time and Events tables (Sections 6.1, 6.2 and 6.3) and in Sections 6.10.1 and 6.10.2.
10. Added information on the handling of biospecimens to section 6.11
11. Section 7.3.3: Noted investigator will collect/report all secondary primary malignancies that occur in subjects on this study for a period up to 3 years following discontinuation of Nab-paclitaxel to Celgene Drug Safety and Risk Management group

THE ATTACHED VERSION DATED March 21, 2016 INCORPORATES THE ABOVE REVISIONS

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LINEBERGER COMPREHENSIVE CANCER CENTER
CLINICAL ONCOLOGY RESEARCH PROGRAM
UNIVERSITY OF NORTH CAROLINA AT CHAPEL HILL

LCCC 1516: A Randomized, Non-comparative Three Arm Phase II Trial of Sequential Consolidation with Pembrolizumab followed by Nab-paclitaxel, Sequential Consolidation with Nab-paclitaxel followed by Pembrolizumab and Concurrent Consolidation with Nab-paclitaxel and Pembrolizumab after Standard First-Line Induction Chemotherapy in Advanced NSCLC

Principal Investigator
Jared Weiss, MD
Division of Hematology/Oncology
3115 Physicians Office Bldg
170 Manning Dr, CB# 7305
Chapel Hill, NC 27599-7305
[redacted]

Co-Investigator(s)
[redacted]

Biostatistician
[redacted]

Clinical Protocol Office (CPO)
Lineberger Comprehensive Cancer Center
The University of North Carolina at Chapel Hill
450 West Drive, 3rd Floor, CB# 7295
Chapel Hill, NC 27599-7295

CPO UNC Cancer Network (UNCCN) Project Manager:
[redacted]

Sponsor: Lineberger Comprehensive Cancer Center
Funding Source: Merck & CO., INC.
Version: April 19, 2017
[redacted]

LCCC 1516: A Randomized, Non-comparative Three-Arm Phase II Trial of Sequential Consolidation with Pembrolizumab followed by Nab-paclitaxel, Sequential Consolidation with Nab-paclitaxel followed by Pembrolizumab and Concurrent Consolidation with Nab-paclitaxel and Pembrolizumab after Standard First-Line Induction Chemotherapy in Advanced NSCLC

Principal Investigator
Jared Weiss, MD
Division of Hematology/Oncology
3115 Physicians Office Bldg
170 Manning Dr, CB# 7305
Chapel Hill, NC 27599-7305
[redacted]

Signature Page

The signature below constitutes the approval of this protocol and the attachments, and provides the necessary assurances that this trial will be conducted according to all stipulations of the protocol, including all statements regarding confidentiality, and according to local legal and regulatory requirements and applicable U.S. federal regulations and ICH guidelines.

Principal Investigator (PI) Name:_____

PI Signature: _____

Date: May 23, 2017

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1.0 BACKGROUND AND RATIONALE

1.1 Study Synopsis

This open-label, three-arm, non-comparative randomized phase II study is designed to evaluate three different sequences of double-consolidation with the humanized monoclonal antibody targeted against cell surface receptor programmed cell death-1 (PD-1), pembrolizumab, and nab-paclitaxel in patients with advanced NSCLC post induction chemotherapy. While the goal of each arm is to guarantee exposure to each of these two agents to patients who have not progressed post induction chemotherapy, they do so with different sequence. In ARMs A and B, consolidation is sequential, with either pembrolizumab followed by nab-paclitaxel (ARM A), or nab-paclitaxel followed by pembrolizumab (ARM B. In ARM C, consolidation is concurrent, with the two agents administered concurrently. Effective at the time of approval of this amendment, only ARM A will be enrolling new subjects.

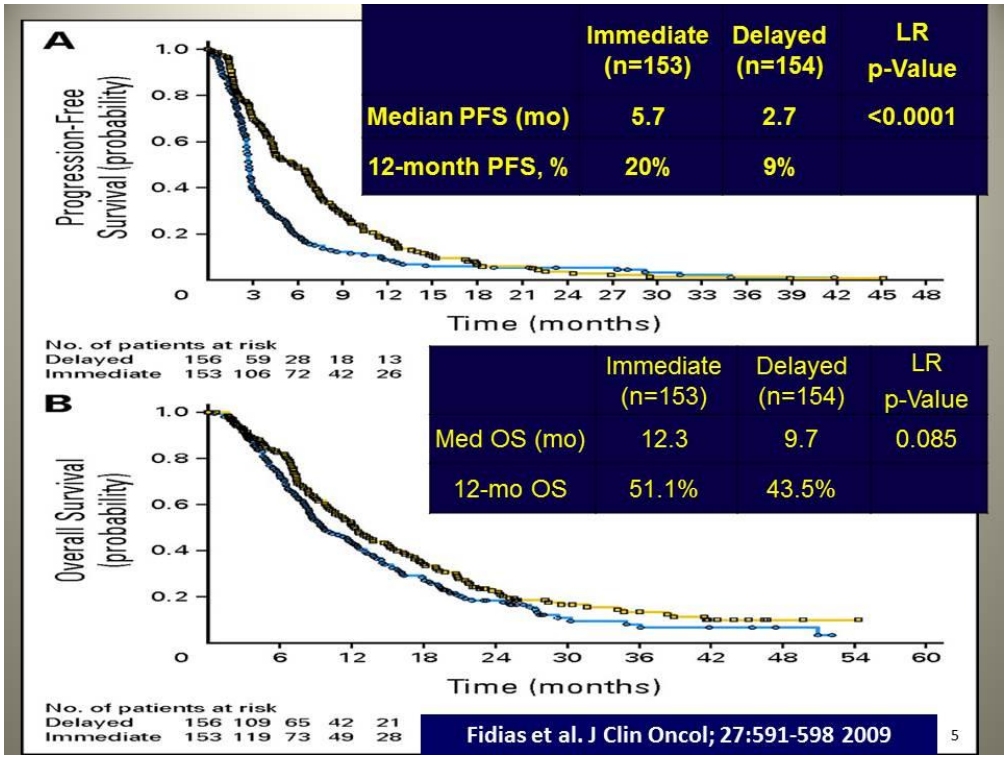
We plan to enroll 35 patients into the study, with a primary objective of estimating overall survival (OS) in each arm. Secondary objectives include estimating rates of response (via RECIST1.1 and Immune Related Response Criteria (irRC)), clinician observed and patient reported toxicity, progression-free survival and quality of life in each arm.

1.2 Duration of therapy for metastatic NSCLC

The standard of care to treat metastatic NSCLC is a platinum-based doublet of chemotherapy ("induction" therapy). Two trials established the appropriate duration of induction therapy. One trial randomized patients to 4 cycles of treatment followed by observation vs. treatment until intolerance or progressive disease (PD); there was no survival advantage for indefinite therapy [2]. The other randomized patients with no PD after 2 cycle of platinum-based doublet therapy to two additional cycles of therapy or to four additional cycles of therapy; again, there was no survival advantage for prolongation of induction therapy [3]. These two trials established 4 cycles of platinum-based doublet therapy as the standard of care.

Recently, a series of trials have demonstrated a survival advantage when this initial induction regimen is followed by "maintenance" therapy, via use of a new agent ("switch maintenance") or by continuing one or more of the non-platinum drugs used in induction ("continuation maintenance"). These trials have demonstrated small survival advantages, but at the cost of denying patients a treatment break. Switch maintenance has shown a larger survival advantage than continuation maintenance, likely reflecting the value of guaranteed exposure to non-cross resistant therapy [4]. One historic trial demonstrated a PFS advantage, with a strong trend towards an OS advantage with fixed duration switch maintenance (hereafter called "consolidation") [1]. In this trial, patients in the

experimental arm received six cycles of consolidation docetaxel, while patients in the control arm were observed.



At the time of PD, patients in the observation arm who received second- line therapy (referred to as "delayed" therapy in slide above) received docetaxel; 40% of the 154 patients in the observation arm did not receive second- line docetaxel (mostly their PFS events were death, or they were too sick from symptoms of progression to receive docetaxel). Amongst the 60% who were able to receive it, survival was identical to that in the experimental arm (the experimental arm is referred to as "immediate" in the slide above), suggesting that the greatest benefit of switch maintenance is guaranteed exposure to a non-cross-resistant agent.

	Number	Randomized Pts	Pts Who Actually Received docetaxel
Delayed Docetaxel	91 (59%)	9.7 mo	12.5 mo
Immediate Docetaxel	142 (93%)	12.3 mo	NA

The current trial seeks to guarantee exposure to two non-cross resistant agents, with a goal of improving OS.

1.3 Pembrolizumab (MK-3475)

Pembrolizumab (MK-3475) is a potent and highly selective intravenous humanized mAb) of the immunoglobulin (Ig) G4/kappa isotype that directly blocks the interaction between PD-1 and its ligands, PD-L1 and PDL-2. This

blockade enhances functional activity of the target lymphocytes to facilitate an antitumor immune response, leading to tumor regression and immune rejection of the tumor. Indications currently under investigation by the manufacturer of pembrolizumab include non-small cell lung cancer and glioblastoma. Keytruda™ (Pembrolizumab) has recently been approved (at a dose of 2 mg/kg IV every 3 weeks) in the United Stated for the treatment of patients with unresectable or metastatic melanoma and disease progression following ipilumumab and, if BRAF V600 mutation positive, a BRAF inhibitor. Further development of pembrolizumab in non-metastatic melanoma is ongoing.[5]

1.3.1 Pharmaceutical and Therapeutic Background

The importance of intact immune surveillance in controlling outgrowth of neoplastic transformation has been known for decades [6]. Accumulating evidence shows a correlation between tumor-infiltrating lymphocytes (TILs) in cancer tissue and favorable prognosis in various malignancies [7-11]. In particular, the presence of CD8+ T-cells and the ratio of CD8+ effector T-cells / FoxP3+ regulatory T-cells seems to correlate with improved prognosis and long-term survival in many solid tumors.

The PD-1 receptor-ligand interaction is a major pathway hijacked by tumors to suppress immune control. The normal function of PD-1, expressed on the cell surface of activated T-cells under healthy conditions, is to down-modulate unwanted or excessive immune responses, including autoimmune reactions. PD-1 (encoded by the gene PDCD1) is an immunoglobulin (Ig) superfamily member related to CD28 and CTLA-4 that has been shown to negatively regulate antigen receptor signaling upon engagement of its ligands (PD-L1 and/or PD-L2) [12, 13]. The structure of murine PD-1 has been resolved [9]. PD-1 and family members are type I transmembrane glycoproteins containing an Ig Variable-type (V-type) domain responsible for ligand binding and a cytoplasmic tail which is responsible for the binding of signaling molecules. The cytoplasmic tail of PD-1 contains 2 tyrosine-based signaling motifs, an immunoreceptor tyrosine-based inhibition motif (ITIM) and an immunoreceptor tyrosine-based switch motif (ITSM).

Following T-cell stimulation, PD-1 recruits the tyrosine phosphatases SHP-1 and SHP-2 to the ITSM motif within its cytoplasmic tail, leading to the dephosphorylation of effector molecules such as CD3ζ, PKCθ and ZAP70, all of which are involved in the CD3 T-cell signaling cascade [12, 14-16]. 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 [13; 14]. PD-1 is expressed on activated lymphocytes including peripheral CD4+ and CD8+ T-cells, B-cells, T regs and Natural Killer cells [17, 18]. Expression has also been shown during thymic development on CD4-CD8- (double negative) T-cells as well as subsets of macrophages and dendritic cells [19].

The ligands for PD-1 (PD-L1 and PD-L2) are constitutively expressed or can be induced in a variety of cell types, including non-hematopoietic tissues as well as in various tumors [19-22]. Both ligands are type I transmembrane receptors containing both IgV- and IgC-like domains in the extracellular region and short cytoplasmic regions with no known signaling motifs. Binding of either PD-1 ligand 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 protein 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 [23]. Although healthy organs express little (if any) PD-L1, a variety of cancers are known to express abundant levels of this T-cell inhibitor. PD-1 has been suggested to regulate tumor-specific T-cell expansion in subjects with melanoma (MEL) [24]. This suggests that the PD-1/PD-L1 pathway plays a critical role in tumor immune evasion and should be considered as an attractive target for therapeutic intervention.

1.3.2 Pre-clinical Findings

Pembrolizumab strongly enhances T-lymphocyte immune responses in cultured blood cells from healthy human donors, cancer patients, and primates. In T-cell activation assays using human donor blood cells, the EC50 (concentration where 50% of the maximum effect is achieved) has been reported to be ~0.1 to 0.3 nM. Levels of interleukin-2 (IL-2), tumor necrosis factor alpha (TNFα), interferon gamma (IFN□), and other cytokines are modulated by MK-3475. The antibody potentiates existing immune responses only in the presence of antigen and does not nonspecifically activate T-cells.[5]

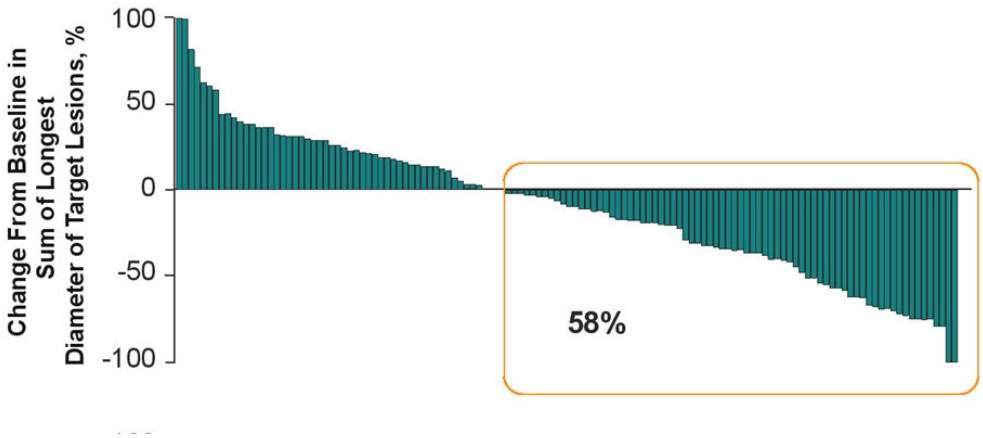
Using an anti-murine PD-1 analog antibody, PD-1 blockade has been shown to significantly inhibit tumor growth in a variety of syngeneic murine tumor models. In these experiments in mice, anti-PD-1 therapy is synergistic with chemotherapeutic agents such as gemcitabine and 5-fluorouracil (5-FU) and combination therapy results in increased complete tumor regression rates in vivo.[5]

The safety of MK-3475 was characterized in the 1-month repeat-dose toxicity study in cynomolgus monkeys when administered as intravenous (IV) doses of 6, 40 or 200 mg/kg once a week (a total of five doses) and in the 6-month repeat-dose toxicity study in the same specids when administered as IV doses of 6, 40 or 200 mg/kg every other week (a total of 12 doses). MK-3475 was well-tolerated with a systemic exposure (area under the curve (AUC)) of up to ~170,000 μg.day/mL over the course of the 1-month study, and with an AUC of up to approximately 67,500 μg.day/mL over the course of the 6-month study. No findings of toxicological significance were observed in either study and the No Observed Adverse Event Level (NOAEL) was ≥200 mg/kg. In addition, no

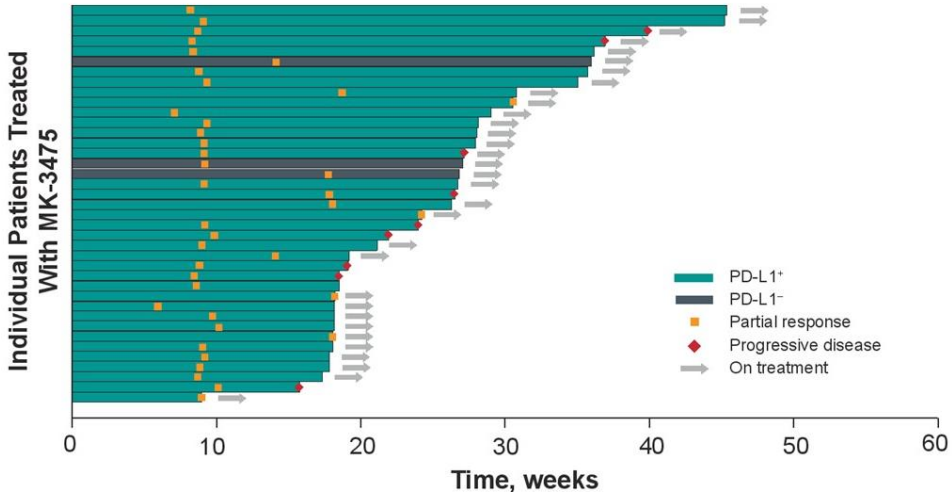
findings of toxicological relevance were observed in the in vitro tissue cross-reactivity study using human and cynomolgus monkey tissues.[5]

1.4 Clinical Efficacy of Pembrolizumab in human NSCLC

Pembrolizumab is very active against human NSCLC. For example, in a second line study using pembrolizumab as monotherapy, 58% of tumors had some reduction in size[25]:



Most of these responses occurred by 10 weeks and many were durable:

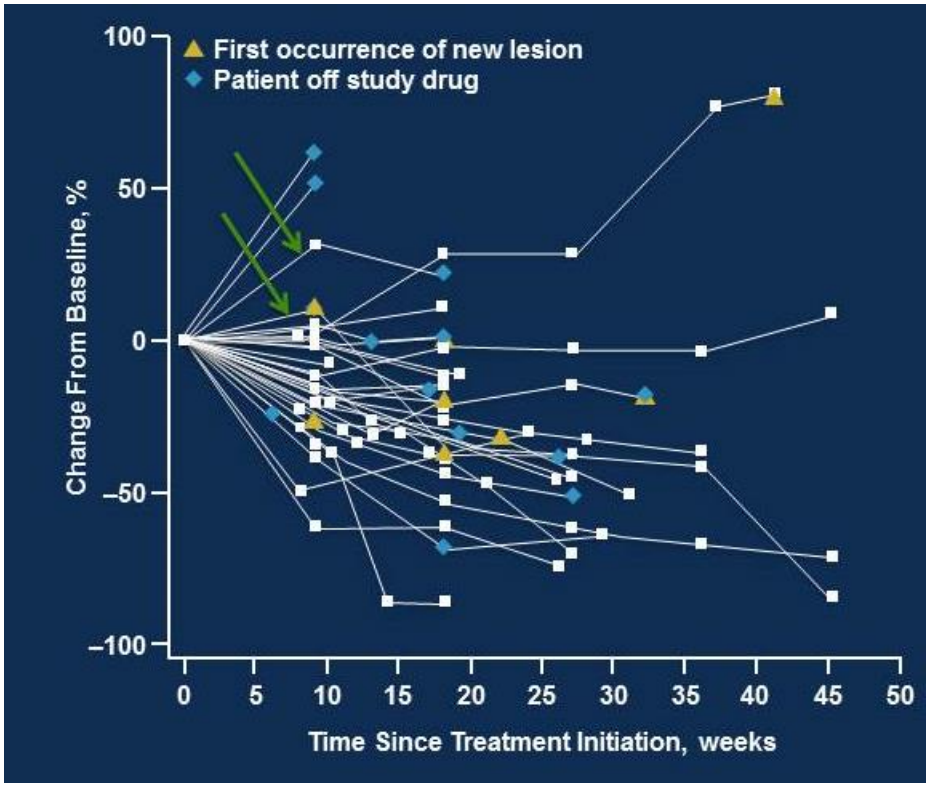


While pembrolizumab is very active, it is has very low toxicity. Overall toxicity in 119 patients treated in the study just referenced with a higher dose (10mg/kg Q3W) than that proposed in LCCC1516 (200mg fixed dose) was as follows:

Drug-Related Adverse Events with Incidence ≥ 5%[25]		
Adverse event %	**Any grade (%)**	**Grade 3-5 (%)**
Any	58	10
Fatigue	16	<1

Arthralgia	8	<1
Decreased appetite	8	0
Pruritis	8	0
Diarrhea	7	0
Nausea	4	0
Pyrexia	6	0
Rash	5	0
Hypothyroidism	3	0

In pretreated NSCLC patients, only 1/38 experienced a grade 3-5 event, pulmonary edema. Therefore, in addition to being very active, pembroliuzmab is far less toxic than the cytotoxic agents typically used for NSCLC. Pembrolizumab, along with other PD1 and PDL1 inhibitors, are however, associated with a novel problem: pseudo-progression:



[26]

In the above spider plot, the green arrows represent this phenomenon, where the cancer appears to grow, but later shrinks. The two dominant explanations are that immunotherapy takes time to work in some cancers and that immune infiltration causes inflammation and takes up space. Regardless, it creates a novel problem—a review of the spider plots of pembrolizumab, other anti-PD1 agents, and anti-PDL1 agents, both in NSCLC and in other cancers, reveals that the majority of apparent progression is, in fact, real progression. New strategies are needed to address this problem.

1.5 Nab-paclitaxel (Abraxane®)

The active cytotoxic agent in nanoalbumin bound paclitaxel (henceforth nab-paclitaxel) is paclitaxel, an antimicrotubule agent that promotes the assembly of microtubules from tubulin dimers and stabilizes microtubules by preventing depolymerization. Nab-paclitaxel delivers the paclitaxel bound to albumin and has several theoretic advantages over paclitaxel [27]. First, the cremophor solvent is not needed. Cremophor requires special glass or non-PVC infusion systems, premedication with histamine 1 and 2 blockers, causes infusion reactions and may contribute to peripheral neuropathy. As albumin facilitates the administration of water-insoluble compounds, effective active dose-delivery of albumin bound drugs may be higher than when drugs are administered without albumin. Infusion time with nab-paclitaxel is faster than with paclitaxel. Binding of the active drug to albumin may increase tumor-specificity, perhaps due to increased endothelial cell binding and transcytosis of the albumin-bound drug versus cremophor-based paclitaxel formulations.[28] Critically for this study, nab-paclitaxel, unlike paclitaxel and most other cytotoxic agents used in NSCLC, does not require steroid premedication.

Nab-paclitaxel showed improved response rates (RR) compared to standard paclitaxel when combined with carboplatin for the treatment of advanced NSCLC.[29] Response rate to standard carboplatin and paclitaxel was 25%; with carboplatin and nab-paclitaxel it was 33% (p=.005); most of this difference was driven by subjects with squamous histology (24% vs 41% RR). Although effective dose delivery was higher with nab-paclitaxel (82 mg/m^2/week) compared to standard paclitaxel (65 mg/m^2/week) the overall toxicity profile, with the exception of anemia and thrombocytopenia, favored nab-paclitaxel, (table below summarizes the most common grade 3 and 4 treatment related adverse events):

Toxicity	**Nab-paclitaxel (n=514) %**		**Paclitaxel (n=524) %**		**p value**
	Grade 3	Grade 4	Grade 3	Grade 4	
Sensory Neuropathy	3	0	11	<1	<0.001*
Myalgia	<1	0	2	0	0.011*
Arthralgia	0	0	2	0	0.008*
Neutropenia	33	14	32	26	<0.001*
Thrombocytopenia	13	5	7	2	<0.001†
Anemia	22	5	6	<1	0.001†
*P<0.05 in favor of nab-paclitaxel †P<0.05 in favor of paclitaxel					

1.6 Combination of Pembrolizumab plus Chemotherapy

Several phase I/II studies are ongoing evaluating the combination of pembrolizumab with chemotherapy, including a Merck-sponsored study combining pembrolizumab with either cisplatin and pemetrexed or carboplatin and paclitaxel in NSCLC (NCT01840579). A second Merck-sponsored phase I/II trial (NCT02039674) is ongoing in unresectable or metastatic NSCLC, and includes a number of arms combining fixed dose pembrolizumab with paclitaxel (200mg/m^2) and carboplatin every 3 weeks, each given on D1 of every 3 week cycle, with or without bevacizumab. A third multi-arm phase I/II trial in patients with metastatic solid tumors (NCT02331251) is ongoing. Arm 3 of this trial includes a fixed dose of pembrolizumab on D1combined with gemcitabine (1000mg/m^2 D1 and D8) and nab-paclitaxel 125mg/m2 (D1&D8) every 3 weeks.

Safety data is pending from these studies. However, the major toxicities of pembrolizumab including low grade nausea, anorexia, arthralgia, pruritis, diarrhea and rash should not overlap with the major toxicities of nab-paclitaxel as outlined above, and the mechanisms of action are distinct (meaning we expect no more than additive toxicity). Therefore, no serious safety issues are anticipated as a result of this combination given the low likelihood of overlapping toxicities. Any unexpected toxicities from the chemotherapy combination trials just summarized and sponsored by Merck will be shared with the PI of LCCC1516 and can be used to supplement toxicity monitoring if needed. In this trial, toxicity will be monitored continuously, with sequential boundaries employed to suspend the trial if excessive toxicity is seen. If the study reaches a stopping boundary, it may be terminated by the PI, or submitted to the DSMC with a description of the toxicities and a rationale for why the study should be continued.

1.7 Study Rationale

- Improve survival: The primary goal of the trial is to guarantee exposure to 2 additional active agents during first line therapy.
- Give patients a defined end to 1st line treatment: While patients value improvements in survival and are willing to be treated longer if they can live longer, many patients also want a defined end to 1st line therapy.
- Evaluate defined-duration checkpoint inhibitory therapy: Existing studies of PD1 and PDL1 inhibitors almost universally study therapy until intolerance or progression. It is possible that similar benefits can be achieved with defined-duration therapy.
- Explore the optimal sequencing of multiple consolidations: No statistical comparison is planned between the three initial arms, although it is possible that one sequence may result in a much greater difference compared to the common null hypothesis than the others. If pembrolizumab and nab-paclitaxel have synergistic activity, survival may be optimal with immediate concurrent consolidation with both agents. Further, survival may be optimal with this approach because it guarantees immediate exposure to both agents. On the other hand, toxicity (specifically ≥ Grade 2 treatment-related adverse events (AEs))

may be lower with serial administration of the consolidation agents; if such improved tolerance leads to greater feasibility, survival might be improved with sequential administration. Further, if the agents have any antagonism or if a longer duration of treatment is superior, then survival might be better with sequential administration. Results from this trial will also provide estimates that can be used to power a future confirmatory comparative study.

- Demonstrate potential additive or synergistic effects of chemotherapy and immunotherapy: While other planned studies combine chemotherapy and PD-1 inhibition, they suffer from the need to utilize steroids to protect against nausea and anaphylaxis from cytotoxic agents. Because nab-paclitaxel uniquely does not require steroids, it might decrease the risk of steroid-related depletion of activated tumor-specific T cells.

1.7.1 Rationale for Dose Selection of Pembrolizumab

An open-label Merck-sponsored Phase I trial (Protocol 001) evaluated 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 dose levels were well tolerated and no dose-limiting toxicities (DLTs) 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. No maximally tolerated dose (MTD) has been identified to date. Recent data from other clinical studies within the pembrolizumab program have shown that a lower dose of pembrolizumab and a less frequent schedule may be sufficient for target engagement and clinical activity.

Pharmacokinetic (PK) data analysis of pembrolizumab administered Q2W and Q3W showed slow systemic clearance, limited volume of distribution, and a long half-life. [5] Pharmacodynamic (PD) data (IL-2 release assay) suggested that peripheral target engagement is durable (>21 days). This early PK and PD data provides scientific rationale for testing a Q2W and Q3W dosing schedule.

A population PK analysis of pembrolizumab has been performed using serum concentration time data from 476 patients. Within the resulting population PK model, clearance and volume parameters of pembrolizumab were found to be dependent on body weight. The relationship between clearance and body weight, with an allometric exponent of 0.59, is within the range observed for other antibodies and supports both body weight normalized dosing or a fixed dose across all body weights (Merck, written communication).

The choice of the 200 mg every 3 weeks as an appropriate dose for the switch to fixed dosing of pembrolizumab (which is pending FDA approval, and which is incorporated into this study) is based on simulations performed using the population PK model of pembrolizumab showing that the fixed dose of 200 mg every 3 weeks will provide exposures that 1) are optimally consistent with those obtained with the 2 mg/kg dose every 3 weeks (the current FDA approved dose),

2) will maintain individual patient exposures in the exposure range established in melanoma as associated with maximal efficacy response and 3) will maintain individual patients exposure in the exposure range established in melanoma that are well tolerated and safe (Merck, written communication). The fixed dosing regimen will also reduce potential for dosing errors and reduce the complexity associated with weight-based dosing.

A fixed dose regimen will simplify the dosing regimen to be more convenient for physicians and to reduce potential for dosing errors. A fixed dosing scheme will also reduce complexity in the logistical chain at treatment facilities and reduce wastage.

1.8 Correlative Studies

Exploratory objectives based [redacted]

Additional details regarding correlative studies can be found in the laboratory manual.

2.0 STUDY OBJECTIVES

2.1 Primary Objective

Estimate OS after sequential consolidation with pembrolizumab followed by nab-paclitaxel (ARM A), sequential consolidation with nab-paclitaxel followed by pembrolizumab (ARM B) and concurrent consolidation with nab-paclitaxel and pembrolizumab (ARM C) after standard first-line induction chemotherapy in advanced NSCLC

2.2 Secondary Objectives

2.2.1 Estimate PFS in each ARM with pembrolizumab and nab-paclitaxel per RECIST1.1 and iRRC

2.2.2 Estimate overall rates of response via RECIST1.1 and iRRC within each ARM

2.2.3 Estimate rates of response via RECIST1.1 and iRRC (the latter if applicable) after each component of therapy in ARMS A and B

2.2.4 Characterize the toxicity profile of each ARM, both provider-defined and patient reported

2.2.5 Describe quality of life over the course of therapy

2.3 Exploratory Objectives

2.4 Endpoints:

2.4.1 Primary Endpoint

OS is defined as the time from D1 of treatment to death from any cause

2.4.2 Secondary Endpoints

- PFS will be defined as the time from D1 of treatment until death or progression.
- Rates of response will be reported in several ways in this study:
  - Via RECIST1.1
  - Via Adapted-iRR (see section 6.13.2 for details)
- Clinician assessed toxicity will be classified and graded according to the National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE, version 4.0)
- Patient assessed toxicity will be classified based on the Patient-Reported Outcome version of the CTCAE (PRO-CTCAE)
- QOL will be evaluated via the FACT-Lung

3.0 PATIENT ELIGIBILITY

3.1 Inclusion Criteria

Patients must meet all of the following inclusion criteria to participate in this study:

3.1.1 Be willing and able to provide written informed consent for the trial

3.1.2 Be ≥ 18 years of age on day of signing informed consent

3.1.3 ECOG Performance Status ≤ 1 (see section 11.3, Appendix C)

3.1.4 Histologically or cytologically confirmed stage IV (metastatic) NSCLC as defined by American Joint Committee on Cancer (AJCC). Recurrent but not metastatic disease is allowed if deemed incurable.

3.1.5 Has completed or scheduled to begin* 4-6 cycles of platinum-based induction chemotherapy that does not include a taxane

- Induction may contain, but is not required to contain bevacizumab, necitumumab or cetuximab. Induction with a platinum doublet plus another biologic agent will be allowed following review by the UNC PI that there is no additional risk to the subject.
- D1 of treatment on LCCC1516 must be 21-42 days from the last day of induction, consistent with timing of standard of care maintenance.

3.1.6 Documentation of target and non-target lesion(s) status per RECIST1.1 (see Section 6.13.1) post induction chemotherapy for patients with evaluable disease.

Note: Evaluable disease is not required for study entry (patients with CR or response sufficient to preclude measurable lesions are not excluded; such patients will be evaluated for PFS and OS, but not for response).

3.1.7 Demonstrate adequate organ function as defined in the table below. All screening labs should be performed within 14 days of treatment initiation.

System	Laboratory Value
Hematological	
Absolute neutrophil count (ANC)	≥1,500 /mcL
Platelets	≥100,000 / mcL
Hemoglobin	≥10 g/dL (acceptable to reach this via transfusion)
Renal	
Calculated creatinine clearance[a]	≥60 mL/min
Hepatic	

Serum total bilirubin	≤ 1.5 X ULN (≤ 3 X ULN if Gilbert's Syndrome) **OR** Direct bilirubin ≤ ULN for subjects with total bilirubin levels > 1.5 ULN
AST (SGOT) and ALT (SGPT)	≤ 2.5 X ULN
Coagulation	
International Normalized Ratio (INR) or Prothrombin Time (PT) Activated Partial Thromboplastin Time (aPTT)	≤1.5 X ULN unless subject is receiving anticoagulant therapy as long as PT or PTT is within therapeutic range of intended use of anticoagulants
[a]Creatinine clearance should be calculated per institutional standard; see section 11.1 Appendix A for Cockcroft-Gault formula.	

3.1.8 Recovered from all reversible toxicities related to their previous treatment (other than alopecia) to ≤grade 1 or baseline.

3.1.9 Patients with brain metastases may participate if they have undergone appropriate treatment for the lesion(s), are at least two weeks post treatment without evidence for post-treatment progression, have no significant neurologic symptoms, and no longer require steroids for the reason of brain metastases.

3.1.10 Female subject of childbearing potential should have a negative urine or serum pregnancy within 72 hours prior to receiving the first dose of study medication. If the urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required.

3.1.11 Female subjects of childbearing potential must be willing to use adequate method of contraception as outlined in Section 5.1.2 – Contraception, for the course of the study through 120 days after the last dose of study medication.

Note: Abstinence is acceptable if this is the usual lifestyle and preferred contraception for the subject.

3.1.12 Male subjects must agree to use an adequate method of contraception as outlined in Section 5.1.2 - Contraception starting with the first dose of study therapy through 120 days after the last dose of study therapy.

3.1.13 **Note: Abstinence is acceptable if this is the usual lifestyle and preferred contraception for the subject.** As determined by the enrolling physician or protocol designee, ability of the patient to understand and comply with study procedures for the entire length of the study

3.2 Exclusion Criteria

Patients meeting any of the following exclusion criteria will not be able to participate in this study:

3.2.1 Patients with *EGFR* mutations expected to be sensitive to EGFR inhibitors and patients with *EML4/ALK* translocations are excluded, unless all available FDA-approved targeted therapy options have been utilized. For example, a patient with exon 19 *EGFR* mutation who has never been treated with an EGFR inhibitor would be excluded. Patients with other sensitizing mutations that become actionable with FDA-approved targeted therapies during the course of this trial (e.g., crizotinib for *MET* deletion 14) will also be expected to have utilized all available FDA-approved targeted therapy options prior to eligibility.

Note: In contrast to the above, a patient with an *EGFR* mutation who has been treated with a first-generation and third generation TKIs and then with four cycles of carboplatin plus pemetrexed would be eligible.

3.2.2 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.

3.2.3 Has a diagnosis of immunodeficiency or is receiving systemic steroid therapy or any other form of immunosuppressive therapy within 7 days prior to the first dose of trial treatment.

3.2.4 Has had prior chemotherapy, targeted small molecule therapy, or radiation therapy within 2 weeks prior to study Day 1. Note: If subject received major surgery, they must have recovered adequately from the toxicity and/or complications from the intervention prior to starting therapy.

3.2.5 Has had a prior monoclonal antibody within 4 weeks prior to study Day 1 or who has not recovered (i.e., ≤ Grade 1 or at baseline and other than alopecia) from adverse events due to agents administered more than 4 weeks earlier. Exceptions to these criteria may be allowed at the discretion of the UNC PI for toxicities that are not expected to be exacerbated by pembrolizumab or nab-paclitaxel.

3.2.6 Has a known additional malignancy that is progressing or requires active treatment. Exceptions include basal cell carcinoma of the skin, squamous cell carcinoma of the skin, or in situ cervical cancer that has undergone potentially curative therapy.

3.2.7 Has an active automimmune disease requiring systemic treatment within the past 3 months or a documented history of clinically severe autoimmune disease, or a syndrome that requires systemic steroids or immunosuppressive agents; subjects with vitiligo or resolved childhood asthma/atopy would be an exception to this rule. Subjects that require intermittent use of bronchodilators or local steroid injections would not be excluded from the study. Subjects with hypothyroidism

stable on hormone replacement or Sjorgen's syndrome will not be excluded from the study.

3.2.8 Has a history of non-infectious pneumonitis that required steroids or evidence of interstitial lung disease or current active, non-infectious pneumonitis.

3.2.9 Has an active infection requiring systemic therapy.

3.2.10 Has a history or current evidence of any condition, therapy, or laboratory abnormality that might confound the results of the trial, interfere with the subject's participation for the full duration of the trial, or is not in the best interest of the subject to participate, in the opinion of the treating investigator.

3.2.11 Has known psychiatric or substance abuse disorders that would interfere with cooperation with the requirements of the trial

3.2.12 Had inadequate home environment or social support to safely complete the trial procedures.

3.2.13 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 trial treatment.

3.2.14 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)

3.2.15 Known hypersensitivity to protein bound paclitaxel

3.2.16 Has received prior therapy with any taxane chemotherapy

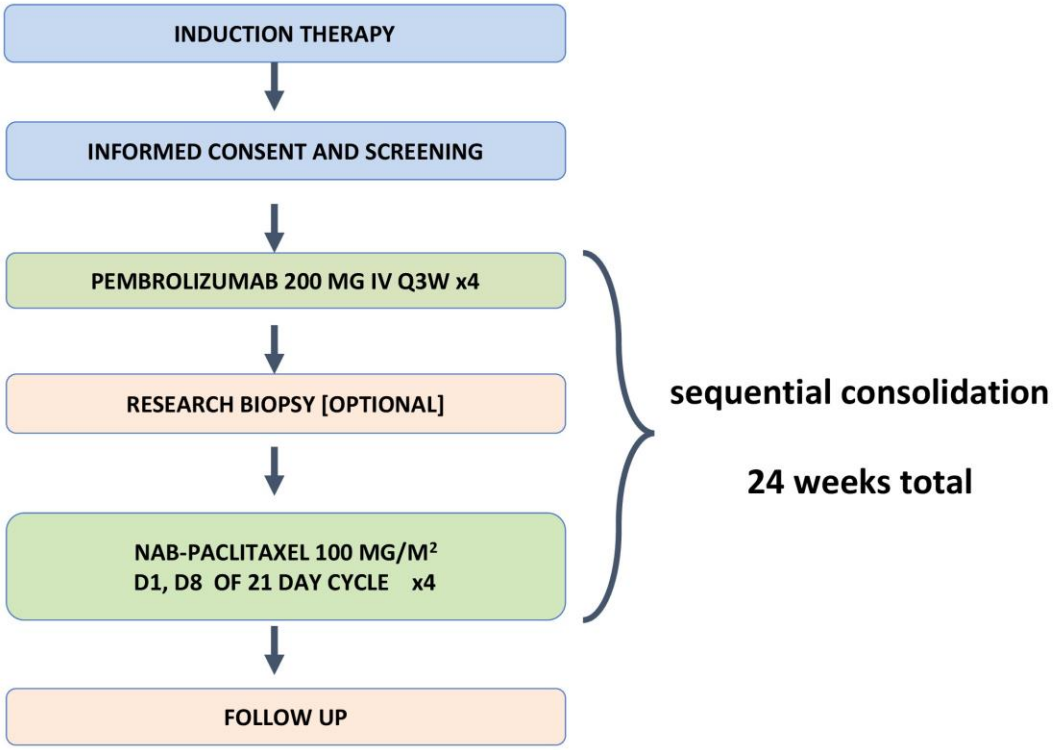
3.2.17 Has a known history of Human Immunodeficiency Virus (HIV) (HIV 1/2 antibodies).

3.2.18 Has known active Hepatitis B (e.g., HBsAg reactive) or Hepatitis C (e.g., HCV RNA [qualitative] is detected).

3.2.19 Has received a live vaccine within 30 days prior to the first dose of trial treatment

4.0 TREATMENT PLAN

4.1 Study Schema



*D1 of treatment on LCCC1516 must be 21-42 days from the last day of induction, consistent with timing of standard care maintenance.
**See section 4.3 of the protocol.

4.2 Treatment Summary by Arm

D1 of treatment on LCCC1516 must be at least 21 and not more than 42 days from the last day of induction, consistent with timing of standard of care maintenance (see inclusion criteria 3.1.5).

Patients will receive 4 x 3-week cycles of pembrolizumab monotherapy. Once this monotherapy is complete, or at the time of progressive disease (PD), whichever occurs first, patients will then receive 4 x 3-week cycles of nab-paclitaxel monotherapy. Patients who have been randomized to **ARM B** will receive the same regimen but in reverse, with nab-paclitaxel monotherapy followed by pembrolizumab. Both **ARMS A** and **B** will receive a total of 24 weeks of therapy. Patients randomized to **ARM C** will receive concomitant nab-paclitaxel plus pembrolizumab for 4x 3 week cycles for a total of 12 weeks of therapy.

4.3 Treatment Decisions Regarding Progressive Disease by ARM

At each imaging time-point throughout the study (see Section 6.0) both RECIST1.1 and adapted irRC will be applied. However, use of these criteria to make treatment decisions based on presence or absence of PD will vary by ARM as outlined below.

4.3.1 ARM A

During the first consolidation with pembrolizumab monotherapy progression will be assessed via an adapted irRC (see section 6.13.2) after cycle 4. All patients will be scanned prior to cycle 3 (after cycle 2), however in patients without symptoms of progression, this data will be used principally for spider-plots and hypothesis generation. If symptoms of progression are evident and accompanied by a rapid decline in ECOG PS, or that in the opinion of the investigator otherwise endangers the patient, it will be acceptable to discontinue pembrolizumab and immediately initiate nab-paclitaxel. During the second consolidation with nab-paclitaxel monotherapy, PD will be based on RECIST1.1 (see section 6.13.1). If progression is noted during the second consolidation, the patient will discontinue protocol mandated therapy, and be followed-up per protocol.

4.3.2 ARM B

During the first consolidation with nab-paclitaxel monotherapy, progression will be based on RECIST1.1 (see section 6.13.1). If there is evidence of progression prior to completion of 4 cycles of Consolidation One, the patient will discontinue Consolidation One early and begin Consolidation Two. During the second consolidation with pembrolizumab monotherapy, treatment decisions will be based on adapted irRC (see section 6.13.2). All patients will be scanned prior to cycle 3 of pembrolizumab (after cycle 2), however in patients without symptoms of progression, this data will be used principally for spider-plots and hypothesis generation. If symptoms of progression are evident and accompanied by a rapid decline in ECOG PS, or that in the opinion of the investigator otherwise endangers the patient, it will be acceptable to discontinue protocol mandated therapy, and follow up patient per protocol.

4.3.3 ARM C

During treatment, PD will be based on RECIST1.1 (see section 6.13.1). In the case of PD, the patient will discontinue protocol mandated therapy, and be followed-up per protocol.

4.4 Details on each Drug for ARMS A-C

In addition to the information provided below, also refer to Section 5, to the respective prescribing information for each agent (http://www.accessdata.fda.gov/scripts/cder/drugsatfda/, and to the Investigator's Brochure for pembrolizumab [5].

4.4.1 Pembrolizumab Dosing Administration for Pembrolizumab Cycles

Pembrolizumab 200 mg will be administered as a 30 minute IV infusion on D1 of each cycle it is scheduled for (see Schema). 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 -5 minutes and +10 minutes is permitted (i.e., infusion time is 30 minutes: -5 min/+10 min). The Pharmacy Manual contains specific instructions for the preparation of the pembrolizumab infusion fluid and administration of infusion solution. This manual is provided as a document separate from the protocol.

NOTE: Subjects should be assessed for possible Events of Clinical Interest (ECI: see the document provided separate from this protocol) prior to each dose. Lab results should be evaluated and subjects should be asked for signs and symptoms suggestive of an immune-related event. Subjects who develop an ECI thought to be immune-related should have additional testing to rule out other etiologic causes. If lab results or symptoms indicate a possible immune-related ECI, then additional testing should be performed to rule out other etiologic causes. If no other cause is found, then it is assumed to be immune-related.

4.4.2 Management of Pembrolizumab Infusion Reactions

Signs and symptoms usually develop during or shortly after drug infusion and generally resolve completely within 24 hours of completion of infusion. Refer to the table below for infusion reaction treatment guidelines associated with administration of pembrolizumab.

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 and monitor symptoms.** 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	Subject may be premedicated 1.5h (± 30 minutes) prior to infusion of pembrolizumab with: Diphenhydramine 50 mg po (or equivalent dose of antihistamine). Acetaminophen 500-1000 mg po (or equivalent dose of antipyretic).

NCI CTCAE Grade	Treatment	Premedication at subsequent dosing
	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.**	
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
Appropriate resuscitation equipment should be available in the room and a physician readily available during the period of drug administration.		

4.4.3 Other Dose Modifications for Pembrolizumab

Adverse events (both non-serious and serious) associated with pembrolizumab exposure may represent an immunologic etiology. These adverse events may occur shortly after the first dose or several months after the last dose of treatment. Pembrolizumab must be withheld for drug-related toxicities and severe or life-threatening AEs as per Table below. See section 4.4.4 for supportive care guidelines, including use of corticosteroids.

Dosing interruptions are permitted in the case of medical / surgical events or logistical reasons not related to study therapy (e.g., elective surgery, unrelated medical events, patient vacation, and/or holidays). Subjects should be placed back on study therapy within 3 weeks of the scheduled interruption, unless otherwise

discussed with the Sponsor. The reason for interruption should be documented in the patient's study record.

If a dose of pembrolizumab is delayed, then the subsequent dose should be administered 3 weeks later. Discontinuation of pembrolizumab for toxicity does not mandate discontinuation of nab-paclitaxel (in concurrent arm (**ARM C**, subjects may continue on nab-paclitaxel alone; in the pembrolizumab first sequential arm (**ARM A**), subjects may proceed to nab-paclitaxel immediately or once toxicity is sufficiently resolved).

Hematological Toxicity Dose Delays or Discontinuation for Pembrolizumab

Toxicity	**Hold Treatment For Grade**	**Timing for Restarting Pembrolizumab***	**Discontinue Subject****
Autoimmune hemolytic anemia, aplastic anemia, disseminated intravascular coagulation, Hemolytic Uremic Syndrome (HUS-Idiopathic or immune), Thrombocytopenia Purpura (ITP), Thrombotic Thrombocytopenic Purpura (TTP) or Any Grade 4 anemia regardless of underlying mechanism	2-3	Toxicity resolves to Grade 0-1.	Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks.
	4	Permanently discontinue**	Permanently discontinue**

**Whenever pembrolizumab is permanently discontinued, patient should still r be followed-up per protocol.

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 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks
	4	Permanently discontinue	Permanently discontinue
AST, ALT, or Increased Bilirubin	2	Toxicity resolves to Grade 0-1	Toxicity does not resolve within 12 weeks of last dose
	3-4	Permanently discontinue (see exception below)[a]	Permanently discontinue
Type 1 diabetes mellitus (if new onset) or Hyperglycemia	T1DM or 3-4	old pembrolizumab for new onset Type 1 diabetes mellitus or Grade 3-4 hyperglycemia associated with evidence of beta cell failure	Resume pembrolizumab when patients 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 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks
Hyperthyroidism	3	Toxicity resolves to Grade 0-1	Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks
	4	Permanently discontinue	Permanently discontinue
Hypothyroidism	2	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	2[b]	Toxicity resolves to Grade 0-1	Permanently discontinue if toxicity develops despite adequate premedication
	3-4	Permanently discontinue	Permanently discontinue
Pneumonitis	2	Toxicity resolves to Grade 0-1	Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks
	3-4	Permanently discontinue	Permanently discontinue
Renal Failure or Nephritis	2	Toxicity resolves to Grade 0-1	Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks
	3-4	Permanently discontinue	Permanently discontinue
All Other Drug-Related Toxicity[c]	3 or Severe	Toxicity resolves to Grade 0-1	Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 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.

[1a] For patients 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 patients should be discontinued.

[2b] 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; Refer to **Error! Reference source not found.** – Infusion Treatment Guidelines for further management details.

[c] Patients 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 12 weeks of the last dose.

4.4.4 Rescue Medications & Supportive Care for Pembrolizumab Cycles

Supportive Care Guidelines

Subjects should receive appropriate supportive care measures as deemed necessary by the treating investigator. Suggested supportive care measures for the management of adverse events with potential immunologic etiology are outlined below Where appropriate, these guidelines include the use of oral or intravenous treatment with corticosteroids as well as additional anti-inflammatory agents if symptoms do not improve with administration of corticosteroids. Note that several courses of steroid tapering may be necessary as symptoms may worsen when the steroid dose is decreased. For each disorder, attempts should be made to rule out other causes such as metastatic disease or bacterial or viral infection, which might require additional supportive care. The treatment guidelines are intended to be applied when the investigator determines the events to be related to pembrolizumab.

Note: if after the evaluation the event is determined not to be related, the investigator does not need to follow the treatment guidance as outlined below. Refer to Section 4.4.3 for dose modification.

It may be necessary to perform conditional procedures such as bronchoscopy, endoscopy, or skin photography as part of evaluation of the event.

Hematologic (see table in Section 4.4.3)
All attempts should be made to rule out other causes such as metastases, sepsis and/or infection. Relevant diagnostic studies such as peripheral blood smear, reticulocyte count, LDH, haptoglobin, bone marrow biopsy or Coomb's test, etc., should be considered to confirm the diagnosis.

For Grade 2 events:

- Hold pembrolizumab
- Prednisone 1-2 mg/kg daily may be indicated
- Consider Hematology consultation
- Permanently discontinue for inability to reduce corticosteroid dose to 10 mg or less of prednisone or equivalent per day within 12 weeks.

Grade 3 events:

- Hematology consultation
- Hold pembrolizumab
- Discontinuation should be considered at discretion of investigator
- Treat with methylprednisolone 125 mg iv or prednisone 1-2 mg/kg p.o. (or equivalent) as appropriate
- Permanently discontinue for inability to reduce corticosteroid dose to 10 mg or less of prednisone or equivalent per day within 12 weeks.

Grade 4 events:

- Hematology consultation
- Discontinue pembrolizumab
- Treat with methylprednisolone 125 mg iv or prednisone 1-2 mg/kg p.o. (or equivalent) as appropriate

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.

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,** administer oral corticosteroids.
- For **Grade 3 or 4 diarrhea/colitis,** 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.

Type 1 diabetes mellitus (TIDM) (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 TIDM and for Grade 3-4 hyperglycemia associated with metabolic acidosis or ketonuria.
- Evaluate patients with serum glucose and a metabolic panel, urine ketones, glycosylated hemoglobin, and C-peptide.

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.

Hyperthyroidism or Hypothyroidism:
Thyroid disorders can occur at any time during treatment; monitor patients 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.

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- **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.

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.

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.

Steven's Johnson Syndrome (SJS) and Toxic Epidermal Necrolysis (TEN)

- For signs and symptoms of SJS or TEN, withhold pembrolizumab and refer the patient for specialized care for assessment and treatment
- If SJS or TEN is confirmed, permanently discontinue pembrolizumab

Immune-mediated myocarditis management

- For suspected immune-mediated myocarditis, ensure adequate evaluation to exclude other etiologies and administer corticosteroids as appropriate

Infusion Reaction

See section 4.4.2

4.4.5 Nab-paclitaxel Premedication

Patients do not require premedication prior to nab-paclitaxel administration, as hypersensitivity reactions are rare.

Administration of solvent-based taxanes (Taxol® and Taxotere®) requires premedication with corticosteroids and histamine receptor blocking agents to prevent the occurrence of hypersensitivity reactions. The solubilizing agents Cremophor® EL and Tween® 80 have long been implicated in adverse events including hypersensitivity reactions due to their detergent-like nature and known ability to induce histamine release. [30] However, the hypersensitizing role of the taxane molecules themselves cannot be ruled out.

In the unlikely event of a mild hypersensitivity reaction, premedication may be administered using the premedication regimen the institution typically uses for solvent based paclitaxel.

In the event of a severe hypersensitivity reaction, discontinue nab-paclitaxel (see section 4.4.8).

4.4.6 Nab-paclitaxel Dosing Administration for Pembrolizumab Cycles

Nab-paclitaxel 100mg/m^2 will be infused over 30 minutes when prescribed by arm (see schema or time and events table). Actual body weight will be used for the dose calculation. It is not a requirement to use in-line filters during the administration of nab-paclitaxel. In any event, filters of pore-size less than 15 micrometers must not be used. If patient body weight changes by >10%,

recalculate the body surface area and dose of nab-paclitaxel. Note: Dose changes will apply for the next cycle; doses will not be changed mid- cycle. Following administration, the intravenous line should be flushed with Sodium Chloride 0.9% solution for injection to ensure administration of the complete dose, according to local practices.

4.4.7 Supportive Care Guidelines for Nab-Paclitaxel

Subjects should receive full supportive care during the study, including transfusion of blood and blood products, and treatment with antibiotics, antiemetics, and analgesics, as appropriate.

Anti-emetic Medications

The recommended regimen will include ondansetron 16 mg by oral, or 8 mg by IV route, or an alternative 5HT-3 antagonist. Aprepitant and dexamethasone use are not recommended as nab-paclitaxel is not sufficiently emetogenic as to require aprepitant and without Cremophor, dexamethasone is not required to prevent infusion reactions. While not recommended, aprepitant is not prohibited--clinicians may adjust the antiemetic regimen as needed for individual patients. Dexamethasone is not allowed in any study arm.

Hematopoietic Growth Factors

Use of erythropoiesis- stimulating agents (ESAs) will not be allowed on this study in the concurrent arm. In **ARMs A and B**, they will be allowed only during nab-paclitaxel monotherapy. If the clinician elects to utilize ESAs, they must be used within FDA-approved guidelines. The use of peg-filgrastim is not allowed in this study.

When filgrastim is used, administer filgrastim 5 mcg/kg/day (rounded to the nearest vial size per investigator/institution's standard of care). The number of days of filgrastim is up to the discretion of the treating MD; however, it is recommended that the patient must start at least 24 hours after the dose of nab-paclitaxel and be held at least 48 hours prior to the next dose. The dose of filgrastim can be adjusted based on the investigator's discretion.

4.4.8 Toxicities and Dosing Delays/Dose Modifications for Nab-Paclitaxel

See section **Error! Reference source not found.** for more detailed information on nab-paclitaxel. Also refer to the Full Prescribing Information for nab-paclitaxel for complete safety information: http://www.accessdata.fda.gov/scripts/cder/drugsatfda/. If more than 2 dose reductions of nab-paclitaxel are required, nab-paclitaxel is to be discontinued. Once a patient's dose has been reduced, the dose reduction will be permanent. Dose re-escalation will not be permitted. Discontinuation of nab-paclitaxel for toxicity does not mandate discontinuation of pembrolizumab (in concurrent arm (ARM C); patients may continue on pembrolizumab alone; in nab-paclitaxel first sequential arm (ARM B), the patient may proceed to pembrolizumab immediately or once toxicity is sufficiently resolved).

For AEs that require dose reductions of nab-paclitaxel, please refer to the dose levels below:

Dose Level	**Nab-paclitaxel dose (mg/m^2)**
0 (starting dose)	100
-1	75
-2	50
-3	0

Hypersensitivity Reactions

Hypersensitivity reactions to nab-paclitaxel rarely occur. If they do occur, minor symptoms such as flushing, skin reactions, dyspnea, lower back pain, hypotension, or tachycardia may require temporary interruption of the infusion. However, severe reactions, such as hypotension requiring treatment, dyspnea requiring bronchodilators, angioedema or generalized urticaria require immediate discontinuation of nab-paclitaxel administration and aggressive symptomatic therapy. Patients who experience a severe hypersensitivity reaction to nab-paclitaxel should not be re-challenged.

Dose Delays and Dose Modifications for nab-paclitaxel		
Hematological Toxicity	**Toxicity grade**	**Dose Level for Subsequent Administration**
Neutropenia or Febrile neutropenia If ANC <1,000/mm^3, hold treatment Resume per table once ANC ≥1,000/mm^3	Grade 2 (ANC <1,500/mm^3 to 1,000/mm^3)	Maintain dose; Consider G-CSF [1]
	Grade 3 (ANC < 1,000/mm^3)	□ 1 dose level and strongly consider G-CSF [1]
	Febrile neutropenia	□ 1 dose level and administer G-CSF[1]
Thrombocytopenia **Day 1**: If platelets <100,000/mm^3 hold treatment. Initiate cycle once platelets ≥100,000/mm^3 **Days 8**: If platelets <75,000/mm^3 hold treatment. Resume per table once platelets ≥75,000/mm^3	Grade 1 (<LLN to 75,000/mm^3)	Maintain dose. If recurrent or early in treatment, □1 dose level
	Grade 2 (<75,000/mm^3 to 50,000/mm^3)	□1 dose level (when treatment resumes)
	Grade 3 (<50,000/mm^3 to 25,000/mm^3)	□2 dose levels (when treatment resumes)
Anemia If Hgb<8 g/dL, transfuse PRBCs. Once Hgb is ≥ 8 g/dL, therapy may resume.	≥Grade 3 (Hgb <8 g/dL)	For Hgb <8 g/dL, consider □1 dose level (when treatment resumes)
Non-hematological Toxicity		
Sensory neuropathy If ≥ grade 3, hold treatment. Resume per table once ≤grade 1	Grade 1	Maintain dose
	Grade 2	□1 dose level
	Grade 3 - 4	□2 dose levels (when treatment resumes)
Hyperbilirubinemia If bilirubin >2mg/dL, hold treatment. . Resume per table once bilirubin ≤2mg/dL	Bili >2 mg/dL	□1 dose level (when treatment resumes)
	Bili >3 mg/dL	□2 dose levels (when treatment resumes)
Transaminase elevation (ALT or AST) If ≥ Grade 2 (>3 x ULN) hold treatments. Resume per table once	Grade 1 (>ULN – 3x ULN)	Maintain dose
	Grade 2 (>3 – 5 x ULN)	□1 dose level (when treatment resumes)

transaminases ≤ 3 x ULN	≥Grade 3 (>5 x ULN)	□2 dose levels (when treatment resumes)
Renal toxicity If serum Cr >2 mg/dL, hold treatment. Resume per table once serum Cr<2 mg/dL	≤Grade 2 (≤ 3 x ULN)	Maintain dose
	≥Grade 3 (>3 x ULN)	□1 dose level (when treatment resumes)
Other non-specified[2] Hold treatment until toxicity resolves to ≤Grade 1. Resume treatment with dose adjusted per table.	≥ Grade 3	□1 dose level (when treatment resumes)
[1] If G-CSF (filgrastim) is given concurrently with nab-paclitaxel, administration may begin 24 hours after nab-paclitaxel is given and should stop at least 48 hours prior to when *nab*-paclitaxel is given the following week. The dose is 5mcg/kg/day rounded to the nearest vial size per investigator/institution's standard of care. See section Note: peg-filgrastim is not permitted during the study. Note that filgrastim may only be used during single-agent nab-paclitaxel therapy; it is not to be used concurrently with pembrolizumab. [2]Excludes alopecia and non-refractory nausea/vomiting		

4.5 Concomitant Medications/ Vaccinations (allowed & prohibited)

Medications or vaccinations specifically prohibited in the exclusion criteria are not allowed during the ongoing trial. If there is a clinical indication for one of these or other medications or vaccinations specifically prohibited during the trial, discontinuation from trial therapy or vaccination may be required. The investigator should discuss any questions regarding this with the Merck Clinical team. The final decision on any supportive therapy or vaccination rests with the investigator and/or the subject's primary physician. No drug interactions studies have been conducted with nab-paclitaxel, a drug metabolized by CYP2C8 and CYP3A4. Caution should be used when administering nab-paclitaxel with medications known to inhibit or induce either CYP2C8 or CYP3A4.

4.5.1 Acceptable Concomitant Medications

All treatments that the investigator considers necessary for a subject's welfare may be administered at the discretion of the investigator in keeping with the community standards of medical care. All concomitant medication will be recorded on the case report form (CRF) including all prescription, over-the-counter (OTC), herbal supplements, and IV medications and fluids. If changes occur during the trial period, documentation of drug dosage, frequency, route, and date may also be included on the CRF.

4.5.2 Prohibited Concomitant Medications

Subjects are prohibited from receiving the following therapies during the Screening and Treatment Phase

- Anti-cancer systemic chemotherapy or biological therapy

- Immunotherapy not specified in this protocol
- Chemotherapy not specified in this protocol
- Investigational agents other than pembrolizumab
- Live vaccines within 30 days prior to the first dose of trial treatment and while participating in the trial. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, chicken pox, yellow fever, rabies, BCG, and typhoid (oral) vaccine. Seasonal influenza vaccines for injection are generally killed virus vaccines and are allowed; however intranasal influenza vaccines (e.g. Flu-Mist®) are live attenuated vaccines, and are not allowed.
- Systemic glucocorticoids for any purpose other than to modulate symptoms from an event of clinical interest of suspected immunologic etiology. The use of physiologic doses of corticosteroids may be approved after consultation with the Sponsor.

- Radiation therapy
    - Note: Radiation therapy to a symptomatic solitary lesion or to the brain may be allowed at the investigator's discretion.

- <u>Hematopoietic Growth Factors:</u> Use of erythropoiesis- stimulating agents (ESAs) will not be allowed on this study in the concurrent arm (ARM C). In the sequential arms (ARMs A and B), they will be allowed only during nab-paclitaxel monotherapy. If the clinician elects to utilize ESAs, they must be used within FDA-approved guidelines. The use of peg-filgrastim is not allowed in this study. Filgrastim administration is allowed with single-agent nab-paclitaxel but not with pembrolizumab (see section 4.4.8).

Subjects who, in the assessment by the investigator, require the use of any of the aforementioned treatments for clinical management should be removed from the trial. Subjects may receive other medications that the investigator deems to be medically necessary

4.6 Duration of Therapy

In the absence of treatment delays due to AEs, treatment may continue until the end of study-defined treatment or until:

- Inter-current illness that prevents further administration of treatment
- Unacceptable toxicity
- Pregnancy
- Patient decides to withdraw from study treatment, **OR**
- General or specific changes in the patient's condition render the patient unacceptable for further treatment in the judgment of the investigator.

4.7 Duration of Follow-Up

After two years of follow-up as described in the time and events table, subsequent follow-up will be per standard of care and the study will follow only for progression and for survival for up to 3 additional years, for a total of 5 years of follow-up after study completion.

4.8 Removal of Patients from Protocol Therapy

Patients will be removed from protocol therapy and the PI notified when any of the criteria listed in section 4.6 apply. The reason for discontinuation of protocol therapy will be documented on the electronic case report form (eCRF).

In case a patient decides to prematurely discontinue protocol therapy ("refuses treatment"), the patient should be asked if she or he may still be contacted for further scheduled study assessments. The outcome of that discussion should be documented in both the medical records and in the eCRF.

4.9 Study Withdrawal

Patients will be removed from protocol therapy and the PI notified when any of the criteria listed in section 4.7 apply. The reason for discontinuation of protocol therapy will be documented on the eCRF.

If a patient decides to withdraw from the study (and not just from protocol therapy) an effort should be made to complete and report study assessments as thoroughly as possible. At the time of withdrawal, the investigator should attempt to establish as completely as possible the reason for the study withdrawal.

- The patient should be asked if they are willing to allow for the abstraction of relevant information from their medical record in order to meet the long term follow up (e.g., survival) objectives outlined in the protocol.
- A complete final evaluation at the time of the patient's study withdrawal should be obtained with an explanation of why the patient is withdrawing from the study.
- If the patient is noncompliant and does not return for an end of study follow up assessment, this should be documented in the eCRF.
- If the reason for removal of a patient from the study is an adverse event, the principal specific event will be recorded on the eCRF.

Excessive patient withdrawals from protocol therapy or from the study can render the study un-interpretable; therefore, unnecessary withdrawal of patients should be avoided.

5.0 DRUG INFORMATION

5.1 Pembrolizumab

Product description:
Pembrolizumab is a humanized monoclonal antibody that blocks the interaction between PD-1 and its ligands, PD-L1 and PD-L2. Pembrolizumab is an IgG4 kappa immunoglobulin with an approximate molecular weight of 149 kDa.

Mechanism of action:
Binding of the PD-1 ligands, PD-L1 and PD-L2, to the PD-1 receptor found on T cells, inhibits T-cell proliferation and cytokine production. Upregulation of PD-1 ligands occurs in some tumors. Signaling through this pathway can contribute to inhibition of active T-cell immune surveillance of tumors. Pembrolizumab is a monoclonal antibody that binds to the PD-1 receptor and blocks its interaction with PD-L1 and PD-L2, releasing PD-1 pathway-mediated inhibition of the immune response, including antitumor immune response. In syngeneic mouse tumor models, blocking PD-1 activity resulted in decreased tumor growth.

Supplier/How Supplied:
Pembrolizumab will be provided at no cost to the study patient by Merck, the manufacturer of the drug. Clinical supplies will be affixed with a clinical label in accordance with regulatory requirements.

This trial is open-label; therefore, the subject, the trial site personnel, the Sponsor 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.

Pembrolizumab is supplied as single-use 100 mg vials containing a sterile, non-pyrogenic, clear to opalescent aqueous solution (25 mg/mL), or as single-use 50 mg vials containing lyophilized powder in a single-dose vial for reconstitution). Pembrolizumab solution for infusion is formulated in 10mM histidine buffer, pH 5.2-5.8, containing 7% sucrose and 0.02% polysorbate 80, supplied in Type I glass vials with a cap color of red, salmon, or blue.

Preparation:
Pembrolizumab solution for infusion must be diluted prior to administration per institutional guidelines. Allow the required number of vials to equilibrate to room temperature. Do not shake the vials. Do not use if opaque or extraneous particulate matter other than translucent to white proteinaceous particles is observed. Do not use if discolored. To prepare the infusion solution add the dose volume of pembrolizumab to an infusion bag containing 0.9% Sodium Chloride Injection, USP or 5% Dextrose Injection, USP. Gently invert the bag 10-15 times

to mix the solution. The final concentration must be between 1 mg/mL to 10 mg/mL.
Compatible IV bag materials: PVC plasticized with DEHP, non-PVC (polyolefin), EVA, or PE lined polyolefin

Storage and Handling:
Store pembrolizumab under refrigeration at 2°C to 8°C (36°F to 46°F) in the original carton to protect from light. Do not freeze. Do not shake.

Clinical supplies must be stored in a secure, limited-access location under the storage conditions specified on the label.

Receipt and dispensing of trial medication must be recorded by an authorized person at the trial site.

Clinical supplies may not be used for any purpose other than that stated in the protocol.

Stability:
Administer prepared solutions immediately after preparation. If not administered immediately, prepared solutions may be stored refrigerated for up to 24 hours. Pembrolizumab solutions may be stored at room temperature for a cumulative time of up to 6 hours. This includes room temperature storage of liquid drug product solution in vials, room temperature storage of infusion solution in the IV bag, and the duration of infusion.

Dose and route of administration:
The recommended dose of pembrolizumab is 200 mg administered as an IV infusion over approximately 30 minutes (range: 25 - 40 minutes) every 3 weeks until disease progression or unacceptable toxicity. Pembrolizumab should be administered using an infusion set containing a low-protein binding 0.2 to 5 μm in-line filter made of polyethersulfone or polysulfone. Infusion rate should not exceed 6.7 mL/min. A central line is not required; however if a subject has a central venous catheter in place, it is recommended that it be used for the infusion. Do not co-administer other drugs through the same infusion line. Following the infusion, flush the IV line with normal saline.

Return and Retention
The investigator is responsible for keeping accurate records of the clinical supplies received from Merck or designee, the amount dispensed to and returned by the subjects and the amount remaining at the conclusion of the trial.

Upon completion or termination of the study, all unused and/or partially used investigational product will be destroyed at the site per UNC IDS drug destruction policy. It is the Investigator's responsibility to arrange for disposal of all empty containers, provided that procedures for proper disposal have been established

according to applicable federal, state, local and institutional guidelines and procedures, and provided that appropriate records of disposal are kept.

Possible side effects: refer to management guidelines in sections **Error! Reference source not found.**, **Error! Reference source not found.** and **Error! Reference source not found.**.

Immune-Mediated Pneumonitis
Pneumonitis occurred in ~2% of melanoma patients treated in clinical trials of pembrolizumab. Fatal cases have occurred. The median time-to-onset was 4.3 months (range: 2 days to 19.3 months). Monitor patients for signs and symptoms of pneumonitis.

Immune-Mediated Colitis
Colitis (including microscopic colitis) occurred in ~2% of patients with melanoma treated in clinical trials of pembrolizumab. The median time-to-onset was 3.4 months (range 10 days to 9.7 months). Monitor patients for signs and symptoms of colitis.

Immune-Mediated Hepatitis
Hepatitis (including autoimmune hepatitis) occurred in 0.5% of melanoma patients treated in clinical trials of pembrolizumab. The time-to-onset was 26 days (range: 8 days to 21.4 months). Monitor patients for signs and symptoms of hepatitis.

Immune-Mediated Hypophysitis
Hypophysitis occurred in 0.8% of melanoma patients treated in clinical trials of pembrolizumab. The time-to-onset was 3.3 months (range 1 day to 7.2 months). Monitor patients for signs and symptoms of hypophysitis.

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

Immune-Mediated Hyperthyroidism
Hyperthyroidism occurred in 3.3% of patients receiving pembrolizumab in clinical trials. The median time-to-onset was 1.4 months (range: 1 day to 21.9 months). Monitor patients for signs and symptoms of hypothyroidism.

Immune-Mediated Nephritis and Renal Dysfunction
Nephritis occurred in (0.4%) patients of melanoma patients treated in clinical trials of pembrolizumab. The median time-to-onset of autoimmune nephritis was 5.1 months (ranges: 12 days to 12.8 months). Monitor patients for signs and symptoms of nephritis and renal dysfunction.

Other Immune-Mediated Adverse Reactions
Other clinically important immune-mediated AEs can occur. The following clinically significant, immune-mediated AEs occurred in less than 1% of patients treated with pembrolizumab, including exfoliative dermatitis, uveitis, arthritis, myositis, Guillain-Barré syndrome, vasculitis, myasthenia gravis, pancreatitis, hemolytic anemia, partial seizures arising in a patient with inflammatory foci in brain parenchyma.

Infusion-related Reactions
Infusion-related reactions have been reported in 0.1% of patients receiving pembrolizumab in clinical trials. Monitor patients for signs and symptoms of infusion-related reactions including rigors, chills, wheezing, pruritus, flushing, rash, hypotension, hypoxemia, and fever.

Steven's Johnson Syndrome (SJS) and Toxic Epidermal Necrolysis (TEN)
The risk of SJS and TEN is reported at approximately 0.4 – 7 cases per million patient years in the general adult population. Independent risk factors include certain medications such as anticonvulsants, sulfonamides, aminopenicillins, allopurinol, and NSAIDs. Non-medication triggers include infection, contrast media, and vaccinations. Malignancy is associated with an increased mortality rate in patients with SJS and TEN.

Myocarditis
A total of 6 cases of myocarditis have been reported in patients treated with pembrolizumab in clinical trials in an expanded access program. There was one fatal case reported in a clinical trial [60]. Immune-mediated myocarditis should be suspected if other causes of myocarditis, such as infection or prior radiation therapy have been excluded. Risk factors include certain medications and treatment modalities such as radiation, anthracycline, alkylating agents and most recently checkpoint inhibitors.

Embryofetal Toxicity
Based on its mechanism of action, pembrolizumab may cause fetal harm when administered to a pregnant woman. Animal models link the PD-1/PDL-1 signaling pathway with maintenance of pregnancy through induction of maternal immune tolerance to fetal tissue.

Handling and Disposal: Please see policy on hazardous drugs:

http://intranet.unchealthcare.org/intranet/hospitaldepartments/safetynet/policies/hazardousdrugs.pdf

Local requirements for disposal of hazardous drugs should be followed at each participating clinical site. See section **Error! Reference source not found.** for details.

Precautions:
Pre-existing hypocalcemia must be corrected prior to initiating therapy with denosumab. See section **Error! Reference source not found.** for details.

For additional information, please refer to the full prescribing information on pembrolizumab is available at:
https://www.merck.com/product/usa/pi_circulars/k/keytruda/keytruda_pi.pdf

5.1.1 Contraindications

There are no reported contraindications associated with the use of pembrolizumab.

Pembrolizumab may have adverse effects on a fetus in utero. Furthermore, it is not known if pembrolizumab has transient adverse effects on the composition of sperm.

5.1.2 Contraception

Pembrolizumab may have adverse effects on a fetus in utero. Furthermore, it is not known if pembrolizumab has transient adverse effects on the composition of sperm.

For this trial, male subjects will be considered to be of non-reproductive potential if they have azoospermia (whether due to having had a vasectomy or due to an underlying medical condition).

Female subjects will be considered of non-reproductive potential if they are either:
(1) postmenopausal (defined as at least 12 months with no menses without an alternative medical cause; in women < 45 years of age a high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a post-menopausal state in women not using hormonal contraception or hormonal replacement therapy. In the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.);
OR
(2) have had a hysterectomy and/or bilateral oophorectomy, bilateral salpingectomy or bilateral tubal ligation/occlusion, at least 6 weeks prior to screening;
OR
(3) has a congenital or acquired condition that prevents childbearing.

Female and male subjects of reproductive potential must agree to avoid becoming pregnant or impregnating a partner, respectively, while receiving study drug and for 120 days after the last dose of study drug by complying with one of the following:
(1) practice abstinence† from heterosexual activity;

OR
(2) use (or have their partner use) acceptable contraception during heterosexual activity.

Acceptable methods of contraception are‡:
Single method (one of the following is acceptable):

- intrauterine device (IUD)
- vasectomy of a female subject's male partner
- contraceptive rod implanted into the skin

Combination method (requires use of two of the following):

- diaphragm with spermicide (cannot be used in conjunction with cervical cap/spermicide)
- cervical cap with spermicide (nulliparous women only)
- contraceptive sponge (nulliparous women only)
- male condom or female condom (cannot be used together)
- hormonal contraceptive: oral contraceptive pill (estrogen/progestin pill or progestin-only pill), contraceptive skin patch, vaginal contraceptive ring, or subcutaneous contraceptive injection.

†Abstinence (relative to heterosexual activity) can be used as the sole method of contraception if it is consistently employed as the subject's preferred and usual lifestyle and if considered acceptable by local regulatory agencies and ERCs/IRBs. Periodic abstinence (e.g., calendar, ovulation, sympto-thermal, post-ovulation methods, etc.) and withdrawal are not acceptable methods of contraception.

‡If a contraceptive method listed above is restricted by local regulations/guidelines, then it does not qualify as an acceptable method of contraception for subjects participating at sites in this country/region.

Subjects should be informed that taking the study medication may involve unknown risks to the fetus (unborn baby) if pregnancy were to occur during the study. In order to participate in the study subjects of childbearing potential must adhere to the contraception requirement (described above) from the day of study medication initiation (or 14 days prior to the initiation of study medication for oral contraception) throughout the study period up to 120 days after the last dose of trial therapy. If there is any question that a subject of childbearing potential will not reliably comply with the requirements for contraception, that subject should not be entered into the study.

5.1.3 Use in Pregnancy

If a subject inadvertently becomes pregnant while on treatment with pembrolizumab, the subject will immediately be removed from the study. The site will contact the subject at least monthly and document the subject's status until the pregnancy has been completed or terminated. The outcome of the

pregnancy will be reported to the Sponsor and to Merck without delay and within 24 hours to the Sponsor and within 2 working days to Merck if the outcome is a serious adverse experience (e.g., death, abortion, congenital anomaly, or other disabling or life-threatening complication to the mother or newborn).

The study investigator will make every effort to obtain permission to follow the outcome of the pregnancy and report the condition of the fetus or newborn to the Sponsor. If a male subject impregnates his female partner the study personnel at the site must be informed immediately and reported to the Sponsor and Merck as described above.

See section 7.3.3 for detailed information on reporting of suspected pregnancies, pregnancies, and outcome of any pregnancy to the UNCCN Project Manager, Merck, and Celgene.

Male Subjects
Male patients treated with nab-paclitaxel are advised not to father a child during and up to 6 months after treatment.

5.1.4 Use in Nursing Women

It is unknown whether pembrolizumab is excreted in human milk. Since many drugs are excreted in human milk, and because of the potential for serious adverse reactions in the nursing infant, subjects who are breast-feeding are not eligible for enrollment.

5.1.5 Overdose of Pembrolizumab

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. Appropriate supportive treatment should be provided if clinically indicated.

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 within 24 hours to the UNCCN Project Manager who will report the event within 2 working days hours to Merck Global Safety. (Attn: Worldwide Product Safety; FAX 215 993-1220) (see section 7.3.3).

5.2 Nab-paclitaxel (Abraxane®; ABI-007)

Nab-paclitaxel is a protein-bound form of paclitaxel indicated in the United States for the treatment of breast cancer after failure of combination chemotherapy for metastatic disease or relapse within 6 months of adjuvant chemotherapy. Prior therapy should have included an anthracycline unless clinically contraindicated. It is also indicated for locally advanced or metastatic NSCLC as first-line treatment in combination with carboplatin in patients who are not candidates for curative surgery or radiation therapy. See:
http://www.accessdata.fda.gov/scripts/cder/drugsatfda/
for additional information, and the nab-paclitaxel investigator's brochure for complete information.

5.2.1 Packaging, Labeling, Storage and Supply of nab-paclitaxel

Nab-paclitaxel (Abraxane®) will be supplied by Celgene Corporation, in single-use vials at no cost to the patient. Each single-use 50 mL vial will contain paclitaxel (100 mg) and human albumin (HA; approximately 900 mg). Commercial drug will be supplied. Each milliliter (mL) of reconstituted suspension contains 5 mg paclitaxel. Un-reconstituted nab-paclitaxel (Abraxane®) should be stored at controlled room temperature (20° to 25°C or 68° to 77°F) in its original carton to protect from bright light. Unopened vials are stable until the date indicated on the package when stored between 20°C to 25°C (68°F to 77°F), in the original package. Neither freezing nor refrigeration adversely affects the stability of the product.

Reconstituted nab-paclitaxel (Abraxane®) should be used immediately. If not used immediately, the vial of reconstituted nab-paclitaxel (Abraxane®) must be placed in its carton in a refrigerator at 2° to 8°C (36° to 46°F) for a maximum of 8 hours. If not used immediately, each vial of reconstituted suspension should be replaced in the original carton to protect it from bright light. Discard any unused portion. Both forms should be stored in an area free of environmental extremes and must be accessible only to study personnel.

Temperature records for nab-paclitaxel (Abraxane®) must be kept for verification of proper study drug storage.

If storing reconstituted nab-paclitaxel (Abraxane®), some settling may occur. Ensure complete re-suspension by mild agitation prior to use.

The suspension for infusion prepared as recommended in an infusion bag should be used immediately, but may be stored at ambient temperature (approximately 25°C) and lighting conditions for up to 4 hours.

5.2.2 Reconstitution of nab-paclitaxel

Nab-paclitaxel will be reconstituted by appropriate study personnel and administered to the patient in the study site setting at weekly intervals. The

investigator will calculate the body surface area (BSA) of the patient in order to determine the total amount of nab-paclitaxel to be administered.

Reconstitution and use of nab-paclitaxel:

1. Calculate the patient's body surface area at the beginning of the study and if the weight changes by >10%.
2. Calculate the total dose (in mg) to be administered by:
   Total Dose (mg) = BSA x (study dose mg/m^2)
3. Calculate the total number of vials required by:
   Total Number of Vials = $\frac{\text{Total Dose (mg)}}{\text{100 mg/vial}}$

   Round up the number of vials to be reconstituted to the next higher whole number when a fractional number of vials is obtained by the above formula (e.g., if the total number of vials = 4.05 or 4.5, then 5 vials would be reconstituted).
4. Using sterile technique, prepare the vials for reconstitution.
5. Swab the rubber stoppers with alcohol.
6. Reconstitute each nab-paclitaxel (Abraxane®) vial by injecting 20 mL of 0.9% Sodium Chloride Injection, USP or equivalent into each vial over a period of not less than 1 minute (Note: change the syringes after reconstituting every 3 vials).
   - **Slowly** inject the 20 mL of 0.9% Sodium Chloride Injection, USP, over a minimum of **1 minute**, using the sterile syringe directing the solution flow onto the **inside wall** of the vial.
   - **DO NOT INJECT** the 0.9% Sodium Chloride Injection, USP solution directly onto the lyophilized cake as this will result in foaming.
   - 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.
   - **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. Rapid agitation or shaking will result in foaming.
   - **If foaming or clumping occurs, stand solution for at least 15 minutes until foam subsides.**
   - Each mL of reconstituted product will contain 5 mg of paclitaxel.
7. Calculate the exact total dosing volume of 5 mg/mL suspension required for the patient: **Dosing volume (mL) = total dose (mg)/5 (mg/mL)**
8. The reconstituted sample should be milky and homogeneous without visible particulates. If particulates or settling are visible, the vial should be **gently** inverted again to ensure complete resuspension, prior to use. Discard the reconstituted suspension if precipitates are observed.

9. Once the exact volume of reconstituted Abraxane® has been withdrawn from the vials, discard any excess solution left over in accordance with standard operating procedures.
10. Further dilution is not necessary. Inject the calculated dosing volume of reconstituted Abraxane® suspension into an empty sterile, standard PVC IV bag using an injection port. Inject perpendicularly into the center of the injection port to avoid dislodging plastic material into the IV bag.
11. Administer the calculated dosing volume of reconstituted Abraxane® suspension by IV infusion over 30 minutes. The use of in-line filters is not recommended because the reconstituted solution may clog the filter.
12. Following administration, the intravenous line should be flushed with Sodium Chloride 0.9% solution for injection to ensure administration of the complete dose, according to local practices.

5.2.3 Dose and Schedule of nab-paclitaxel

See Schema.

5.2.4 Administration

Nab-paclitaxel will be infused intravenously over 30 minutes. Actual body weight will be used for the calculation.

NOTE: It is not a requirement to use filter needles in the preparation of, or in-line filters during the administration of nab-paclitaxel. In any event, filters of pore-size less than 15 micrometers must **not** be used.

5.2.5 Receipt and Return of nab-paclitaxel

Upon receipt of the study drug supplies from Celgene Corporation

Celgene Corporation
86 Morris Avenue
Summit, NJ 07901

The investigator or designee will conduct an inventory and sign both copies of the study drug receipt form and forward one copy to the address indicated on the form. One copy of the receipt and the packing slip must be retained in the investigational drug services (IDS) records.

No supplies will be shipped to any site until regulatory approval has been obtained. Investigational sites will be supplied with Abraxane® upon identification and screening of a potential trial subject. Upon identification of a potential subject, sites must fax a completed Drug Request Form to Celgene Corporation. Allow at least 5 working days for drug shipment. There are no shipments on Fridays or holidays. For re-supply of drug, please complete and fax the Drug Request Form to Celgene Corporation at 908-673-2779.

If the investigational site does not have a policy, procedure or SOP detailing the process to follow for study drug destruction, the study drug must then be returned

to Celgene using the Drug Return Form provided in the package containing the study drug. The following information must be recorded on the site's pharmacy drug accountability log: quantity of vials to be returned, expiration date and lot number. A copy of the Drug Return Form and the study drug should be returned to Celgene Clinical Supplies Dept. using the mailing address on the packaging slip that came with the original study drug order. A copy of the Drug Return Form should be retained at the clinical site. In the event of study completion or termination, a copy of all pharmacy records (drug dispensing log, drug accountability log and any destruction memos) must be mailed to Celgene Medical Operations.

If the investigational site has a policy, procedure or SOP detailing the process to follow for study drug destruction, the pharmacist or designee can choose to destroy the study drug on site. The following information must be recorded on the site's pharmacy drug accountability log: quantity of vials destroyed, expiration date and lot number. The pharmacist must document that the study drug was destroyed in accordance with their institution's drug destruction policy or SOP. A drug destruction memo and the site's drug destruction SOP/policy should be sent to Celgene Medical Operations Dept. A copy of the drug destruction memo should be retained at the clinical site. In the event of study completion or termination, a copy of all pharmacy records (drug dispensing log, drug accountability log and any destruction memos) must be mailed to Celgene Medical Operations.

5.2.6 Clinical Safety Summary

See prescribing information for information on nab-paclitaxel when used according to its FDA indication in the treatment of metastatic breast cancer and dosed every 3 weeks or when used in NSCLC dosed days 1, 8 and 15 of every 21 day cycle in combination with carboplatin on day 1:
http://www.accessdata.fda.gov/scripts/cder/drugsatfda

When used in combination with carboplatin in NSCLC, the most common reactions (≥10%) included anemia (98%), neutropenia (85%), thrombocytopenia (68%), alopecia (56%), peripheral neuropathy (48%), nausea (27%), fatigue (25%), decreased appetite (17%), asthenia (16%), constipation (16%), diarrhea (15%), vomiting (12%), dyspnea (12%), peripheral edema (10%), arthralgia (13%), rash (10%), and myalgia (10%).

When administered weekly as a single agent at 100mg/m^2 in 65 patients with locally advanced breast cancer for 12 doses, no grade 4 nab-paclitaxel adverse events were reported. The most common (% of patients) nab-paclitaxel-related adverse events included neutropenia (grade 2: 6%, grade 3: 3%), febrile neutropenia (grade 3: 2%), fatigue (grade 2: 26%, grade 3:6%) neuropathy (grade 2: 11%, grade 3: 5%), nausea (grade 2: 10%), vomiting (grade 2: 8% , grade 3: 2%), and diarrhea (grade 2: 9%, grade 3: 5%). Dose reductions or omissions were required in 14 (2%) of doses [31].

The following adverse events are associated with nab-paclitaxel when studied in metastatic breast cancer:

Hematologic: Myelosuppression, primarily neutropenia, is dose dependent and reversible, but dose limiting. Thrombocytopenia is uncommon, while anemia occurred in 33% (severe in <1%) of patients in the randomized trial.

Infections: Infectious episodes were reported in 24% of patients in the randomized phase III trial in metastatic breast cancer.

Hypersensitivity: Hypersensitivity reactions (Grade 1 or 2) occurred on the day of nab-paclitaxel administration in the randomized phase III trial in metastatic breast cancer and consisted of dyspnea (1%) and flushing, hypotension, chest pain, and arrhythmias (all <1%).

Cardiovascular: Hypotension occurred in 5% and bradycardia (during the infusion) in <1% of patients in the randomized Phase III trial. Severe cardiovascular events possibly related to nab-paclitaxel occurred in approximately 3%, and included cardiac ischemia/infarction, chest pain, cardiac arrest, supraventricular tachycardia, edema, thrombosis, pulmonary thromboembolism, pulmonary emboli, and hypertension. Strokes and TIAs have been reported.

ECG abnormalities: occurred in 35% of patients who had a normal ECG at baseline in the randomized Phase III trial in metastatic breast cancer.

Respiratory: Following treatment with nab-paclitaxel, dyspnea (12%), cough (7%) and pneumothorax (<1%) were reported in the randomized Phase III trial in metastatic breast cancer.

Neurologic: Sensory neuropathy occurs frequently with nab-paclitaxel (71% in the randomized clinical trial, 10% severe). It is dose-dependent, and increases with cumulative dose.

Vision: Ocular/visual disturbances occurred in 13%; 1% were severe and included keratitis and blurred vision.

Arthralgia/Myalgia: Symptoms occurred in 44% of patients in the randomized clinical trial (8% of patients experienced severe symptoms).

Hepatic: Exposure and toxicity of paclitaxel can be increased with hepatic impairment. Grade 3 or 4 elevations in GGT occurred in 14% of patients in the randomized Phase III trial.

Renal: Elevated serum creatinine occurred in 11% (1% severe) of patients in the randomized Phase III trial.

General Toxicity Information

Drug Interactions: No drug interactions studies have been conducted with nab-paclitaxel, a drug metabolized by CYP2C8 and CYP3A4. Caution should be used when administering nab-paclitaxel with medications known to inhibit or induce either CYP2C8 or CYP3A4.

Injection site reactions: These reactions occur infrequently with nab-paclitaxel and were mild in the randomized clinical trial.

Use in patients with hepatic impairment: The starting dose of nab-paclitaxel should be reduced for patients with moderate and severe hepatic impairment.

Use in pregnancy: Nab-paclitaxel is pregnancy category D. Men should also be advised not to father a child while receiving treatment with nab-paclitaxel.

Albumin: Nab-paclitaxel contains human albumin, and thus carries an extremely remote risk for transmission of viral diseases, and Creutzfeldt-Jakob Disease.

Other potential risks associated with nab-paclitaxel include mucositis, bilirubin/liver enzyme elevations, edema, alopecia, asthenia, nail changes, dehydration and pyrexia.

See the nab-paclitaxel prescribing information and investigator's brochure for additional information on post-marketing toxicities reported with nab-paclitaxel.

5.2.7 Overdose of Nab-paclitaxel

Overdose, as defined for this protocol section 5.2.7, refers to nab-paclitaxel dosing only.

On a per dose basis, an overdose is defined as the following amount over the protocol-specified dose of nab-paclitaxel assigned to a given patient, regardless of any associated adverse events or sequelae.

PO any amount over the protocol-specified dose

IV 10% over the protocol-specified dose

SC 10% over the protocol-specified dose

On a schedule or frequency basis, an overdose is defined as anything more frequent than the protocol required schedule or frequency.

On an infusion rate basis, an overdose is defined as any rate faster than the protocol-specified rate. For nab-paclitaxel, an infusion completed in less than 25

minutes may increase Cmax by approximately 20%, therefore a nab-paclitaxel infusion completed in less than 25 minutes will meet the infusion rate criterion for an overdose.

Complete data about drug administration, including any overdose, regardless of whether the overdose was accidental or intentional, should be reported on the eCRF and to Celgene Global Drug Safety and Risk Management (FAX 908-673-9115; see section 7.3.3).

6.0 EVALUATIONS AND ASSESSMENTS

6.1 Time and Events Table ARM A: Sequential therapy: Pembrolizumab then Nab-paclitaxel

		Consolidation One: Pembrolizumab				3 weeks post D1 of cycle 4, begin Consolidation Two[4]	**Consolidation Two: Nab-paclitaxel**			
Procedure	**Screening[1]**	**D1 of 3 week cycle (x4)[3]**					**Within every 3 week cycle (x4)[3]**		**End of Treatment[5]**	**Follow-up[6]**
		C1[2]	**C2**	**C3**	**C4**		**D1**	**D8**		
Informed Consent	X									
Medical History[7]	X	X	X	X	X		X		X	
Physical Exam (PE)	X	X	X	X	X		X		X	X[6]
Charleson Co-morbidity Index	X									
ECOG PS	X	X	X	X	X		X		X	X
Weight	X	X	X	X	X		X		X	
CBC w/differential	X	X	X	X	X		X	X	X	X
Serum chemistries[8]	X	X	X	X	X		X		X	X
Liver function tests[9]	X	X	X	X	X		X		X	X
Pregnancy Testing[10]	X[10]									
Coagulation, urinalysis[11]	X[11]			X[11]			X[11, 12]			
Thyroid panel[13]	X[13]			X[13]			X[12, 13]			
Uric Acid	X	X	X	X	X		X[12]			
Tumor Imaging[14]	X			X			X[14]		X	X[6]
Toxicity assessment		X	X	X	X		X	X[15]	X	
Respiratory signs/symptoms[16]	X	X	X	X	X					
Pembrolizumab		X	X	X	X					
Nab-paclitaxel							X	X		
Concomitant Med Rev	X	X	X	X	X		X			
Survival assessment										X
PRO-CTCAE[17]		X		X			X[17]		X	X[17]
Quality of Life[17]		X		X			X[17]		X	X[17]
Blood/Serum samples		X[18]	X[18]	X[18]	X8[7]		X[18]		X[18]	X[18]
Archival Tissue	X[19]									
Research Biopsies[4]										

Key to Time and Events Table Footnotes

[1]Unless otherwise noted, screening evaluations to take place within 2 weeks of day 1 of study treatment. Archival tissue must be made available.

[2]Laboratory evaluations on day 1 of cycle 1 need be repeated only if >7 days have elapsed between screening laboratory tests and day 1.

[3]A window of +/- 3 days will apply to each cycle.

[4]Patients may begin nab-paclitaxel earlier if they experience progression during initial consolidation with pembrolizumab. **NOTE:** post-pembrolizumab, an optional tumor biopsy will be requested in up to 12 patients in ARM A only. See section 6.11.2 and the laboratory manual for additional details.

[5]The end of treatment visit should only occur when patients permanently stop study treatment and should be performed 30 days (+/-7 days) after the last dose of treatment. All adverse events and concomitant medications should be followed up until the 30-day End of Treatment (EOT) visit. Patients who have an ongoing ≥grade 2 or serious AE (SAE) at the EOT will continue to be followed until the event is resolved or deemed irreversible by the investigator. Repeat tumor imaging at this visit required.

[6]Long-term follow-up visits will take place per standard of care every 2 (preferred) to 3 months (depending on insurance coverage) for 24 months and will include radiographic tumor evaluation. After 24 months, patient will be followed-up per standard of care (SOC), with documentation in the eCRF limited to progression and survival noted at their SOC MD visits for up to 5 years.

[7] Complete history at baseline only (including smoking history), thereafter focused history on symptoms/toxicity; PE to include height at baseline only; medical history at baseline should include information on molecular status of tumor if known. See section 6.4 for additional information.

[8] Serum chemistries and electrolytes to include sodium, potassium, chloride, bicarbonate, BUN, serum creatinine, glucose, calcium, magnesium, albumin

[9]Liver function tests (LFTs) include total bilirubin, alkaline phosphatase, AST, ALT

[10]Serum or urineβ-HCG to be done within 72 hours of day 1 of treatment in women of childbearing potential; if a urine test is done and it is positive or cannot be confirmed as negative, a serum pregnancy test will be required.

[11]Coagulation includes PT/INR and PTT; urinalysis (UA) includes blood, glucose, protein, specific gravity, and microscopic exam if abnormal results are noted

[12]C1D1 of nab-paclitaxel therapy only, however, if clinically indicated, (including if they are previously abnormal), testing, should be repeated C3D1

[13]Thyroid panel includes TSH, T3 and free T4. If consistent with institutional standard of care, it is acceptable to obtain TSH alone and only obtain T3 and free T4 if clinically useful.

[14]CT scan of chest (if PET/CT scan done, use of CT portion of imaging for tumor evaluation acceptable as long as it is of diagnostic quality); screening radiologic evaluation may take place within 4 weeks of treatment initiation and modality should remain consistent throughout the trial (note that initial imaging with PET/CT and subsequent comparison of CT to the CT portion of the original is allowed, as long as the CT component of the original PET/CT is of diagnostic quality). MRI of brain should be performed at screening only to evaluate for the presence of brain metastases (which will exclude study participation). If patient in unable to tolerate MRI or has contraindication to MRI a head CT scan with and without contrast

is acceptable. During consolidation two, repeat imaging on D1 of cycles 1 and 3. Imaging may be done up to 7 days prior to day of treatment.

[15]Cycle 1 D8 of consolidation two will also serve as the 30 day post end of pembrolizumab safety check. Serious adverse events (SAEs) or any grade of Events of Clinical Interest (see sections **Error! Reference source not found.** and 7.3 and the ECI Guidance Document that is provided as a document separate from this protocol) that occur within 90 days post pembrolizumab must be recorded. Toxicity assessment is not required on D8 of C2-4.

[16]Perform baseline assessment and check for history of pneumonitis, monitor for respiratory signs/symptoms while patients are on pembrolizumab and manage toxicity for pneumonitis as outlined in section **Error! Reference source not found.**.

a) If applicable: ongoing patients are to be evaluated for active pneumonitis. Patients with a history of pneumonitis should be re-consented for this trial to consider if they should discontinue pembrolizumab or continue treatment based on the risk of fatal pneumonitis related to pembrolizumab therapy.

[17]See section 6.10 for assessment tools; PRO-CTCAE and quality of life to be obtained on odd –numbered cycles only (1, 3) of both consolidations), end of treatment, and at first follow-up visit only

[18]See section 6.11 and laboratory manual for additional information on correlatives; on D1 of each cycle of each consolidation regimen (including consolidation two), at the end of treatment visit, and at the second follow-up visit, collect 8.5 mLs of blood into each of 3 ACD (acid citrate dextrose = yellow top) tubes + 5 mLs of blood into SST tube for serum collection (See section 6.5.1).

[19]Archival tissue, if available, may be obtained at any point during conduct of the study.

6.2 Time and Events ARM B: Sequential therapy: Nab-paclitaxel then Pembrolizumab

		Consolidation One: Nab-paclitaxel		3 weeks post D1 of cycle 4, begin Consolidation Two[4]	**Consolidation Two: Pembrolizumab**					
Procedure	**Screening [1]**	**Within every 3 week cycle (x4)[3]**			**D1 of 3 week cycle (x4)[3]**				**End of Treatment[5]**	**Follow-up[6]**
		D1[2]	**D8**		**C1**	**C2**	**C3**	**C4**		
Informed Consent	X									
Medical History[7]	X	X			X	X	X	X	X	
Physical Exam (PE)	X	X			X	X	X	X	X	X[6]
Charleson Co-morbidity Index	X									
ECOG PS	X	X			X	X	X	X	X	X
Weight	X	X			X	X	X	X	X	
CBC w/differential	X	X	X		X	X	X	X	X	X
Serum chemistries[8]	X	X			X	X	X	X	X	X
Liver function tests[9]	X	X			X	X	X	X	X	X
Pregnancy Testing[10]	X[10]									
Coagulation, urinalysis[11]	X[11]				X[11]		X[11]			
Thyroid panel[12]	X[12]				X[12]		X[12]		X[12]	
Uric Acid	X				X	X	X	X		
Tumor Imaging[13]	X	X[18]			X		X		X	X[6]
Toxicity assessment		X			X	X	X	X	X[5]	X[14]
Respiratory signs/symptoms[19]	X				X	X	X	X	X	
Pembrolizumab					X	X	X	X		
Nab-paclitaxel		X	X							
Concomitant Med Rev	X	X			X	X	X	X		
Survival assessment										X
PRO-CTCAE[15]		X[15]			X		X		X	X[15]
Quality of Life[15]		X[15]			X[15]		X[15]		X[15]	X[15]
Blood/Serum samples		X[16]			X[16]	X[16]	X[16]	X[16]	X[16]	X[16]
Archival Tissue	X[17]									

Key to Time and Events Table Footnotes

[1]Unless otherwise noted, screening evaluations to take place within 2 weeks of day 1 of study treatment. Archival tissue must be made available to confirm eligibility

[2]Laboratory evaluations on day 1 of cycle 1 need be repeated only if >7 days have elapsed between screening laboratory tests and day 1.

[3]A window of +/- 3 days will apply to each cycle.

[4]Patients may begin pembrolizumab earlier if they experience progression during initial consolidation with nab-paclitaxel.

[5]The end of treatment visit should only occur when patients permanently stop study treatment and should be performed 30 days (+/-7 days) after the last dose of treatment. All adverse events and concomitant medications should be followed up until the 30-day End of Treatment (EOT) visit. Patients who have an ongoing ≥grade 2 or serious AE (SAE) at the EOT will continue to be followed until the event is resolved or deemed irreversible by the investigator. Repeat tumor imaging at this visit required.

[6]Long-term follow-up visits will take place per standard of care every 2 (preferred) to 3 months (depending on insurance coverage) for 24 months and will include radiographic tumor evaluation. After 24 months, patient will be followed-up per standard of care (SOC), with documentation in the eCRF limited to progression and survival noted at their SOC MD visits for up to 5 years.

[7] Complete history at baseline only (including smoking history), thereafter focused history on symptoms/toxicity; PE to include height at baseline only; medical history at baseline should include information on molecular status of tumor if known. See section 6.4 for additional information.

[8] Serum chemistries and electrolytes to include sodium, potassium, chloride, bicarbonate, BUN, serum creatinine, glucose, calcium, magnesium, albumin

[9]Liver function tests (LFTs) include total bilirubin, alkaline phosphatase, AST, ALT

[10]Serum or urine β-HCG to be done within 72 hours of day 1 of treatment in women of childbearing potential. If a urine test is done and it is positive or cannot be confirmed as negative, a serum pregnancy test will be required.

[11]Coagulation includes PT/INR and PTT; urinalysis (UA) includes blood, glucose, protein, specific gravity, and microscopic exam if abnormal results are noted

[12]Thyroid panel includes TSH, T3 and free T4. If consistent with institutional standard of care, it is acceptable to obtain TSH alone and only obtain T3 and free T4 if clinically useful.

[13]CT scan of chest (if PET/CT scan done, use of CT portion of imaging for tumor evaluation acceptable as long as the CT is of diagnostic quality); screening radiologic evaluation may take place within 4 weeks of treatment initiation and modality should remain consistent throughout the trial (note that initial imaging with PET/CT and subsequent comparison of CT to the CT portion of the original is allowed as long as the CT component of the original PET/CT is of diagnostic quality). MRI of brain should be performed at screening only to evaluate for the presence of brain metastases (which will exclude study participation). If patient in unable to tolerate MRI or has contraindication to MRI a head CT scan with and without contrast is acceptable. During consolidation one, repeat imaging on D1 of cycle 3 only. Imaging may be done up to 7 days prior to day of treatment.

[14]Serious adverse events (SAEs) or any grade of Events of Clinical Interest (see sections**Error! Reference source not found.** and 7.3 and the ECI Guidance Document that is provided as a document separate from

this protocol) occur within 90 days of the end of pembrolizumab (or prior to start of new anti-cancer therapy) must be recorded. NOTE: This 90 day follow-up for safety does not necessarily require an on-site visit.

[15]See section 6.10 for tools. PRO-CTCAE and quality of life to be obtained on odd –numbered cycles only (1, 3 of both consolidations), end of treatment, and at first-follow-up visit only

[16]See section See section 6.11 and laboratory manual for additional information on correlatives; on D1 of cycle 1 of each consolidation regimen (including consolidation two), at the end of treatment visit, and at the second follow-up visit, collect 8.5 mLs of blood into each of 3 ACD (acid citrate dextrose = yellow top) tubes + 5 mLs of blood into SST tube for serum collection for biocorrelative studies.

[17]Archival tissue, if available, may be obtained at any point during conduct of the study

[18]Prior to cycle 3 only.

[19]Perform baseline assessment and check for history of pneumonitis, monitor for respiratory signs/symptoms while patients are on pembrolizumab and manage toxicity for pneumonitis as outlined in section **Error! Reference source not found.**.

a) If applicable: ongoing patients are to be evaluated for active pneumonitis. Patients with a history of pneumonitis should be re-consented for this trial to consider if they should discontinue pembrolizumab or continue treatment based on the risk of fatal pneumonitis related to pembrolizumab therapy.

6.3 Time and Events ARM C: Concurrent Therapy: Pembrolizumab and Nab-paclitaxel

Procedure	Screening[1]	C1D1 [2,3]	C1D8 [3]	C2D1[3]	C2D8[3]	C3D1[3]	C3D8[3]	C4D1[3]	C4D8[3]	End of Treatment[4]	Follow-up[5]
Informed Consent	X										
Medical History[6]	X	X		X		X		X		X	
Physical Exam (PE)	X	X		X		X		X		X	X[5]
Charleson Co-morbidity Index	X										
ECOG PS	X	X		X		X		X		X	X
Weight	X	X		X		X		X		X	
CBC w/differential	X	X	X	X	X	X	X	X	X	X	X
Serum chemistries[7]	X	X		X		X		X		X	X
Liver function tests[8]	X	X		X		X		X		X	X
Pregnancy Testing[9]	X[9]										
Coagulation, urinalysis[10]	X[10]					X[10]					
Thyroid panel[11]	X[11]					X[11]				X[11]	
Uric Acid	X	X		X		X		X		X	
Tumor Imaging[12]	X					X				X	X[5]
Toxicity assessment		X		X		X		X		X[4]	X[13]
Respiratory signs/symptoms[14]	X	X		X		X		X		X	
Pembrolizumab		X		X		X		X			
Nab-paclitaxel		X	X	X	X	X	X	X	X		
Concomitant Med Rev	X	X		X		X		X			
Survival assessment											X
PRO-CTCAE[15]		X				X				X	X[18]
Quality of Life[15]		X				X				X	X[18]
Blood/Serum samples[16]		X		X		X		X		X	X[16]
Archival Tissue	X[17]										

Key to Time and Events Table Footnotes

[1]Unless otherwise noted, screening evaluations to take place within 2 weeks of day 1 of study treatment. Archival tissue must be made available to confirm eligibility

[2]Laboratory evaluations on day 1 of cycle 1 need be repeated only if >7 days have elapsed between screening laboratory tests and day 1.

[3]A window of +/- 3 days will apply to each cycle.

[4]The end of treatment visit should only occur when patients permanently stop study treatment and should be performed 30 days (+/-7 days) after the last dose of treatment. All adverse events and concomitant medications should be followed up until the 30-day End of Treatment (EOT) visit. Patients who have an ongoing ≥grade 2 or serious AE (SAE) at the EOT will continue to be followed until the event is resolved or deemed irreversible by the investigator. Repeat tumor imaging at this visit required.

[5]Long-term follow-up visits will take place per standard of care every 2 (preferred) to 3 months (depending on insurance coverage) for 24 months and will include radiographic tumor evaluation. After 24 months, patient will be followed-up per standard of care (SOC), with documentation in the eCRF limited to progression and survival noted at their SOC MD visits for up to 5 years.

[6] Complete history at baseline only (including smoking history), thereafter focused history on symptoms/toxicity; PE to include height at baseline only; medical history at baseline should include information on molecular status of tumor if known. See section 6.4 for additional information.

[7] Serum chemistries and electrolytes to include sodium, potassium, chloride, bicarbonate, BUN, serum creatinine, glucose, calcium, magnesium, albumin

[8]Liver function tests (LFTs) include total bilirubin, alkaline phosphatase, AST, ALT

[9]Serum or urine β-HCG to be done within 72 hours of day 1 of treatment in women of childbearing potential; If a urine test is done and it is positive or cannot be confirmed as negative, a serum pregnancy test will be required.

[10]Coagulation includes PT/INR and PTT; urinalysis (UA) includes blood, glucose, protein, specific gravity, and microscopic exam if abnormal results are noted

[11]Thyroid panel includes TSH, T3 and free T4. If consistent with institutional standard of care, it is acceptable to obtain TSH alone and only obtain T3 and free T4 if clinically useful.

[12]CT scan of chest (if PET/CT scan done, use of CT portion of imaging for tumor evaluation acceptable as long as the CT is of diagnostic quality); screening radiologic evaluation may take place within 4 weeks of treatment initiation and modality should remain consistent throughout the trial (note that initial imaging with PET/CT and subsequent comparison of CT to the CT portion of the original is allowed as long as the CT component of the original PET/CT is of diagnostic quality). MRI of brain should be performed at screening only to evaluate for the presence of brain metastases (which will exclude study participation). If patient in unable to tolerate MRI or has contraindication to MRI a head CT scan with and without contrast is acceptable. Imaging may be done up to 7 days prior to day of treatment if scheduled for a day treatment is due.

[13]Serious adverse events (SAEs) or any grade of Events of Clinical Interest (see sections **Error! Reference source not found.** and 7.3 and the ECI Guidance Document that is provided as a document separate from this protocol) occur within 90 days of the end of pembrolizumab (or prior to start of new anti-cancer therapy) must be recorded. NOTE: This 90 day follow-up for safety does not necessarily require an on-site visit.

[14]Perform baseline assessment and check for history of pneumonitis, monitor for respiratory signs/symptoms while patients are on pembrolizumab and manage toxicity for pneumonitis as outlined in section **Error! Reference source not found.**.

a) If applicable: ongoing patients are to be evaluated for active pneumonitis. Patients with a history of pneumonitis should be re-consented for this trial to consider if they should discontinue pembrolizumab or continue treatment based on the risk of fatal pneumonitis related to pembrolizumab therapy.

[15]See section 6.10 for tools; PRO-CTCAE and quality of life to be obtained on odd –numbered cycles only (1, 3), end of treatment and at first two follow-up visits only

[16]See section 6.11 for additional information on correlatives; on D1 of cycle 1, at the end of treatment visit, and at the second follow-up visit, collect 8.5 mLs of blood into each of 3 ACD (acid citrate dextrose = yellow top) tubes tubes + 5 mLs of blood into SST tube for serum collection for biocorrelative studies.

[17]Archival tissue, if available, may be obtained at any point during conduct of the study

6.4 Pre-Study Assessments in ARMS A, B and C

Clinical evaluation: complete medical history, physical examination to include height and weight, ECOG performance status (see Appendix C), and Charleston Comorbidity index (see Appendix B)

Laboratory studies:

- **Pregnancy Test**: A urine or serum pregnancy test (β-HCG) is required for all women of childbearing potential at screening within 72 hours prior to the first dose of treatment under this protocol. If a urine test is done and it is positive or cannot be confirmed as negative, a serum pregnancy test will be required.
- **CBC with differential**
- **Serum Chemistries:** sodium, potassium, chloride, bicarbonate, BUN, serum creatinine (calculate creatinine clearance via Cockcroft-Gault, see Appendix A), glucose, calcium, magnesium, albumin
- **LFTs:** These include total bilirubin (direct and indirect), alkaline phosphatase AST (SGOT), ALT (SGPT)
- **Uric Acid**
- **Urinalysis:** blood, glucose, protein, specific gravity, and microscopic exam if abnormal results are noted
- **Coagulation Panel:** PT/INR and PTT
- **Thyroid Panel:** TSH, T3 and free T4. If consistent with institutional standard of care, it is acceptable to obtain TSH alone and only obtain T3 and free T4 if clinically useful

Check respiratory history (signs/symptoms)

Concomitant medications review:

Tumor imaging**:** CT scan of the chest or PET-CT that covers the chest within 4 weeks prior to treatment; MRI of the brain (if patient unable to tolerate MRI or has contraindication to MRI, a head CT scan with or without contrast is acceptable).

Archival tissue**:** request access to archival tissue to support correlative studies (see section 6.11.1)

Molecular status: To the extent known, molecular status will be reported. If additional information on molecular status is learned subsequent to screening, it may be entered at a later time. When available, de-identified (to subject number) molecular pathology reports should be submitted as source documents

6.5 During Treatment ARM A

6.5.1 Treatment Assessments: D1 of each Cycle of Consolidation One (Pembrolizumab); NOTE: See section 6.10 for schedule of QOL and PRO-CTCAE assessments

Clinical evaluation: Focused history on symptoms/toxicity, physical examination to include weight, and ECOG performance status

Laboratory studies:

- **CBC with differential**

- **Serum Chemistries:** sodium, potassium, chloride, bicarbonate, BUN, serum creatinine (calculate creatinine clearance via Cockcroft-Gault, see section 11.1 Appendix A), glucose, calcium, magnesium, albumin
- **LFTs:** These include total bilirubin (direct and indirect), alkaline phosphatase AST (SGOT), ALT (SGPT)
- **Uric Acid**

Check Respiratory signs/ Symptoms
Concomitant Medications: Review any changes
Toxicity: Assessed according to the NCI CTCAE v4.0
Blood draws for Correlative Studies : collect 8.5 mLs of blood into each of 3 ACD (acid citrate dextrose = yellow top) tubes + 5 mLs of blood into SST tube for serum collection for biocorrelative; additional information provided in laboratory manual.

6.5.2 Treatment Assessments: D1 of Cycle 3 of Consolidation One (Pembrolizumab)

Laboratory studies:

- **Urinalysis:** blood, glucose, protein, specific gravity, and microscopic exam if abnormal results are noted
- **Coagulation Panel:** PT/INR and PTT
- **Thyroid Panel:** TSH, T3 and free T4. If consistent with institutional standard of care, it is acceptable to obtain TSH alone and only obtain T3 and free T4 if clinically useful

Check Respiratory signs/ Symptoms
Tumor imaging**:** Remain consistent with baseline imaging; Brain MRI does NOT need to be repeated unless clinically indicated.
Blood draws for Correlative Studies: collect 8.5 mLs of blood into each of 3 ACD (acid citrate dextrose = yellow top) tubes + 5 mLs of blood into SST tube for serum collection for biocorrelative; additional information provided in laboratory manual.

6.5.3 Prior to Beginning of Consolidation Two

Optional tumor biopsy (Applies only to subjects enrolled at UNC): to be performed in up to 12 patients in ARM A only. See section 6.11.2 and laboratory manual for additional details.

6.5.4 Treatment Assessments: D1 of each Cycle of Consolidation Two (Nab-paclitaxel); NOTE: See section 6.10 for schedule of QOL and PRO-CTCAE assessments

Clinical evaluation: Focused history on symptoms/toxicity, physical examination to include weight, and ECOG performance status
Laboratory studies:

- **CBC with differential**

- **Serum Chemistries:** sodium, potassium, chloride, bicarbonate, BUN, serum creatinine (calculate creatinine clearance via Cockcroft-Gault, see Appendix A), glucose, calcium, magnesium, albumin
- **LFTs:** These include total bilirubin (direct and indirect), alkaline phosphatase AST (SGOT), ALT (SGPT)
- **Uric Acid: (Cycle 1 only unless clinically indicated, if so repeat Cycle 3)**
- **Urinalysis:** blood, glucose, protein, specific gravity, and microscopic exam if abnormal results are noted; **(Cycle 1 only unless clinically indicated, if so repeat Cycle 3)**
- **Coagulation Panel:** PT/INR and PTT; **(Cycle 1 only unless clinically indicated, if so repeat Cycle 3)**
- **Thyroid Panel:** TSH, T3 and free T4. If consistent with institutional standard of care, it is acceptable to obtain TSH alone and only obtain T3 and free T4 if clinically useful; **(Cycle 1 only unless clinically indicated, if so repeat Cycle 3)**

Concomitant Medication: Review any changes
Toxicity: Assessed according to the NCI CTCAE v4.0
Blood draws for Correlative Studies: collect 8.5 mLs of blood (to fill line of 10mL as each tube starts with 2mL acid citrate dextrose) into each of 3 ACD (acid citrate dextrose = yellow top) tubes + 5mLs of blood into SST tube for serum collection for biocorrelative studies.

6.5.5 Treatment Assessments: D1 of Cycles 1 and 3 of Consolidation Two (Nab-paclitaxel)

Tumor imaging**:** Remain consistent with baseline imaging; Brain MRI does NOT need to be repeated unless clinically indicated.

6.5.6 Treatment Assessments: D8 of each Cycle of Consolidation Two (Nab-paclitaxel)

Laboratory studies:

- **CBC with differential**

Toxicity (Cycle 1 D8 only; not needed Cycles 2-4): Assessed according to the NCI CTCAE v4.0; **NOTE:** Serious adverse events (SAEs) or any grade of Events of Clinical Interest (see section 7.3 and the ECI Guidance Document that is provided as a document separate from this protocol) that occur within 90 days post pembrolizumab must be recorded, this should correspond to approximately Cycle 1 D8 of Consolidation Two.

6.6 During Treatment ARM B

6.6.1 Treatment Assessments: D1 of each Cycle of Consolidation One (Nab-paclitaxel): NOTE: See section 6.10 for schedule of QOL and PRO-CTCAE assessments

Clinical evaluation: Focused history on symptoms/toxicity, physical examination to include weight, and ECOG performance status

Laboratory studies:

- **CBC with differential**
- **Serum Chemistries:** sodium, potassium, chloride, bicarbonate, BUN, serum creatinine (calculate creatinine clearance via Cockcroft-Gault, see Appendix A), glucose, calcium, magnesium, albumin
- **LFTs:** These include total bilirubin (direct and indirect), alkaline phosphatase AST (SGOT), ALT (SGPT)

Concomitant Medications: Review any changes
Toxicity: Assessed according to the NCI CTCAE v4.0
Blood draws for Correlative Studies: collect 8.5 mLs of blood into each of 3 ACD (acid citrate dextrose = yellow top) tubes + 5mLs of blood into SST tube for serum collection for biocorrelative studies.

6.6.2 Treatment Assessments: D1 of Cycle 3 of Consolidation One (Nab-paclitaxel)

Tumor imaging**:** Remain consistent with baseline imaging; Brain MRI does NOT need to be repeated unless clinically indicated.

6.6.3 Treatment Assessments: D8 of each Cycle of Consolidation One (Nab-paclitaxel)

Laboratory studies:

- **CBC with differential**

6.6.4 Treatment Assessments: D1 of each Cycle of Consolidation Two (Pembrolizumab); NOTE: See section 6.10 for schedule of QOL and PRO-CTCAE assessments

Clinical evaluation: Focused history on symptoms/toxicity, physical examination to include weight, and ECOG performance status
Laboratory studies:

- **CBC with differential**
- **Serum Chemistries:** sodium, potassium, chloride, bicarbonate, BUN, serum creatinine (calculate creatinine clearance via Cockcroft-Gault, see Appendix A), glucose, calcium, magnesium, albumin
- **LFTs:** These include total bilirubin (direct and indirect), alkaline phosphatase AST (SGOT), ALT (SGPT)
- **Uric Acid**

Check Respiratory signs/ Symptoms
Concomitant Medications: Review and changes
Toxicity: Assessed according to the NCI CTCAE v4.0
Blood draws for Correlative Studies: collect 8.5 mLs of blood into each of 3 ACD (acid citrate dextrose = yellow top) tubes + 5mLs of blood into SST tube for serum collection for biocorrelative studies.

6.6.5 Treatment Assessments: D1 of Cycles 1 and 3 of Consolidation Two (Pembrolizumab)

Laboratory studies:

- **Urinalysis:** blood, glucose, protein, specific gravity, and microscopic exam if abnormal results are noted
- **Coagulation Panel:** PT/INR and PTT
- **Thyroid Panel:** TSH, T3 and free T4. If consistent with institutional standard of care, it is acceptable to obtain TSH alone and only obtain T3 and free T4 if clinically useful

Check Respiratory signs/ Symptoms
Tumor imaging**:** Remain consistent with baseline imaging; Brain MRI does NOT need to be repeated unless clinically indicated.

6.7 During Treatment ARM C

6.7.1 Treatment Assessments: D1 of each Cycle of Concurrent Consolidation (Pembrolizumab plus Nab-paclitaxel): NOTE: See section 6.10 for schedule of QOL and PRO-CTCAE assessments

Clinical evaluation: Focused history on symptoms/toxicity, physical examination to include weight, and ECOG performance status
Laboratory studies:

- **CBC with differential**
- **Serum Chemistries:** sodium, potassium, chloride, bicarbonate, BUN, serum creatinine (calculate creatinine clearance via Cockcroft-Gault, see Appendix A), glucose, calcium, magnesium, albumin
- **LFTs:** These include total bilirubin (direct and indirect), alkaline phosphatase AST (SGOT), ALT (SGPT)
- **Uric Acid:**

Check Respiratory signs/ Symptoms
Concomitant Medications: Review any changes
Toxicity: Assessed according to the NCI CTCAE v4.0
Blood draws for Correlative Studies: collect 8.5 mLs of blood into each of 3 ACD (acid citrate dextrose = yellow top) tubes + 5mLs of blood into SST tube for serum collection for biocorrelative studies.

6.7.2 Treatment Assessments: D8 of each Cycle of Concurrent Consolidation (Pembrolizumab plus Nab-paclitaxel): NOTE: See section 6.10 for schedule of QOL and PRO-CTCAE assessments

Laboratory studies:

- **CBC with differential**

6.7.3 Treatment Assessments: D1 of Cycle 3 of Concurrent Consolidation (Pembrolizumab plus Nab-paclitaxel)

Laboratory studies:

- **Urinalysis:** blood, glucose, protein, specific gravity, and microscopic exam if abnormal results are noted
- **Coagulation Panel:** PT/INR and PTT
- **Thyroid Panel:** TSH, T3 and free T4. If consistent with institutional standard of care, it is acceptable to obtain TSH alone and only obtain T3 and free T4 if clinically useful

Check Respiratory signs/ Symptoms

Tumor imaging**:** Remain consistent with baseline imaging; Brain MRI does NOT need to be repeated unless clinically indicated.

6.8 End of Treatment Assessments ARMS A, B and C (unless otherwise noted)

Clinical evaluation: Focused history on symptoms/toxicity, physical examination to include weight, and ECOG performance status
Laboratory studies:

- **CBC with differential**
- **Serum Chemistries:** sodium, potassium, chloride, bicarbonate, BUN, serum creatinine (calculate creatinine clearance via Cockcroft-Gault, see Appendix A), glucose, calcium, magnesium, albumin
- **LFTs:** These include total bilirubin (direct and indirect), alkaline phosphatase AST (SGOT), ALT (SGPT)
- **Thyroid panel: (ARMS B & C)**
- **Uric Acid (ARM C only)**

Check Respiratory signs/ Symptoms **(ARMS B & C)**
Tumor imaging**:** Remain consistent with baseline imaging; Brain MRI does NOT need to be repeated unless clinically indicated.
Toxicity: Assessed according to the NCI CTCAE v4.0
Blood draws for Correlative Studies: collect 8.5 mLs of blood into each of 3 ACD (acid citrate dextrose = yellow top) tubes + 5mLs of blood into SST tube for serum collection for biocorrelative studies. Additional information provided in laboratory manual

6.9 Long-Term Follow-up Assessments ARMS A, B and C

Note: Long-term follow-up visits will take place per standard of care every 2 (preferred) to 3 months (depending on insurance coverage) for 24 months and will include radiographic tumor evaluation.
Clinical evaluation: Physical Exam, ECOG performance status
Laboratory studies:

- **CBC with differential**
- **Serum Chemistries:** sodium, potassium, chloride, bicarbonate, BUN, serum creatinine (calculate creatinine clearance via Cockcroft-Gault, see Appendix A), glucose, calcium, magnesium, albumin

- **LFTs:** These include total bilirubin (direct and indirect), alkaline phosphatase AST (SGOT), ALT (SGPT)

Tumor imaging**:** Remain consistent with baseline imaging; Brain MRI does NOT need to be repeated unless clinically indicated. Long-term follow-up visits will take place per standard of care every 2 (preferred) to 3 months for 24 months and will include radiographic tumor evaluation. After 24 months, patient will be followed-up per standard of care (SOC), with documentation in the eCRF limited to progression and survival noted at their SOC MD visits for up to 5 years.
Toxicity: Serious adverse events (SAEs) or any grade of Events of Clinical Interest (see section 7.3 and the ECI Guidance Document that is provided as a document separate from this protocol) that occur within 90 days post pembrolizumab must be recorded; this applies in Follow-Up to **ARMs B and C**
Survival: Document survival status
Blood draws for Correlative Studies (**2nd follow-up visit only**): collect 8.5 mLs of blood into each of 3 ACD (acid citrate dextrose = yellow top) tubes + 5mLs of blood into SST tube for serum collection for biocorrelative studies; additional information will provided in the study manual.

6.10 Quality of Life and PRO-CTCAE Assessments

6.10.1 FACT-Lung: Provided as a document separate from this protocol

To be obtained on odd –numbered cycles only (1, 3) of both consolidations in ARMs A and B, and in cycles 1 and 3 of ARM C, at the end of treatment visit for each ARM, at first follow-up visit only in ARMs A and B, and in first two follow-up visits in ARM C.

6.10.2 Patient Reported Outcomes version of the CTCAE:

A subset (25-30) of items pertinent to lung cancer will be drawn from the PRO-CTCAE system. These items will be used to evaluate the presence and/or severity of range of symptoms, as well as the degree to which symptom/toxicity interferes with usual function. This tool will be used on odd –numbered cycles only (1, 3) of both consolidations in ARMs A and B, and in cycles 1 and 3 of ARM C, at the end of treatment visit for each ARM, at first follow-up visit only in ARMs A and B, and in first two follow-up visits in ARM C.

6.11 Correlative Studies

These are described in more detail in the laboratory manual.

Handling of Biospecimens Collected for Correlative Research
Samples will be collected and used only in accordance with the protocol. Study subject biological samples will not be retained or used for any research outside the confines set forth within this protocol and will not be retained for bio-banking. Study subject biological samples will be discarded/destroyed after relevant data are collected for this study.

6.11.1 Archival Tissue for ARMS A-C

Archival tumor tissue form the patient's original diagnostic biopsy will be requested and collected from all enrolled patients. See accompanying laboratory manual for additional details.

6.11.2 Research Biopsies for ARM A

Twelve patients who demonstrate regression of disease (tumor shrinkage > 30%) after 3 months of pembrolizumab monotherapy and consent to optional biopsy (only applies to subjects enrolled at UNC) will undergo repeat biopsy for further analysis of biocorrelatives; see laboratory manual for additional details.

Three (3) twenty-gauge core biopsies and 3 fine needle aspirates (FNA) will be the goal. Ultimately, the ratio of FNA/core biopsies will be up to the discretion of the physician performing the procedure, with primary consideration being safety. Additional details regarding processing, storing and handling tissue will be provided in a separate laboratory manual.

Biological samples collected for the study will be stored at the research laboratories at the Lineberger Comprehensive Cancer Center (LCCC), University of North Carolina at Chapel Hill, NC until the completion of the study. With patient consent, any remaining tumor tissue after protocol specific studies are complete will be stored for future research concerning lung cancer.

Risks associated with lung FNAs and biopsies include the following:

- Likely: local discomfort and minor bleeding
- Less likely: pneumothorax, hemothorax, intraparenchymal hemorrhage, hemoptysis, bronchopleural fistula, air embolism, and vascular injury

Prior to the procedure, the physician performing the procedure will discuss the risks with each study participant and answer any questions. Patients receiving therapeutic anticoagulation, with abnormal coagulation studies, or thrombocytopenia (defined as platelet count <50,000) will not undergo biopsy until and unless these resolve because of the increased risk of potential complications under these circumstances. After lung biopsies, patients will be observed for approximately 4 hours (range 4-6 hours) after the procedure, or per institutional standard guidelines. Less than the goal quantity of tissue is acceptable for each type of biopsy, and will be left to the clinical judgment of the physician performing the procedure.

6.11.3 Serial Blood Samples for ARMS A-C

On D1 of cycle 1 of each consolidation regimen (including consolidation two) for ARMS A and B, and on D1 of cycle 1 of ARM C, at the end of treatment visit for ARMS A-C, and at the second follow-up visit for ARMS A-C, collect 8.5 mLs of blood (to fill line of 10mL as each tube starts with 2mL acid citrate dextrose) into

each of 3 ACD (acid citrate dextrose = yellow top) tubes + 5 mLs of blood into SST tube for serum collection for biocorrelative studies. Additional details can be found in the laboratory manual.

6.12 Assessment of Safety

Any patient who receives treatment on this protocol will be evaluable for toxicity. Each patient will be assessed periodically for the development of any toxicity according to the Time and Events table (section 6.0). Toxicity will be assessed according to the NCI CTCAE v4. Toxicities will be characterized in terms regarding seriousness, causality, toxicity grading, and action taken with regard to trial treatment.

For subjects receiving treatment with pembrolizumab all AEs of unknown etiology associated with pembrolizumab exposure should be evaluated to determine if it is possibly an event of clinical interest (ECI) of a potentially immunologic etiology (termed immune-related adverse events, or irAEs); see the separate ECI guidance document (provided as a document separate from this protocol) regarding the identification, evaluation and management of potential irAEs.

Please refer to section 7.2 detailed information regarding the assessment and recording of AEs.

6.13 Assessment of Efficacy

Patients who have received at least 1 dose of nab-paclitaxel or pembrolizumab will be evaluable for assessment of response and progression. Patients whose cancer growth is documented by physical examination without imaging confirmation will count as progression.

6.13.1 Assessment of Disease-Tumor Measurement Based on RECIST 1.1

Measurable disease will be defined as the presence of at least one measurable lesion that can be accurately measured in at least one dimension with the longest diameter a minimum size of:

- ≥10mm by CT scan (CT scan slice thickness no greater than 5 mm)
- 10mm caliper measurement by clinical exam (lesions which cannot be accurately measured with calipers should be recorded as non-measurable).
- 20 mm by chest x-ray.

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

All other lesions, including small lesions (longest diameter <10mm or pathological lymph nodes with ≥10 to <15 mm short axis) as well as truly non-measurable lesions, will be considered non-measurable. Lesions considered truly non-measurable include:leptomeningeal disease; ascites; pleural/pericardial effusion; inflammatory breast disease; lymphangitic involvement of skin or lung, abdominal masses/abdominal organomegaly identified by physical exam that is not measurable by reproducible imaging techniques.

All measurements should be recorded in metric notation, using calipers if clinically assessed. All baseline evaluations should be performed as close as possible to the treatment start and never more than 4 weeks before the beginning of the treatment. The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging based evaluation should always be done rather than clinical examination unless the lesion(s) being followed cannot be imaged but are assessable by clinical exam. Clinical lesions will only be considered measurable when they are superficial and ≥10 mm diameter as assessed using calipers (e.g. skin nodules). For the case of skin lesions, documentation by color photography including a ruler to estimate the size of the lesions is recommended.

Baseline Documentation of Target and Non-Target Lesions
All measurable lesions up to a maximum of 5 lesions total (and a maximum of two lesions per organ) representative of all involved organs should be identified as target lesions and will be recorded and measured at baseline.

Target lesions should be selected on the basis of their size (lesions with the longer diameter), be representative of all involved organs, but in addition should be those that lend themselves to reproducible repeated measurements.

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, only the short axis is added into the sum. The baseline sum diameters will be used as reference to further characterize the objective tumor response of the measurable dimension of the disease.

All other lesions (or sites of disease) including pathological lymph nodes should be identified as non-target lesions and should also be recorded at baseline. In subsequent assessments, *non-index* lesions will be recorded as "stable or decreased disease," "absent," or "progression."

Evaluation of Target Lesions using RECIST 1.1 Criteria
Complete response (CR)−Disappearance of all target lesions. Any pathological lymph node (LN) (whether target or non-target) must have decreased in short axis to <10mm.

Partial response (PR)−At least a 30% decrease in the sum of the LD of the target lesions taking as reference the baseline sum LD.

Progressive Disease (PD)−At least a 20% increase in the sum of the LD of the target lesions taking as reference the smallest sum LD recorded since the treatment started including baseline 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 5mm. The appearance of one or more new lesions also constitutes PD.

Stable disease (SD)−Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD taking as references the smallest sum LD since the treatment started.

Nonprogressive disease: Measurable disease is not required for this study. Patients with CR at the time of study entry or otherwise nonmeasurable disease will be assessed for progression. In the event of PD, this should be noted. In the absence of meeting criteria for progression, nonprogressive disease should be coded (NPD).

Evaluation of Non-Target Lesions using RECIST 1.1 Criteria
Complete response (CR)−Disappearance of all non-target. All LN must be non-pathological in size (<10mm short axis).

Non-complete response (non-CR)/non-progression (non-PD)−Persistence of one or more non-target lesion(s) or/and 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.

6.13.2 irRC for this study (Adapted from [32, 33]

New measurable lesions in irRC:
New measurable lesions will not necessarily constitute PD or preclude partial response (PR). Rather, the difference between the current size of a measurable lesions and its size prior to meeting criteria for measurability will be added to the sum of tumor measurements.

Definition of Response Using irRC

- irComplete Response (irCR): Complete disappearance of all lesions (whether measurable or not) and no new lesions. Lymph nodes must decrease to <10mm. It is the judgment of the investigator whether a nonmeasurable radiographic nodule is likely cancerous; only nodules felt likely cancerous will preclude the judgement of irCR.

- irPartial Response (irPR): Decrease in tumor burden > 30%, relative to baseline (or, for the case of measurement of response for individual sequenced treatments, from the beginning of that treatment), of 30% or greater in the sum of the longest diameter of all index lesions plus new measurable lesions. The appearance of new measurable lesions is factored into the overall tumor burden, but does not automatically qualify as progressive disease.

- irStable Disease (irSD): Does not meet criteria for irCR or irPR, in the absence of PD.

- irProgressive Disease (irPD): At least 20% increase in tumor burden (i.e., taking sum of the longest diameter of all index lesions and any newly measurable lesions) when compared to disease burden at nadir; minimum 5mm absolute increase in tumor burden required. The investigator may assign the designation of irPD for massive and unequivocal worsening of non-target lesions alone.

- Nonprogressive disease: Measurable disease is not required for this study. Patients with CR at the time of study entry or otherwise nonmeasurable disease will be assessed for progression. In the event of PD, this should be noted. In the absence of meeting criteria for progression, nonprogressive disease should be coded (NPD).

Immmune-related Best Overall Response (irBOR):
IrBOR is the best response observed during the relevant time period. Of note, when total tumor burden increases and the patient is maintained on therapy, and tumor then shrinks (pseudo-progression) the second measurement will be utilized.

Designation of pseudo-progression:
The phenomenon of pseudo-progression is of particular interest in this trial. For the purpose of this trial, pseudo-progression will be defined as any $\geq$ 10% increase in tumor burden followed by a $\geq$ 10% decrease in tumor burden prior to change in therapy. Such occurrences will be noted for the purpose of exploratory hypothesis-generating analyses.

7.0 ADVERSE EVENTS

7.1 Definitions

7.1.1 Adverse Event (AE)

An adverse event (AE) is any untoward medical occurrence (e.g., an abnormal laboratory finding, symptom, or disease temporally associated with the use of a drug) in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not related to the medicinal product.

Hospitalization for elective surgery or routine clinical procedures that are not the result of an AE (e.g., surgical insertion of central line) need not be considered AEs and should not be recorded as an AE. Disease progression should not be recorded as an AE, unless it is attributable by the investigator to the study therapy.

All adverse events that occur after the consent form is signed but before treatment 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.

From the time of treatment through 30 days following cessation of treatment, all adverse events must be reported by the investigator. Such events will be recorded at each examination on the Adverse Event case report forms/worksheets. The reporting timeframe for adverse events meeting any serious criteria is described in section 7.1.4. The investigator will make every attempt to follow all subjects with non-serious adverse events for outcome.

Adverse events will not be collected for subjects during the pre-screening period (for determination of archival tissue status) as long as that subject has not undergone any protocol-specified procedure or intervention. If the subject requires a blood draw, fresh tumor biopsy etc., the subject is first required to provide consent to the main study and AEs will be captured according to guidelines for standard AE reporting.

7.1.2 Suspected Adverse Reaction (SAR)

A suspected adverse reaction (SAR) is any AE for which there is a *reasonable possibility* that the drug is the cause. *Reasonable possibility* means that there is evidence to suggest a causal relationship between the drug and the AE. A

suspected adverse reaction implies a lesser degree of certainty about causality than adverse reaction, which means any adverse event caused by a drug.

Causality assessment to a study drug is a medical judgment made in consideration of the following factors: temporal relationship of the AE to study drug exposure, known mechanism of action or side effect profile of study treatment, other recent or concomitant drug exposures, normal clinical course of the disease under investigation, and any other underlying or concurrent medical conditions. Other factors to consider in considering drug as the cause of the AE:

- Single occurrence of an uncommon event known to be strongly associated with drug exposure (e.g., angioedema, hepatic injury, Stevens-Johnson Syndrome)
- One or more occurrences of an event not commonly associated with drug exposure, but otherwise uncommon in the population (e.g., tendon rupture); often more than once occurrence from one or multiple studies would be needed before the sponsor could determine that there is *reasonable possibility* that the drug caused the event.
- An aggregate analysis of specific events observed in a clinical trial that indicates the events occur more frequently in the drug treatment group than in a concurrent or historical control group.

7.1.3 Unexpected AE or SAR

An AE or SAR is considered unexpected if the specificity or severity of it is not consistent with the applicable product information (e.g., Investigator's Brochure (IB) for an unapproved investigational product or package insert/summary of product characteristics for an approved product). Unexpected also refers to AEs or SARs that are mentioned in the IB as occurring with a class of drugs or as anticipated from the pharmacological properties of the drug, but are not specifically mentioned as occurring with the particular drug under investigation.

7.1.4 Serious AE or SAR

An AE or SAR is considered serious if, in the view of either the investigator or sponsor, it results in any of the following outcomes:

- Death;
- Is life-threatening (places the subject at immediate risk of death from the event as it occurred);
- Requires inpatient hospitalization (>24 hours) or prolongation of existing hospitalization*
- Results in congenital anomaly/birth defect;
- Results in a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions;
- Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require

medical or surgical intervention to prevent one of the outcomes listed in the definition. For reporting purposes, also consider the occurrences of pregnancy as an event which must be reported as an important medical event.

*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.

- Note: In addition to the above criteria, adverse events meeting either of the below criteria, although not serious per ICH definition, are reportable to the Merck in the same timeframe as SAEs to meet certain local requirements. Therefore, these events are considered serious by Merck for collection purposes.
    - Is a new cancer (that is not a condition of the study);
    - Is associated with an overdose.

For the time period beginning when the consent form is signed until treatment, any serious adverse event, or follow up to a serious adverse event, including death due to any cause other than progression of the cancer under study that occurs to any subject must be reported within 24 hours to the Sponsor and within 2 working days to Merck Global Safety if it causes the subject to be excluded from the trial, or is the result of a protocol-specified intervention, including but not limited to washout or discontinuation of usual therapy, diet, placebo treatment or a procedure.

For the time period beginning at treatment through 90 days following cessation of treatment, or 30 days following cessation of treatment if the subject initiates new anticancer therapy, whichever is earlier, any serious adverse event, or follow up to a serious adverse event, including death due to any cause other than progression of the cancer under study whether or not related to the Merck product, must be reported within 24 hours to the Sponsor and within 2 working days to Merck Global Safety.

Additionally, any serious adverse event, considered by an investigator who is a qualified physician to be related to Merck product that is brought to the attention of the investigator at any time following consent through the end of the specified safety follow-up period specified in the paragraph above, or at any time outside of the time period specified in the previous paragraph also must be reported immediately to the Sponsor and to Merck Global Safety.

All subjects with serious adverse events must be followed up for outcome.
SAE reports and any other relevant safety information are to be forwarded to the Merck Global Safety facsimile number: +1-215-993-1220

7.2 Documentation of non-serious AEs or SARs

For **non-serious** AEs or SARs, documentation must begin from signing of the informed consent and continue through the 30 day follow-up period after treatment is discontinued.

Collected information should be recorded in the eCRF for that patient. Please include a description of the event, its severity or toxicity grade, onset and resolved dates (if applicable), and the relationship to the study drug. Documentation should occur at least monthly.

7.3 SAEs or Serious SARs and Events of Clinical Interest

7.3.1 Timing

All SAEs from the time of the signing of the informed consent document until 90 days after the last dose of study drug (or to the initiation of new anti-cancer treatment, whichever is earliest) will be documented and reported to Celgene and to Merck (see details on reporting in Section 7.3.3)

7.3.2 Documentation and Notification

SAEs or Serious SARs must be recorded in the SAE console within Oncore™ for that patient within 24 hours of learning of its occurrence. Additionally, the NCCN Project Manager must also be notified via email of all SAEs within 24 hours of learning of its occurrence.

7.3.3 Reporting of SAEs, Events of Clinical Interest, Pregnancies and Overdoses

IRB Reporting Requirements:

UNC:

- The UNC-IRB will be notified of all SAEs that qualify as an Unanticipated Problem as per the UNC IRB Policies using the IRB's web-based reporting system (see section 9.5.3) within 7 days of the Investigator becoming aware of the problem.

Affiliate sites:

- For affiliate sites using a local IRB of record, please submit adverse events per local IRB policy.

  Any SAEs that qualify as an Unanticipated Problem will be entered into Oncore and reported to the UNC IRB by the UNC Research Personnel using the IRB's web-based reporting system (see section 9.5.3) within 7 days of the Investigator becoming aware of the problem.

Pregnancies (Information for Reporting to Merck)

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. Pregnancies and lactations that occur after the consent form is signed but before treatment 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.

It is the responsibility of investigators or their designees to report any pregnancy or lactation in a subject (spontaneously reported to them), including the pregnancy of a male subject's female partner that occurs during the trial or within 120 days of completing the trial completing the trial, or 30 days following cessation of treatment if the subject initiates new anticancer therapy, whichever is earlier, as a serious adverse event within 24 hours to the UNCCN Project Manager who will report the event within 2 days to Merck Global Safety (see contact information below).

The patient is to be discontinued immediately from any protocol directed therapy. The study investigator will make every effort to obtain permission to follow the outcome of the pregnancy and report the condition of the fetus or newborn to the UNCCN Project Manager. All subjects and female partners of male subjects who become pregnant must be followed to the completion/termination of the pregnancy. Pregnancy outcomes of death, spontaneous abortion, congenital anomaly, missed abortion, benign hydatidiform mole, blighted ovum, fetal death, intrauterine death, miscarriage and stillbirth or other disabling or life-threatening complications to the mother or newborn must be reported as SAEs. If the pregnancy continues to term, the outcome (health of infant) must also be reported. Such events must be reported within 24 hours to the UNCCN Project Manager who will report the event within 2 days to Merck Global Safety.

<u>Pregnancies (Information for Reporting to Celgene)</u>
Pregnancies and suspected pregnancies (including a positive pregnancy test regardless of age or disease state) of a female subject occurring while the subject is on IP, or within 28 days of the subject's last dose of nab-paclitaxel, are considered immediately reportable events. Nab-paclitaxel is to be discontinued immediately. The pregnancy, suspected pregnancy, or positive pregnancy test must be reported to Celgene Drug Safety immediately by facsimile, or other appropriate method, using the Pregnancy Initial Report Form, or approved equivalent form. The female subject may be referred to an obstetrician-gynecologist (not necessarily one with reproductive toxicity experience) or another appropriate healthcare professional for further evaluation.

The Investigator will follow the female subject until completion of the pregnancy, and must notify Celgene Drug Safety immediately about the outcome of the pregnancy (either normal or abnormal outcome) using the Pregnancy Follow-up Report Form, or approved equivalent form.

If the outcome of the pregnancy was abnormal (e.g., spontaneous or therapeutic abortion), the Investigator should report the abnormal outcome as an AE. If the abnormal outcome meets any of the serious criteria, it must be reported as an SAE to Celgene Drug Safety immediately by facsimile, or other appropriate method, within 24 hours of the Investigator's knowledge of the event using the SAE Report Form, or approved equivalent form.

All neonatal deaths that occur within 28 days of birth should be reported, without regard to causality, as SAEs. In addition, any infant death after 28 days that the Investigator suspects is related to the in utero exposure to the IP should also be reported to Celgene Drug Safety immediately by facsimile, or other appropriate method, within 24 hours of the Investigator's knowledge of the event using the SAE Report Form, or approved equivalent form.

It is the responsibility of investigators or their designees to report any pregnancy or suspected pregnancy to Celgene Global Drug Safety Risk Management using a Pregnancy Report Form within 24 hours (see contact information below). If a female partner of a male subject taking nab-paclitaxel becomes pregnant, the male subject taking nab-paclitaxel should notify the Investigator, and the pregnant female partner should be advised to call their healthcare provider immediately. Male patients treated with nab-paclitaxel are advised not to father a child during and up to 6 months after treatment.

The pregnancy, suspected pregnancy, or positive pregnancy test must be reported to the UNCCN Project Manager within 24 hours via facsimile to 919-966-4300. The female subject should be referred to an obstetrician-gynecologist, preferably one experienced in reproductive toxicity for further evaluation and counseling.

FDA Expedited Reporting requirements:
If an investigator deems that an event is both a serious SAR AND unexpected, it must also (in addition to Oncore) be recorded on the MedWatch Form 3500A as per 21 CFR 312.32. The MedWatch form should be faxed to the UNCCN Project Manager at 919-966-4300 (or emailed, with address provided at the Start up Meeting (SIM)) along with supporting documentation defining the event and causality. The UNCCN Project Manager will send report to the manufacturers. The MedWatch 3500a form can be accessed at:

http://www.fda.gov/Safety/MedWatch/HowToReport/DownloadForms/default.htm

(Please be sure and access form 3500a, and not form 3500). UNC, as the Sponsor of the study, will make the final determination regarding FDA submission.

Once the UNC Principal Investigator determines an event is a serious SAR AND unexpected, the MedWatch 3500A form will be submitted to the FDA.

The UNCCN Project Manager will also be responsible for informing each Affiliate site of all serious and unexpected SARs reported to the FDA via fax as soon as possible.

Expedited Reporting by Investigator to Celgene
For the purpose of regulatory reporting, Celgene Drug Safety will determine the expectedness of events of being related to nab-paclitaxel (ABRAXANE®) based on the Investigator Brochure. In the United States, all suspected unexpected serious adverse reactions (SUSARs) will be reported in an expedited manner in accordance with 21 CFR 312.32.

SAEs are defined above. The investigator must inform Celgene in writing using a Celgene SAE form or MEDWATCH 3500A form of any SAE within 24 hours of being aware of the event. The written report must be completed and supplied to the UNC Research Personnel within 24 hours (the UNC Research Personnel will then fax to Celgene). The initial report must be as complete as possible, including an assessment of the causal relationship between the event and the investigational product(s). 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) must be documented on a follow-up report. A final report to document resolution of the SAE is required. The Celgene tracking number 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 patient records.

Any overdose of nab-paclitaxel (see Section 5.2.7) should be reported within 24 hours to Celgene.

The investigator will collect and report all secondary primary malignancies that occur in subjects on this study for a period up to 3 years following discontinuation of Nab-paclitaxel to the Celgene Drug Safety and Risk Management group.

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

Merck Reporting Requirements:
Any SAE, or follow up to a SAE, including death due to any cause other than progression of the cancer under study that occurs to any subject from the time the consent is signed through 90 days following cessation of treatment, or the

initiation of new anti-cancer therapy, whichever is earlier, whether or not related to Merck product, must be reported within 24 hours to the UNCCN Project Manager who will report the event within 2 working days to Merck Global Safety. All subjects with serious adverse events must be followed up for outcome.

Non-serious Events of Clinical Interest will be forwarded to Merck Global Safety and will be handled in the same manner as SAEs.

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

SAE reports and any other relevant safety information are to be forwarded to the UNC Research Personnel via facsimile at 919-966-4300, or scanned and emailed to UNC Research Personnel (CPOMultiCenter@med.unc.edu) who will then fax to the Merck Global Safety facsimile number: +1-215-993-1220.

All 15-Day Reports and Annual Progress Reports must be submitted as required to FDA. Investigators will cross-reference these reports to the Merck Investigational Compound Number (IND, CSA, etc.) at the time of submission. Additionally investigators will submit a copy of these reports to Merck & Co., Inc. (Attn: Worldwide Product Safety; FAX 215 993-1220) at the time of submission to FDA.

Events of Clinical Interest

Selected non-serious and serious adverse events are also known as Events of Clinical Interest (ECI) and must be reported within 24 hours to the Sponsor and within 2 working days to Merck Global Safety. (Attn: Worldwide Product Safety; FAX 215 993-1220).

For the time period beginning when the consent form is signed until treatment, any ECI, or follow up to an ECI, that occurs to any subject must be reported within 24 hours to the Sponsor and within 2 working days to Merck Global Safety if it causes the subject to be excluded from the trial, or is the result of a protocol-specified intervention, including but not limited to washout or discontinuation of usual therapy, diet, placebo treatment or a procedure.

For the time period beginning at treatment through 90 days following cessation of treatment, or 30 days following cessation of treatment if the subject initiates new anticancer therapy, whichever is earlier, any ECI, or follow up to an ECI, whether or not related to Merck product, must be reported within 24 hours to the Sponsor and within 24 hours to Merck Global Safety.

Events of clinical interest for this trial include:
1. an overdose of Merck product, as defined in Section 5.1.5 Pembrolizumab Overdose for This Protocol and Reporting of Overdose to the Sponsor, 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.

Pregnancy and Lactation
See above in this section for additional information. Such events must be reported within 2 working days to Merck Global Safety. (Attn: Worldwide Product Safety; FAX 215 993-1220).

Protocol-Specific Exceptions to Serious Adverse Event Reporting
Efficacy endpoints as outlined in this section will not be reported to Merck unless there is evidence suggesting a causal relationship between the drug and the event. Any such event will be submitted to the Sponsor within 24 hours and to Merck Global Safety within 2 working days either by electronic or paper media. Specifically, the suspected/actual events covered in this exception include any event that is disease progression of the cancer under study.

The Sponsor will monitor unblinded aggregated efficacy endpoint events and safety data to ensure the safety of the subjects in the trial. Any suspected endpoint which upon review is not progression of the cancer under study will be forwarded to Merck Global Safety as a SAE within 2 working days of determination that the event is not progression of the cancer under study

Hospitalization related to convenience (e.g.transportation issues etc.) will not be considered a SAE.

7.4 Data and Safety Monitoring Plan

The Principal Investigator will provide continuous monitoring of patient safety in this trial with periodic reporting to the Data and Safety Monitoring Committee (DSMC).

Meetings/teleconferences will be held at a frequency dependent on study accrual, and in consultation with the study Biostatistician. These meetings will include the investigators as well as protocol nurses, clinical research associates, regulatory associates, data managers, biostatisticians, and any other relevant personnel the

principal investigators may deem appropriate. At these meetings, the research team will discuss all issues relevant to study progress, including enrollment, safety, regulatory, data collection, etc.

The team will produce summaries or minutes of these meetings. These summaries will be available for inspection when requested by any of the regulatory bodies charged with the safety of human subjects and the integrity of data including, but not limited to, the oversight (Office of Human Research Ethics (OHRE) Biomedical IRB, the Oncology Protocol Review Committee (PRC) or the North Carolina TraCS Institute Data and Safety Monitoring Board (DSMB).

The UNC LCCC Data and Safety Monitoring Committee (DSMC) will review the study on a regular (quarterly to annually) basis, with the frequency of review based on risk and complexity as determined by the UNC Protocol Review Committee. The UNC PI will be responsible for submitting the following information for review: 1) safety and accrual data including the number of patients treated; 2) significant developments reported in the literature that may affect the safety of participants or the ethics of the study; 3) preliminary response data; and 4) summaries of team meetings that have occurred since the last report. Findings of the DSMC review will be disseminated by memo to the UNC PI, PRC, and the UNC IRB and DSMB.

8.0 STATISTICAL CONSIDERATIONS

8.1 Study Design

This open-label, three-arm, non-comparative randomized phase II study is designed to evaluate three different sequences of double-consolidation with pembrolizumab and nab-paclitaxel in patients with advanced NSCLC post induction chemotherapy. In ARMs A and B, consolidation is sequential, with either pembrolizumab followed by nab-paclitaxel (ARM A), or nab-paclitaxel followed by pembrolizumab (ARM B). In ARM C, consolidation is concurrent, with the two agents administered concurrently.

The primary objective is to estimate overall survival in each arm. Secondary objectives include estimating rates of response (via RECIST1.1 and Immune Related Response Criteria (irRC)), clinician observed and patient reported toxicity, and quality of life in each arm.

8.2 Sample Size and Accrual

In the Fidias trial referred to earlier [1], cytotoxic consolidation therapy provided an overall survival advantage of 2.6 months. While data are currently limited, we believe pembrolizumab, particularly in patients with tumors known to be PD-L1(+), could yield at least an additional 2.6 months. Given the null hypothesis of 9.7 months (using data from the Fidias trial), our alternative hypothesis is that double consolidation will yield a median OS of at least 15 months. Assuming uniform accrual, no loss to follow-up, exponentially distributed times, and a one-side alpha of 0.1, 35 patients per arm provide 80% power to detect this level of improvement. We anticipate accrual to take 18 months, with follow-up time of at least 12 months. This calculation was made using the SWOG Statistical Center online tool for one arm survival (https://stattools.crab.org/#).

We will consider any of the 3 ARMS worthy of additional study if the lower end of the 95% confidence interval for the estimated median OS is greater than 9.7 months, and the interval includes or exceeds 15 months.

8.3 Data Analysis Plans

The primary endpoint is the estimation of OS from the first day of study treatment, and will be done using the Kaplan-Meier (KM) method separately for each arm. The median OS will be provided along with a 95% confidence interval. If the intervals for any of the arms exclude the null hypothesis of 9.7 months, and include the alternative hypothesis of 15 months, data from those arms will be combined to provide an aggregate estimate. This will be done in the absence of a formal test to determine equivalence given the sample size.

All patients who receive at least one dose of treatment will be included in these estimates, with censoring used as needed (ex. if a patient drops out of the study, or analysis is done before all patients have had the event of interest). The KM

method, along with Log-rank tests, will be used for exploratory objectives which include comparisons between groups (ex. biological markers).

Progression Free Survival (PFS) will also be reported and estimated in two different ways. Traditional PFS will be defined as the time from D1 of treatment until death or first progression. We will define Off Treatment PFS as the time from D1 of treatment until death, progression that results in the patient coming off of treatment, or any progression after treatment completion. For Off Treatment PFS, the patients in the sequential arms (A&B) will not be considered a progression if they progress on the first treatment and then switch to the second treatment early. For example, a patient on the sequential pembrolizumab then nab-paclitaxel arm whose cancer progresses at 6 weeks on pembrolizumab, but then completes 12 weeks of nab-paclitaxel followed by progression 16 weeks later, would be an Off Treatment PFS of 34 weeks.

Descriptive statistics (percentages and means/standard deviations) will be used to summarize the response rates and quality of life scores. Depending on the availability of data, longitudinal models may be used to describe changes in quality of life scores over time. Fisher's exact tests and Wilcoxon rank sum tests will be used to explore the association of exploratory endpoints (ex. biological biomarkers) with response as appropriate.

A spider plot (example in section 1.4) will be used to show changes from baseline in tumor response over time. With one line per patient (color coded based on treatment), the reader can see how tumor growth changed over time, and in conjunction with changes in treatment.

Safety will be evaluated by reporting any clinically relevant toxicity (both patient and physician reported). Additionally, continuous monitoring for toxicity will be employed for Arm C. Sequential boundaries will be used to monitor for unexpected toxicity in > 10% of patients. For this study this will be defined as any grade 3 or higher toxicity other than grade 3 neutropenia, grade 3 immune-related hepatitis, grade 3 immune-related colitis, grade 3 immune-related pneumonitis, grade 3 sensory neuropathy or grade 3 anemia that occurs during the first two cycles of treatment.

The accrual will be halted if excessive numbers of patients experience an unacceptable toxicity --that is, if the number of patients is equal to or exceeds b_n out of n patients with full follow-up (see table below). This is a Pocock-type stopping boundary that yields the probability of crossing the boundary at most 0.05 when the rate of unacceptable toxicity is equal to the acceptable rate of 10%. [http://cancer.unc.edu/biostatistics/program/ivanova/ContinuosMonitoringForToxicity

Number of Patients, n	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20
Boundary, b_n	-	2	3	3	3	4	4	4	4	5	5	5	5	5	6	6	6	6	6	

Number of Patients, n	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35	36	37	38	39	40
Boundary, b_n	6	7	7	7	7	7	7	8	8	8	8	8	8	9	9	9	9	9	9	9

9.0 STUDY MANAGEMENT

9.1 Institutional Review Board (IRB) Approval and Consent

It is expected that the IRB will have the proper representation and function in accordance with federally mandated regulations. The IRB should approve the consent form and protocol.

In obtaining and documenting informed consent, the investigator should comply with the applicable regulatory requirement(s), and should adhere to Good Clinical Practice (GCP) and to ethical principles that have their origin in the Declaration of Helsinki.

Before recruitment and enrollment onto this study, the patient will be given a full explanation of the study and will be given the opportunity to review the consent form. Each consent form must include all the relevant elements currently required by the FDA Regulations and local or state regulations. Once this essential information has been provided to the patient and the investigator is assured that the patient understands the implications of participating in the study, the patient will be asked to give consent to participate in the study by signing an IRB-approved consent form.

Prior to a patient's participation in the trial, the written informed consent form should be signed and personally dated by the patient and by the person who conducted the informed consent discussion.

9.2 Required Documentation

Before the study can be initiated at any site, the following documentation must be provided to the Clinical Protocol Office (CPO) at the University of North Carolina.

- A copy of the official IRB approval letter for the protocol and informed consent
- IRB membership list
- CVs and medical licensure for the principal investigator and any sub-investigators who will be involved in the study.
- Form FDA 1572 appropriately filled out and signed with appropriate documentation (NOTE: this is required if UNC holds the IND. Otherwise, the Investigator's signature documenting understanding of the protocol and providing commitment that this trial will be conducted according to all stipulations of the protocol is sufficient to ensure compliance)
- CAP and CLIA Laboratory certification numbers and institution lab normal values
- Executed clinical research contract

9.3 Registration Procedures

All patients must be registered with the LCCC CPO UNCCN at the University of North Carolina before enrollment to study. To register a patient call the UNCCN at 919-966-7359 M-F 8:30am- 5pm EST. Fax (919-966-4300) or email (address to be provided at SIM) registration form, signed informed consents and all source documents to confirm eligibility..

9.4 Data Management and Monitoring/Auditing

The CPO UNCCN of the UNC LCCC will serve as the coordinating center for this trial. Data will be collected through a web based clinical research platform, OnCore®. Other study institutions will be given a password to directly enter their own data onto the web site via eCRFs. UNCCN personnel will coordinate and manage data for quality control assurance and integrity.

All data will be collected and entered into OnCore® by Clinical Research Associates (CRAs) from UNC LCCC and participating institutions. The investigators at each site will allow monitors to review all source documents supporting data entered into OnCore®. The UNCCN Data Coordinator can be reached at 919-843-2742 or 1-877-668-0683.

As an investigator initiated study, this trial will also be audited by the Lineberger Cancer Center audit committee every six or twelve months, depending on the participation of affiliate sites.

9.5 Adherence to the Protocol

Except for an emergency situation in which proper care for the protection, safety, and well-being of the study patient requires alternative treatment, the study shall be conducted exactly as described in the approved protocol.

9.5.1 Emergency Modifications

UNC and Affiliate investigators may implement a deviation from, or a change of, the protocol to eliminate an immediate hazard(s) to trial subjects without prior UNC or their respective institution's IRB/IEC approval/favorable opinion.

<u>For Institutions Relying on UNC's IRB:</u>
For any such emergency modification implemented, a UNC IRB modification form must be completed by UNC Research Personnel within five (5) business days of making the change.

<u>For Institutions Relying on Their Own IRB:</u>
For Affiliate investigators relying on their own institution's IRB, as soon as possible after the modification has been made, the implemented deviation or change and the reasons for it should be submitted to:

- To UNC Principal Investigator for agreement

- The Affiliate institution's IRB for review and approval. (Once IRB's response is received, this should be forwarded to the UNCCN Regulatory Associate).

9.5.2 Single Patient/Subject Exceptions

Eligibility single subject exceptions are not permitted for Lineberger Comprehensive Cancer Center Investigator Initiated Trials under any circumstance. Other types of single subject exceptions may be allowed if proper regulatory review has been completed in accordance with for Lineberger Comprehensive Cancer Center's Single Subject Exceptions Policy.

9.5.3 Other Protocol Deviations/Violations

According to UNC's IRB, a protocol deviation is any unplanned variance from an IRB approved protocol that:

- Is generally noted or recognized after it occurs
- Has no substantive effect on the risks to research participants
- Has no substantive effect on the scientific integrity of the research plan or the value of the data collected
- Did not result from willful or knowing misconduct on the part of the investigator(s).

An unplanned protocol variance is considered a violation if the variance meets any of the following criteria:

- Has harmed or increased the risk of harm to one or more research participants.
- Has damaged the scientific integrity of the data collected for the study.
- Results from willful or knowing misconduct on the part of the investigator(s).
- Demonstrates serious or continuing noncompliance with federal regulations, State laws, or University policies.

If a deviation or violation occurs please follow the guidelines below:

For Institutions Relying on UNC's IRB:
Protocol Deviations: UNC or Affiliate personnel will record the deviation in OnCore®, and report to any sponsor or data and safety monitoring committee in accordance with their policies. Deviations should be summarized and reported to the IRB at the time of continuing review.

Protocol Violations: Violations should be reported by UNC personnel within one (1) week of the investigator becoming aware of the event using the same IRB online mechanism used to report Unanticipated Problems.

For Institutions Relying on Their Own IRB:
In addition to adhering to the policies regarding protocol compliance set forth by your institution's IRB, the following is also required:

Protocol Deviations: In the event a deviation from protocol procedures is identified, record the deviation in OnCore®.

Protocol Violations: Any protocol violation that occurs must be reported to your IRB per institutional policies and reported to the UNCCN Project Manager within 5 days. UNC-CH will determine if the violation affects the safety of the patient and integrity of the data. Once your institution's IRB response is received, please forward to the UNCCN Regulatory Associate.

Unanticipated Problems:
Affiliate Sites:
Any events that meet the criteria for "Unanticipated Problems (UPs)" as defined by UNC's IRB must also be reported to the UNCCN Project Manager. The UNCCN Project Manager will report the event to the UNC IRB using the IRB's web-based reporting system. Examples of such UPs include a lost or stolen laptop computer that contains sensitive study information.

UNC
Any events that meet the criteria for "Unanticipated Problems" as defined by UNC's IRB must be reported by the Study Coordinator using the IRB's web-based reporting system.

9.6 Amendments to the Protocol

Should amendments to the protocol be required, the amendments will be originated and documented by the Principal Investigator at UNC. It should also be noted that when an amendment to the protocol substantially alters the study design or the potential risk to the patient, a revised consent form might be required.

For Institutions Relying on UNC's IRB:
The written amendment, and if required the amended consent form, must be sent to UNC's IRB for approval prior to implementation.

For Institutions Relying on Their Own IRB:
Investigators must submit the UNC IRB approved amendment to their institution's IRB for approval. For multi-center studies, any affiliate site must submit their informed consent revisions to the UNCCN Regulatory Associate prior to submission to their IRB.

9.7 Record Retention

Study documentation includes all eCRFs, data correction forms or queries, source documents, Sponsor-Investigator correspondence, monitoring logs/letters, and

regulatory documents (e.g., protocol and amendments, IRB correspondence and approval, signed patient consent forms).

Source documents include all recordings of observations or notations of clinical activities and all reports and records necessary for the evaluation and reconstruction of the clinical research study.

Government agency regulations and directives require that all study documentation pertaining to the conduct of a clinical trial must be retained by the study investigator. In the case of a study with a drug seeking regulatory approval and marketing, these documents shall be retained for at least two years after the last approval of marketing application in an International Conference on Harmonization (ICH) region. In all other cases, study documents should be kept on file until three years after the completion and final study report of this investigational study.

9.8 Obligations of Investigators

The Principal Investigator is responsible for the conduct of the clinical trial at the site in accordance with Title 21 of the Code of Federal Regulations and/or the Declaration of Helsinki. The Principal Investigator is responsible for personally overseeing the treatment of all study patients. The Principal Investigator must assure that all study site personnel, including sub-investigators and other study staff members, adhere to the study protocol and all FDA/GCP/NCI regulations and guidelines regarding clinical trials both during and after study completion.

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11.0 APPENDICES

11.1 Appendix A Cockcroft-Gault Formula

$$\text{Estimated creatinine clearance (mL/min)} = \frac{(140 - \text{age in years}) \times (\text{weight in kg})}{72 \times (\text{serum creatinine in mg/dL})}$$

For females, use 85% of calculated creatinine clearance value.

11.2 Appendix B Charlson Comorbidity Index Scoring System

Table 1. Charlson Comorbidity Index Scoring System

Score	Condition
1	Myocardial infarction (history, not ECG changes only)
	Congestive heart failure
	Peripheral vascular disease (includes aortic aneurysm ≥6 cm)
	Cerebrovascular disease: CVA with mild or no residua or TIA
	Dementia
	Chronic pulmonary disease
	Connective tissue disease
	Peptic ulcer disease
	Mild liver disease (without portal hypertension, includes chronic hepatitis)
	Diabetes without end-organ damage (excludes diet-controlled alone)
2	Hemiplegia
	Moderate or severe renal disease
	Diabetes with end-organ damage (retinopathy, neuropathy, nephropathy, or brittle diabetes)
	Tumor without metastases (exclude if >5 y from diagnosis)
	Leukemia (acute or chronic)
	Lymphoma
3	Moderate or severe liver disease
6	Metastatic solid tumor
	AIDS (not just HIV positive)

NOTE. For each decade > 40 years of age, a score of 1 is added to the above score.
Abbreviations: ECG, electrocardiogram; CVA, cerebrovascular accident; TIA, transient ischemic attack; AIDS, acquired immunodeficiency syndrome; HIV, human immunodeficiency virus.

11.3 Appendix C: ECOG Performance Status

Grade	Description
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (e.g., light housework, office work).
2	In bed <50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead.
* As published in Am. J. Clin. Oncol.: *Oken, M.M., Creech, R.H., Tormey, D.C., Horton, J., Davis, T.E., McFadden, E.T., Carbone, P.P. Toxicity and Response Criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol* 5:649-655, 1982. The Eastern Cooperative Oncology Group, Robert Comis M.D., Group Chair.	