STUDY NUMBER: CASE 6115

Clinicaltrials.gov #: NCT03121352

Protocol Date: 04.04.2022

STUDY TITLE: **Pilot Study of Carboplatin, Nab-Paclitaxel and Pembrolizumab for Metastatic Triple-Negative Breast Cancer**

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SPONSOR: Case Comprehensive Cancer Center

SUPPORT/FUNDING: Merck

SUPPLIED AGENT***:*** Pembrolizumab

IND #: [redacted]

[redacted] AGENT***(S):*** Nab-paclitaxel, Carboplatin

SUMMARY OF CHANGES

Protocol Date	Section	Change
11/01/2016		Initial IRB approval
02/07/2017	6.2	Revised to indicate that steroids are permitted as an anti-emetic during chemotherapy.
	11.2	Revised to indicate the timing of the tests and procedures: the text was changed from Day 1 of cycle 1-3 to Day 1 of cycle 1-n[1], Day 8 of cycle 1-3 was changed to Day 8 of Cycle 1- n[1] and Day 15 of cycle 1-3 was changed to Day 15 of cycle 1- n[1] and End of Treatment was changed to 30 Day Follow-up; in addition footnote #1 was added to clarify that patients may receive treatment for up to 24 months; a row was added to clarify that the thyroid hormone tests are being done at Screening and on Day 1 of each cycle and that this test is not included with the serum chemistries done weekly.
02/22/2017	8.1	Revised to include the updated risk profile from Investigator Brochure v13
	10.4	Updated with the contact information for the central laboratory that will be processing the biopsy samples for PDL-1 expression testing and to indicate that samples will be shipped in batches
	11.1	Text was added to clarify that T4 testing is for Thyroxine
	11.2	Revised to clarify that T4 testing is for Thyroxine and that Urinalysis is performed at screening
10/16/2017	Cover page	Revised to add IND # and update institution name from University Hospitals Case Medical Center to University Hospitals Cleveland Medical Center, version date
	Treatment Schema	Carboplatin changed to AUC 4.5 and nab-paclitaxel to 75 mg/m^2.
	Protocol Synopsis-Interventions	Carboplatin changed to AUC 4.5 and nab-paclitaxel to 75 mg/m^2.
	1.3	NB: For the first 2 patients entered into this study at dosing levels of carboplatin AUC 6 and nab-paclitaxel 100 mg/m^2, there were significant treatment delays with subsequent dose reductions because of prolonged thrombocytopenia and profound asthenia. Therefore, moving forward, it was decided to reduce the starting doses of carboplatin and nab-paclitaxel by 25% (i.e., carboplatin at AUC 4.5 and nab-paclitaxel at 75mg/m^2).
	4.1.2	Subjects must have received no more than 2 prior therapies for metastatic triple-negative breast cancer.
	6.1	Patients will then receive 3 cycles of CNP. Carboplatin (C) will be administered intravenously (IV) on day 1 of a 21-day cycle at AUC 4.5. Nab-paclitaxel (N) will be administered at 75 mg/m^2 IV on days 1, 8 and 15 of a 21-day cycle. Pembrolizumab (P) will be administered at a dose of 200 mg IV on day 15 of each cycle, prior to any chemotherapy.
	6.1.1	C, Carboplatin, AUC 4.5 IV day 1 of 21-day cycle N, Nab-paclitaxel, 75mg/m^2 IV days 1, 8 and 15 of 21-day cycle

<table>
<tr><td></td><td></td><td>P, Pembrolizumab, 200 mg IV every 21 days

NB: If there is a treatment delay on day 8 because of low blood counts (ANC or platelets), then day 8 nab-paclitaxel will be held. If blood counts have recovered on day 15, then nab-paclitaxel will be administered at 75% dose from the day 1 dose in combination with the standard dose of pembrolizumab (200 mg IV). If blood counts have not recovered by day 15, nab-paclitaxel will continue to be held but pembrolizumab will be administered as a single agent.</td></tr>
<tr><td></td><td>6.1.2</td><td>Carboplatin starting dose level: Dose level 0 at AUC 4.5 given IV every 3 weeks.
Carboplatin does reductions will occur for any ≥ grade 3 hematologic toxicity or a ≥ grade 2 non-hematologic toxicity.
The carboplatin dose will be reduced by 25% (AUC 3.4) for all subsequent cycles of therapy.

Nab-paclitaxel starting dose level: Dose level 0 at 75 mg/m^2 given IV weekly.
The first and subsequent doses of nab-paclitaxel will be delayed until ANC > 1000/µl and platelets > 100,000/µl and resolution of any grade ≥2 non-hematologic toxicities except residual grade 2 neuropathy.
In patients experiencing febrile neutropenia or delay of recovering of ANC to > 1000/µl beyond day 21 of the preceding cycle or the development of grade ≥3 non-hematologic toxicities, subsequent doses of nab-paclitaxel will be reduced by 25% to 56 mg/m2 for all subsequent cycles of therapy. For recurrence of these dose-limiting toxicities, protocol therapy will be discontinued.</td></tr>
<tr><td></td><td>6.2.3</td><td>The carboplatin dose will be reduced by 25% (AUC 3.4).
In patients experiencing febrile neutropenia or delay of recovering of ANC to > 1000/µl beyond day 21 of the preceding cycle or the development of grade >3 non-hematologic toxicities, subsequent doses of nab-paclitaxel will be reduced by 25% to 56 mg/m^2. For recurrence of these dose-limiting toxicities, protocol therapy will be discontinued.
<table>
<tr><td>Dose level</td><td>C</td><td>N</td><td>P</td></tr>
<tr><td>-1</td><td>Dose level 0 - 25% (AUC 3.4)</td><td>Dose level 0 - 25% (56mg/m^2)</td><td>200 mg IV</td></tr>
<tr><td>0</td><td>AUC 4.5</td><td>75 mg/m^2</td><td>200 mg IV</td></tr>
</table></td></tr>
<tr><td></td><td>9.2.1</td><td>Route of administration: AUC 4.5 IV on Day 1 of 21-day cycle.</td></tr>
<tr><td></td><td>11.1.2</td><td>C, Carboplatin, will be administered AUC 4.5 IV day 1 of 21-day cycle.
N, Nab-paclitaxel, will be administered 75 mg/m^2 IV days 1, 8 and 15 of 21-day cycle.
P, Pembrolizumab, will be administered 200 mg IV every 21 days .</td></tr>
</table>

12/04/17	Cover page	Revised version date
	7.0	Dose Modification Table for the management of immune-related adverse events associated with Pembrolizumab updated to include new risks identified in Investigator Brochure v15
	8.1	Revised to include the updated risk profile from Investigator Brochure v15
01/18/18	Cover page	Revised version date
	10.0	Corrections have been made to the biopsy collection and specimen processing paragraphs regarding the type of samples being obtained
	11.2	Study Calendar has been revised to indicate that the post-treatment biopsy is taken after the completion of 3 cycles of treatment not at the 30 day follow-up time point
06/28/18	Cover page	Revised version date
	6.1	Revised to clarify the timing of radiologic restaging.
	6.1.1	Revised to clarify that missed doses of paclitaxel are not made up in order to maintain dosing of pembrolizumab every 3 weeks
	6.1.2	Revised to clarify carboplatin dosing and criteria for removal from study due to treatment delay
	7.0	Revised to clarify timing of dose delays/dose modifications
	10.0	Revised to clarify that the biopsy can be obtained with a range of needle gauges per institutional practice
	11.1.1	Revised to clarify that screening studies and evaluations can be completed within 28 days of study entry
	11.2	Revised to specify the lab tests that can be done within the 3 day window
09/17/18	Cover page	Revised version date
	3.4	Revised to clarify duration of treatment for patients who respond
	6.1	Text added to clarify that patients experiencing pseudo-progression will be able to continue to receive an additional 3 cycles of treatment
	6.1.2	Revised to clarify criteria for dose reductions
	6.2	Revised to clarify when the use of growth factor support is appropriate
	8.1	The risks of pembrolizumab have updated to be consistent with the changes in the latest Investigator Brochure
	8.4.6	The FDA reporting requirements for Serous Adverse Events have been added in this section.
	10.0	Revised to have the needle gauge range consistent throughout
	11.2	Footnotes have been added to the Study Calendar to clarify the timing of the optional biopsy and Cycle 3 disease assessment scans
11/12/18	Cover page	Revised version date
	6.1.2	Revised to clarify the circumstances where patients can continue to receive treatment even though one or more of the medications needs to be discontinued: patients who have an allergic reaction to carboplatin can continue to be treated with nab-paclitaxel as a single agent on days 1 and 8 and nab-paclitaxel with pembrolizumab on day 15 for each subsequent cycle; patients who experience a grade $\geq$2 toxicity that persists resulting in a treatment delay of more than 4 weeks attributable to carboplatin and/or nab-paclitaxel but not pembrolizumab, may continue on single-agent pembrolizumab given every 3 weeks intravenously as long as there is evidence for ongoing clinical benefit to the patient (i.e., regression or stability of metastatic disease); however, patients who have a grade $\geq$2

		toxicity that persists resulting in a treatment delay of more than 4 weeks where attribution to either carboplatin, nab-paclitaxel or pembrolizumab cannot be distinguished, then protocol treatment will be discontinued and the patient will be removed from the study.
01/14/19	Cover page	Revised version date
	11.2	Revised to clarify the timing of study visits and tests for patients who had discontinued chemotherapy due to toxicities experienced but who tolerate and continue to receive pembrolizumab
	Appendix II	Title corrected
08/16/19	Cover page	Revised version date; updated the contact information for the study coordinator
	8.1	The risks of pembrolizumab were updated to be consistent with the changes in the latest Investigator Brochure
	11.2	Revised to clarify that the tests for the 30 day follow-up visit can be done within a 3 day window
	13.1	Revised to indicate the use of the 21 CFR Part 11 compliant electronic data capture system, Forte EDC in addition to OnCore®
10/02/19	Cover page	Revised version date
	6.1.2	Revised to clarify that the protocol does not allow for dose delays for study medications; since the drug is held not delayed patients continue to be treated per the study schedule with no change for subsequent cycles.
	8.2	The risks of Carboplatin were revised to correct the typographical error under LESS COMMON third bullet point. It should be cough instead of bough.
05/31/21	Cover page	Revised version date; updated the study staff and the contact information for the study coordinator
	6.2	Revised to clarify which influenza vaccines are permitted and the use of systemic coriticosteroids
	7.0	Dose Modification Table for the management of immune-related adverse events associated with Pembrolizumab updated to include new risks identified in Investigator Brochure v20; revised to clarify timing of dose delays/dose modifications
	8.1	The risks of pembrolizumab were updated to be consistent with the changes in the latest Investigator Brochure
04/04/22	Cover page	Revised version date
	6.4	The sponsor has decided to limit the follow-up period to at least 12 months after the post 30 day follow-up.
	11.1.4	The sponsor has decided to limit the follow-up period to at least 12 months after the post 30 day follow-up.

TREATMENT SCHEMA

Day	1	8	15	22	29	36	43	50	57
C	X			X			X		
N	X	X	X	X	X	X	X	X	X
P			X			X			X

C, Carboplatin, AUC 4.5 IV day 1 of 21-day cycle
N, Nab-paclitaxel, 75mg/m^2 IV days 1, 8 and 15 of 21-day cycle
P, Pembrolizumab, 200 mg IV every 21 days

Protocol Synopsis:

Protocol Number/Title	Case 6115: Pilot Study of Carboplatin, Nab-Paclitaxel and Pembrolizumab for Metastatic Triple-Negative Breast Cancer
Study Phase	Pilot
Brief Background/Rationale	Given the significant activity of single-agent pembrolizumab in a heavily pre-treated cohort of patients with mTNBC and the favorable cytotoxic and immunomodulatory properties of carboplatin and nab-paclitaxel, there is a strong rationale to treat patients with mTNBC with the combination of carboplatin (C), nab-paclitaxel (N) and pembrolizumab (P) (CNP).
Primary Objective	Primary Endpoint(s) Determine overall response rate (ORR) in patients treated with CNP.
Secondary Objective(s)	Determine progression-free survival (PFS) in patients treated with CNP. Determine disease control rate (DCR) in patients treated with CNP.
Correlative Objective(s)	Correlative Endpoint(s) Identify pathologic and genomic correlates of response to CNP. Determine safety/tolerability of CNP.
Sample Size	30 patients
Disease sites/Conditions	Metastatic Triple-Negative Breast Cancer
Interventions	C, Carboplatin, AUC 4.5 IV day 1 of 21-day cycle N, Nab-paclitaxel, 75mg/m^2 IV days 1, 8 and 15 of 21-day cycle P, Pembrolizumab, 200 mg IV every 21 days

Abbreviations

CCCC	Case Comprehensive Cancer Center
CRF	Case Report Form
DCRU	Dahm's Clinical Research Unit
DSTC	Data Safety Toxicity Committee
FDA	Food and Drug Administration
ICF	Informed Consent Form
IRB	Institutional Review Board
PRMC	Protocol Review and Monitoring Committee
SOC	Standard of Care
CCF	Cleveland Clinic Foundation
UH	University Hospitals
TNBC	Triple Negative Breast Cancer
mTNBC	Metastatic Triple Negative Breast Cancer
BC	Breast Cancer
EGFR	Epidermal Growth Factor Receptor
TIL	Tumor-infiltrating lymphocytes
Tregs	Regulatory T-Cells
MDSC	Myeloid-derived Suppressor Cells
C	Carboplatin
N	Nab-paclitaxel
P	Pembrolizumab
CNP	Carboplatin, nab-paclitaxel, pembrolizumab

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1.0 Introduction

1.1 Background of Study Disease

Triple-negative breast cancer (TNBC) constitutes 10-15% of newly-diagnosed breast cancer (BC) and is associated with an aggressive phenotype and a high risk of distant metastases with decreased survival [1-4]. Molecular profiling of TNBC has demonstrated that the majority of cases have a basal-like subtype with high expression of the epidermal growth factor receptor (EGFR), basal cytokeratins, and genes involved in proliferation [5, 6]. Unlike ER+ and HER2+ BC, there are no targeted agents against TNBC and clinical trials of therapeutic agents against putative biological targets of metastatic TNBC, such as EGFR [7, 8] and poly-ADP-ribose polymerase [9], have been largely negative in terms of improved survival.

TNBC is characterized by tumor-infiltrating lymphocytes (TIL) [10], which are composed of a variety of cells including natural killer cells, B lymphocytes and CD4+ and CD8+ T cells [11]. Of note, studies have demonstrated that BC associated with high levels of TIL has a better prognosis than BC associated with low or no TIL [12-14]. Also, the presence of TIL in the tumor microenvironment appears to be indicative of an immune recognition of tumor-associated antigens, particularly in highly proliferative tumors [11].

However, potent immune suppressive signals exist within the tumor microenvironment which are mediated by infiltrating cells such as regulatory T cells (Tregs) and myeloid-derived suppressor cells (MDSC) [15-20] as well as by cell-surface ligand/receptor interactions such as those mediated, for example, by programmed death 1 (PD-1) with its ligand, PD-L1 [reviewed in 21]. TIL express high levels of PD-1 [22] which, when bound by its cognate receptor PD-L1 on tumor cells, causes apoptosis of the PD-1+ CD8+ cytotoxic T cell [21].

It has been shown that PD-L1 is expressed in some TNBC and such PD-L1+ TNBC has a greater CD8 (+) T cell infiltrate than PD-L1 negative tumors [23]. Therefore, one approach to decrease immune suppression in the tumor microenvironment of TNBC is to interfere with the PD-1/PD-L1 signaling pathway. Thus, a recent phase Ib study of single-agent pembrolizumab in 32 patients with advanced TNBC [24] has demonstrated that 16.1% of patients had a partial response to therapy and 9.7% had stable disease. These findings attest to the effectiveness of single-agent pembrolizumab in a subset of heavily pre-treated patients with recurrent/metastatic TNBC.

1.2 Name and Description of Chemo-Immunotherapy

Metastatic TNBC (mTNBC) is responsive to cytotoxic chemotherapy and the combination of carboplatin and nab-paclitaxel has been shown to be a particularly effective regimen with an excellent safety profile when combined with antibody-based therapy [25, 26]. In particular, a phase 2 clinical trial (25) of nab-paclitaxel given at 100 mg/m^2 weekly for 3/4 weeks, carboplatin given at AUC 2 weekly for 3/4 weeks and

bevacizumab given at 100 mg/m^2 every 2 weeks demonstrated significant activity in patients with mTNBC with an overall response rate of 85% and a median progression-free survival of 9.2 months.

Studies have also demonstrated that immunotherapy of cancer is augmented by concomitant cytotoxic chemotherapy [reviewed in 27]. It appears that the 2 major immunomodulatory mechanisms mediated by chemotherapy involve, first, the downregulation of infiltrating immune suppressor cells such as Tregs and MDSC [28] and, second, an increase in local tumor antigen release and the subsequent uptake and processing of such antigens by dendritic cells, which in turn prime cytotoxic CD8+ T cells against the tumor targets [29, 30]. Of significant interest, carboplatin [31-33] has favorable immunomodulatory properties and is also an active agent against TNBC (14, 34).

1.3 Rationale

Given the significant activity of single-agent pembrolizumab in a heavily pre-treated cohort of patients with mTNBC and the favorable cytotoxic and immunomodulatory properties of carboplatin and nab-paclitaxel, there is a strong rationale to treat patients with mTNBC with the combination of carboplatin (C), nab-paclitaxel (N) and pembrolizumab (P) (CNP).

NB: For the first 2 patients entered into this study at dosing levels of carboplatin AUC 6 and nab-paclitaxel 100 mg/m^2, there were significant treatment delays with subsequent dose reductions because of prolonged thrombocytopenia and profound asthenia. Therefore, moving forward, it was decided to reduce the starting doses of carboplatin and nab-paclitaxel by 25% (i.e., carboplatin at AUC 4.5 and nab-paclitaxel at 75mg/m^2).

1.4 Background and rationale of correlative studies

As stated above, TNBC expresses PD-L1 as well as a variety of other genomic markers and these will be assayed in this study. Tumor tissue from the primary and metastatic sites (biopsied pre and post therapy) from up to 30 patients will be used for analysis of PD-L1 expression by immunohistochemistry, TIL scoring (intratumoral and stromal per Loi et al) and genomic analysis. RNA and DNA will be extracted from tumor cores using Qiagen AllPrep FFPE Kit. Affymetrix Human Transcriptome Array (HTA) 2.0 will be used to generate whole genome gene expression data. After normalization and gene-level expression summarization, the Pietenpol molecular subytypes will be assessed TNBC using the online "TNBC type" tool (36).

In addition, newer classifications of TNBC (37) that have identified Basal-Like Immune activated (BLIA) and Basal-like Immune Suppressed (BLIS) phenotypes, will be applied to the dataset. Furthermore, pathway analysis using NCI-PID will be performed to assess differential pathway expression between responders and non-responders. Finally, predefined immune signatures will be scored for each sample (38).

2.0 Objectives

2.1 Primary Objective

- Determine overall response rate (ORR) in patients treated with CNP

2.2 Secondary Objective(s)

- Determine progression-free survival (PFS), and disease control rate (DCR) in patients treated with CNP.
- Determine duration of response in patients treated with CNP.
- Determine safety/tolerability of CNP.

2.3 Correlative Objective(s)

- Identify pathologic and genomic correlates of response to CNP.

3.0 Study Design

3.1 Study design including dose escalation / cohorts

This is prospective pilot clinical trial of CNP in up to 30 patients with mTNBC.

3.2 Number of Subjects

Approximately 30 subjects will be enrolled in this trial.

3.3 Replacement of Subjects

If a subject is not administered the first full cycle of study drug regimen, the subject will be replaced because he/she has not taken enough drug to confirm safety at that dose level.

3.4 Expected Duration of Treatment and Subject Participation

Duration of treatment with P will be limited to 2 years in individual patients, with possibility for an additional year of treatment in patients who stop treatment in a state of response (stable disease or better) and progress. Patients with a confirmed CR will get one additional full course of carboplatin + nab-paclitaxel + pembrolizumab (i.e., 3 doses of pembrolizumab) and will then be restaged. If they continue to be in CR, then all treatment will be stopped and they will get repeat restaging scans every 3 months. If there is a post-CR relapse, then patients will be retreated once again with 3 full cycles of CNP and then restaged. A decision about additional treatment will be made on the basis of the restaging results.

4.0 Subject Selection

Each of the criteria in the sections that follow must be met in order for a subject to be considered eligible for this study. Use the eligibility criteria to confirm a subject's eligibility.

Subject's Name

_____

Medical Record #

_____

Research Nurse / Study Coordinator Signature:

_____

Date _____

Treating Physician [Print]

_____

Treating Physician Signature:

_____

Date _____

4.1 Inclusion Criteria

___ 4.1.1 Subjects must have histologically or cytologically confirmed metastatic triple negative breast cancer.

___ 4.1.2 Subjects must have received no more than 2 prior therapies for metastatic triple-negative breast cancer.

___ 4.1.3 Age ≥ 18 years. Because no dosing or adverse event data are currently available on the use of the proposed investigational drug combination in subjects < 18 years of age, children are excluded from this study.

___ 4.1.4 ECOG Performance Status 0-1 [See Appendix I].

___ 4.1.5 Subjects must have normal organ and marrow function as defined below:

- Hemoglobin ≥ 10.0 g/dl
- Absolute neutrophil count ≥ 1,000/μL
- Platelet count ≥ 100,000/μL

- Total bilirubin within normal institutional limits
- AST (SGOT) ≤ 2.5 X institutional upper limit of normal
- ALT (SGPT) ≤ 2.5 X institutional upper limit of normal
- Serum creatinine ≤ 1.5 normal institutional limits

___ 4.1.6 Life expectancy of 12 weeks or more.

___ 4.1.7 Subjects must have the ability to understand and the willingness to sign a written informed consent document.

___ 4.1.8 Subjects must have measurable disease per RECIST v1.1

___ 4.1.9 Subjects must be willing to undergo a preliminary biopsy of a metastatic focus for research purposes. A second post-treatment biopsy will be offered but will not be mandated.

4.2 Exclusion Criteria

___ 4.2.1 Prior treatment toxicities have not resolved to ≤ Grade 1 according to NCI CTCAE Version 4.0 (except for alopecia and neuropathy).

___ 4.2.2 Subjects receiving any other investigational agents.

___ 4.2.3 Subjects with radiographically stable treated brain metastases are eligible but must not have been on steroid therapy for at least 4 weeks.

___ 4.2.4 History of allergic reactions attributed to compounds of similar chemical or biologic composition to nab-paclitaxel, carboplatin, pembrolizumab, or other agents used in this study.

___ 4.2.5 Subjects with uncontrolled intercurrent illness including, but not limited to ongoing or active infection, symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia, or psychiatric illness/social situations that would limit compliance with study requirements.

___ 4.2.6 Pregnant or breastfeeding women are excluded from this study because the study agents include the potential for teratogenic or abortifacient effects. Because there is an unknown, but potential risk for adverse events in nursing infants secondary to treatment of the mother with the study agents, breastfeeding should be discontinued if the mother is treated with the study agents. These potential risks may also apply to other agents used in this study.

Female subjects 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.

Women of childbearing potential and men must agree to use adequate contraception (hormonal or barrier method of birth control; abstinence) prior to study entry and for the duration of study participation. Should a woman become pregnant or suspect she is pregnant while participating in this study, she should inform her treating physician immediately.

___ 4.2.7 Patients with conditions requiring immunosuppressive medications or chronic infections (including HIV infection, hepatitis B and C).

___ 4.2.8 Patients with chronic autoimmune disease.

___ 4.2.9 Patients with prior therapy with antibodies that modulate T-cell function (e.g., anti-PD-1, anti-PD-L1)

___ 4.2.10 Patients with evidence of active, non-infectious pneumonia.

___ 4.2.11 Patients active infection requiring intravenous systemic therapy.

___ 4.2.12 Patients with known psychiatric or substance abuse disorders that would interfere with cooperation with requirements of the trial.

___ 4.2.13 Patients who have received a live vaccine within 30 days prior to the first dose of pembrolizumab.

___ 4.2.14 Patients with a known additional malignancy that is progressing or requires active treatment (within the last 5 years). Exceptions: basal cell carcinoma of the skin, squamous cell carcinoma of the skin or in situ cervical cancer that has undergone potentially curative therapy.

___ 4.2.15 Patients who have received monoclonal anti-cancer antibody within 4 weeks of first dose of study drugs.

___ 4.2.16 Patients who have received chemotherapy, small molecule targeted therapy or radiation within the 2 weeks of first dose of study drugs.

___ 4.2.17 Patients who have participated in MK-3475 Merck studies.

___ 4.2.18 Patients with carcinomatous meningitis.

4.3 Inclusion of Women and Minorities

Women and members of all races and ethnic groups are eligible for this trial.

5.0 Registration

All subjects who have been consented are to be registered in the OnCore™ Database. For those subjects who are consented, but not enrolled, the reason for exclusion must be recorded.

All subjects will be registered through UHCMC and will be provided a study number by contacting the study coordinator listed on the cover page.

6.0 Treatment Plan

6.1 Treatment Regimen Overview

Patients will initially undergo baseline blood work and radiological staging to determine eligibility for enrollment into the study. Patients must have biopsy-proven mTNBC, which will be obtained as a baseline prior to the start of therapy.

Patients will then receive 3 cycles of CNP. Carboplatin (C) will be administered intravenously (IV) on day 1 of a 21-day cycle at AUC 4.5. Nab-paclitaxel (N) will be administered at 75 mg/m^2 IV on days 1, 8 and 15 of a 21-day cycle. Pembrolizumab (P) will be administered at a dose of 200 mg IV on day 15 of each cycle, prior to any chemotherapy.

Rationale for Pembrolizumab dosing:
A population pharmacokinetic analysis has been performed using serum concentration time data from 476 patients. Within the resulting population PK model, clearance and volume parameters of MK-3475 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 would support both body weight normalized dosing or a fixed dose across all body weights. MK-3475 has been found to have a wide therapeutic range based on the melanoma indication. The differences in exposure for a 200 mg fixed dose regimen relative to a 2 mg/kg Q3W body weight based regimen are anticipated to remain well within the established exposure margins of 0.5 – 5.0 for MK-3475 in the melanoma indication. The exposure margins are based on the notion of similar efficacy and safety in melanoma at 10 mg/kg Q3W vs. the proposed dose regimen of 2 mg/kg Q3W (i.e. 5-fold higher dose and exposure). The population PK evaluation revealed that there was no significant impact of tumor burden on exposure. In addition, exposure was similar between the NSCLC and melanoma indications. Therefore, there are no anticipated changes in exposure between different indication settings.

The rationale for further exploration of 2 mg/kg and comparable doses of pembrolizumab in solid tumors is based on: 1) similar efficacy and safety of pembrolizumab when dosed at either 2 mg/kg or 10 mg/kg Q3W in melanoma patients, 2) the flat exposure-response relationships of pembrolizumab for both efficacy and safety in the dose ranges of 2

mg/kg Q3W to 10 mg/kg Q3W, 3) the lack of effect of tumor burden or indication on distribution behavior of pembrolizumab (as assessed by the population PK model) and 4) the assumption that the dynamics of pembrolizumab target engagement will not vary meaningfully with tumor type.

The choice of the 200 mg Q3W as an appropriate dose for the switch to fixed dosing 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, 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. 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.

Rationale for carboplatin and nab-paclitaxel dosing:
Since pembrolizumab will be administered every 3 weeks, this schedule needed to be adapted to a dosing schedule of carboplatin and abraxane that incorporates a 21-day treatment cycle, which is one that has been used in advanced lung cancer (39). It has therefore been adopted for this clinical trial.

Rationale for CNP dosing schedule:
The rationale for this approach is that, on days 1 and 8 of the first cycle, only CN will be administered to first down regulate immune suppressor cells such as Tregs and MDSC in the tumor microenvironment and, second, to increase local tumor antigen release and uptake by dendritic cells for the priming of antitumor cytotoxic CD8+ T cells. Then, on day 15, P will be administered to enhance newly-generated antitumor CD8+ T cell cytotoxicity. In subsequent cycles, P will be administered every 3 weeks, which is the favored dosing schedule for this compound (Merck, personal communication) and which, by default, will always correspond to concurrent administration with day 15 N.

All trial treatments will be administered on an outpatient basis.

Carboplatin administration may take approximately 60 minutes. Nab-paclitaxel administration may take approximately 30 minutes. Pembrolizumab administration may take approximately 30 minutes.

After completing 3 cycles of CNP, patients will be radiologically restaged by CT chest, abdomen, pelvis and bone scan before starting the next 3 cycles of treatment and clinical responses will be scored according to standard RECIST v1.1 criteria. In an exploratory fashion, responses will also be scored using immune response RECIST (irRECIST) criteria. Patients will then undergo a post-therapy biopsy. Patients with stable or regressing disease will be eligible for 3 additional cycles of CNP whereas patients with progressive disease will be removed from the study. Per the investigators' discretion,

patients with pseudo-progression (as per post cycle 3 scans) according to irRECIST guidelines may receive an additional 3 cycles of treatment.

NB: While we will be scoring screening TNBC biopsies for PD-L1 expression, we will not limit this study to PD-L1 (+) tumors. Our rationale is that chemotherapy may induce an inflammatory T-cell infiltration into an initially PD-L1-negative tumor microenvironment causing a subsequent upregulation of PD-L1 expression on tumor cells by a T cell-derived cytokine such as IFNγ (35). Thus, what was initially PD-L1 negative at the time of the screening biopsy subsequently becomes PD-L1 positive because of chemotherapy-induced inflammatory T cell infiltration and, as a result, benefits from anti-PD1-based therapy.

No investigational or commercial agents or therapies other than those described below may be administered with the intent to treat the subject's malignancy.

6.1.1 Treatment Administration

Day	1	8	15	22	29	36	43	50	57
C	X			X			X		
N	X	X	X	X	X	X	X	X	X
P			X			X			X

C, Carboplatin, AUC 4.5 IV day 1 of 21-day cycle
N, Nab-paclitaxel, 75mg/m^2 IV days 1, 8 and 15 of 21-day cycle
P, Pembrolizumab, 200 mg IV every 21 days

6.1.2 Chemotherapy Dosing Adjustments

A. Carboplatin

- Carboplatin starting dose level: Dose level 0 at AUC 4.5 given IV every 3 weeks. Carboplatin dose capping should follow institutional or ASCO guidelines.
- Carboplatin dose reductions will occur for any ≥ grade 3 hematologic toxicity or a ≥ grade 2 non-hematologic toxicity (see below in C.)

B. Nab-Paclitaxel

- Nab-paclitaxel starting dose level: Dose level 0 at 75 mg/m^2 given IV weekly.
- Nab-paclitaxel dose reductions (25% / 56 mg/m^2) will occur for any ≥ grade 3 hematologic toxicity or a ≥ grade 2 non-hematologic toxicity (see below in C.)

C. Carboplatin and Nab-Paclitaxel

- For ANC < 1000/µl and/or platelets < 100,000/µl, subsequent doses of carboplatin and nab-paclitaxel will be held until ANC ≥ 1000/µl and platelets ≥ 100,000/µl and there is resolution of any grade ≥ 2 non-hematologic toxicities (except residual grade 2 neuropathy) with no dose modification of either drug in subsequent cycles if the hematologic toxicities recover by day 21.
    - If nab-paclitaxel is held on day 8 or day 15 for **two cycles** for either ANC < 1000/µl and/or platelets < 100,000/µl, the subsequent doses of nab-paclitaxel and carboplatin will be dose reduced – these reductions will occur even if ANC ≥ 1000/µl and platelets ≥ 100,000/µl by day 21.
- In patients experiencing febrile neutropenia or delay of recovering of ANC to ≥ 1000/µl beyond day 21 of the preceding cycle or the development of grade ≥ 3 non-hematologic toxicities, subsequent doses of both nab-paclitaxel and carboplatin will be reduced by 25% to 56 mg/m^2 (nab-paclitaxel) and to AUC 3.4 (carboplatin) for all subsequent cycles of therapy.
- If a patient develops an allergic reaction to carboplatin, the patient may still continue with nab-paclitaxel as a single agent on days 1 and 8 and nab-paclitaxel with pembrolizumab on day 15 for each subsequent cycle.
- If a grade ≥2 toxicity persists resulting in treatment being held for more than 4 weeks attributable to carboplatin and/or nab-paclitaxel but not pembrolizumab, patients may continue on single-agent pembrolizumab given every 3 weeks intravenously as long as there is evidence for ongoing clinical benefit to the patient (i.e., regression or stability of metastatic disease)
- If a grade ≥2 toxicity persists resulting in treatment being held for more than 4 weeks where attribution to either carboplatin, nab-paclitaxel or pembrolizumab cannot be distinguished, then protocol treatment will be discontinued. If this occurs, the patient will be removed from the study.

D. Pembrolizumab

- Pembrolizumab will always be administered on day 15 of each cycle of therapy.
- If the administration of nab-paclitaxel is held on day 15 because of non-resolution of toxicities (see above), then pembrolizumab will still be administered as a single agent without nab-paclitaxel.

6.2 General Concomitant Medications and Supportive Care Guidelines

Subjects are prohibited from receiving the following therapies during the Screening and Treatment Phase (including retreatment for post-complete response relapse) of this trial:

- Antineoplastic systemic chemotherapy or biological therapy
- Immunotherapy not specified in this protocol
- Chemotherapy not specified in this protocol
- Investigational agents other than pembrolizumab
- Radiation therapy

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

- 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, varicella/zoster, yellow fever, rabies, BCG, and typhoid vaccine. Seasonal influenza vaccines for injection are generally killed virus vaccines and are allowed; however, intranasal influenza vaccines (eg, FluMist®) 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.

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 including white cell growth factor support that the treating physician deems to be medically necessary. These treatment decisions should be discussed with the principal investigator and handled on an individual patient basis.

The exclusion criteria describe other medications which are prohibited in this trial.

There are no prohibited therapies during the post-treatment follow-up phase.

6.2.1 Supportive Care

- **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** that persists greater than 3 days, administer oral corticosteroids.

- For **Grade 3 or 4 diarrhea/colitis** that persists > 1 week, treat with intravenous steroids followed by high dose oral steroids.
- When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks.

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

  - For **T1DM** or **Grade 3-4** Hyperglycemia
    - Insulin replacement therapy is recommended for Type I diabetes mellitus and for Grade 3-4 hyperglycemia associated with metabolic acidosis or ketonuria.
    - Evaluate 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.
  - **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.

- **Management of Infusion Reactions**: Signs and symptoms usually develop during or shortly after drug infusion and generally resolve completely within 24 hours of completion of infusion.

Table 6.2.1 below shows treatment guidelines for subjects who experience an infusion reaction associated with administration of pembrolizumab (MK-3475).

Table 6.2.1 Infusion Reaction Treatment Guidelines

NCI CTCAE Grade	Treatment	Premedication at subsequent dosing
Grade 1 Mild reaction; infusion interruption not indicated; intervention not indicated	Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator.	None
Grade 2 Requires infusion interruption but responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDS, narcotics, IV fluids); prophylactic medications indicated for < =24 hrs	**Stop Infusion 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 infusion may be restarted at 50% of the original infusion rate (e.g., from 100 mL/hr to 50 mL/hr). Otherwise dosing will be held until symptoms resolve and the subject should be premedicated for the next scheduled dose. **Subjects who develop Grade 2 toxicity despite adequate premedication should be permanently discontinued from further trial treatment administration.**	Subject may be premedicated 1.5h (± 30 minutes) prior to infusion of pembrolizumab (MK-3475) with: Diphenhydramine 50 mg po (or equivalent dose of antihistamine). Acetaminophen 500-1000 mg po (or equivalent dose of antipyretic).
Grades 3 or 4 Grade 3: Prolonged (i.e., not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae (e.g., renal impairment, pulmonary infiltrates) Grade 4: Life-threatening; pressor or ventilatory	**Stop Infusion.** Additional appropriate medical therapy may include but is not limited to: IV fluids Antihistamines NSAIDS Acetaminophen Narcotics Oxygen Pressors Corticosteroids Epinephrine	No subsequent dosing

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

6.3 Criteria for Removal from Study

In the absence of treatment delays due to adverse events, treatment may continue for 24 months or until one of the following criteria applies:

• Disease progression,

• Intercurrent illness that prevents further administration of treatment,

• The investigator considers it, for safety reasons, to be in the best interest of the subject.

• Unacceptable adverse event(s) such as:
  - Unacceptable treatment related toxicity, NCI CTC AE version 4.0 Grade 3 or 4 that fails to recover to baseline or < Grade 3 in the absence of treatment within 4 weeks.
  - Any toxicity or other issue that causes a delay of study drug administration by more than 4 weeks.

• Subject decision to withdraw from treatment (partial consent) or from the study (full consent),
• Pregnancy during the course of the study for a child-bearing participant

• Death

• Sponsor reserves the right to temporarily suspend or prematurely discontinue this study. The date and reason for discontinuation must be documented. Every effort should be made to complete the appropriate assessments.

6.4 Duration of Follow Up

The investigator will capture information after a patient withdraws from study (per patient agreement).

Subjects will be followed for toxicity for 30 days after treatment has been discontinued or until death, whichever occurs first.

The clinical course of each event will be followed no more than 6 months until resolution, stabilization, or until it has been determined that the study treatment or participation is not the cause.

Serious adverse events that are still ongoing at the end of the study period will necessitate follow-up to determine the final outcome. Any serious adverse event that occurs after the study period and is considered to be possibly related to the study treatment or study participation will be recorded and reported immediately.

Patients will be followed for survival every 3 months for at least 12 months after their post study 30-day follow-up.

7.0 Dose Delays/Dose Modifications

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 7.0 below. See Section 6.4 for supportive care guidelines.

Table 7.0 Dose Modification and Toxicity Management Guidelines for Immune-related AEs Associated with Pembrolizumab

General instructions:

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

Immune-related AEs	Toxicity grade or conditions (CTCAEv4.0)	Action taken to pembrolizumab	irAE management with corticosteroid and/or other therapies	Monitor and follow-up
Pneumonitis	Grade 2	Withhold	• Administer corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper • Add prophylactic antibiotics for opportunistic infections	• Monitor participants for signs and symptoms of pneumonitis • Evaluate participants with suspected pneumonitis with radiographic imaging and initiate corticosteroid treatment •
	Grade 3 or 4, or recurrent Grade 2	Permanently discontinue		

Diarrhea / Colitis	Grade 2 or 3	Withhold	• Administer corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper	• Monitor participants for signs and symptoms of enterocolitis (ie, diarrhea, abdominal pain, blood or mucus in stool with or without fever) and of bowel perforation (ie, peritoneal signs and ileus). • Participants with ≥ Grade 2 diarrhea suspecting colitis should consider GI consultation and performing endoscopy to rule out colitis. • Participants with diarrhea/colitis should be advised to drink liberal quantities of clear fluids. If sufficient oral fluid intake is not feasible, fluid and electrolytes should be substituted via IV infusion.
	Recurrent Grad3 or Grade 4	Permanently discontinue		
AST / ALT elevation or Increased bilirubin	Grade 2	Withhold	• Administer corticosteroids (initial dose of 0.5- 1 mg/kg prednisone or equivalent) followed by taper	• Monitor with liver function tests (consider weekly or more frequently until liver enzyme value returned to baseline or is stable
	Grade 3 or 4	Permanently discontinue	• Administer corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper	
Type 1 diabetes mellitus (T1DM) or Hyperglycemia	Newly onset T1DM or Grade 3 or 4 hyperglycemia associated with evidence of β-cell failure	Withhold	• Initiate insulin replacement therapy for participants with T1DM • Administer anti-hyperglycemic in participants with hyperglycemia	• Monitor participants for hyperglycemia or other signs and symptoms of diabetes.
Hypophysitis	Grade 2	Withhold	• Administer corticosteroids and initiate hormonal replacements as clinically indicated.	• Monitor for signs and symptoms of hypophysitis (including hypopituitarism and adrenal insufficiency)
	Grade 3 or 4	Withhold or permanently discontinue[1]		

Hyperthyroidism	Grade 2	Continue	• Treat with non-selective beta-blockers (eg, propranolol) or thionamides as appropriate	• Monitor for signs and symptoms of thyroid disorders.
	Grade 3 or 4	Withhold or permanently discontinue[1]		
Hypothyroidism	Grade 2-4	Continue	• Initiate thyroid replacement hormones (eg, levothyroxine or liothyroinine) per standard of care	• Monitor for signs and symptoms of thyroid disorders.
Nephritis: grading according to increased creatinine or acute kidney injury	Grade 2	Withhold	• Administer corticosteroids (prednisone 1-2 mg/kg or equivalent) followed by taper.	• Monitor changes of renal function
	Grade 3 or 4	Permanently discontinue		
Neurological Toxicities	Grade 2	Withhold	• Based on severity of AE administer corticosteroids	• Ensure adequate evaluation to confirm etiology and/or exclude other causes
	Grade 3 or 4	Permanently discontinue		
Myocarditis	Grade 1 or 2	Withhold	• Based on severity of AE administer corticosteroids	• Ensure adequate evaluation to confirm etiology and/or exclude other causes
	Grade 3 or 4	Permanently discontinue		
Exfoliative Dermatologic Conditions	Suspected SJS, TEN, Or DRESS	Withhold	• Based on severity of AE administer corticosteriods	• Ensure adequate evaluation to confirm etiology and/or exclude other causes
	Confirmed SJS, TEN, Or DRESS	Permanently discontinue		
All other immune-related AEs	Persistent Grade 2	Withhold	• Based on type and severity of AE administer corticosteroids	• Ensure adequate evaluation to confirm etiology and/or exclude other causes
	Grade 3	Withhold or discontinue based on the type of event. Events that require discontinuation include and not limited to: Gullain-Barre Syndrome, encephalitis		
	Grade 4 or recurrent Grade 3	Permanently discontinue		

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

NOTE:

For participants with Grade 3 or 4 immune-related endocrinopathy where withhold of pembrolizumab is required, pembrolizumab may be resumed when AE resolves to ≤ Grade 2 and is controlled with hormonal replacement therapy or achieved metabolic control (in case of T 1DM).

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 4 weeks of the scheduled interruption, unless otherwise discussed with the Sponsor. The reason for interruption should be documented in the patient's study record.

8.0 Adverse Events and Potential Risks

8.1 Pembrolizumab

MK-3475 (pembrolizumab) is an agent involved in the blockage of "immune checkpoints". This may result in severe and possibly fatal immune-mediated side effects probably due to stimulation and growth of immune cells (T-cells). Immune-mediated side effects have been reported in patients receiving MK-3475 (pembrolizumab). In clinical trials, most immune-mediated side effects went away when pembrolizumab was stopped for a short time, steroids were taken and other supportive care given.

MK-3475 can cause the immune system to attack normal organs and tissues in many areas of your body and can affect the way they work. These problems can sometimes become serious or life-threatening.

1. Lung problems (pneumonitis). Symptoms of pneumonitis may include:
- shortness of breath
- chest pain
- new or worse cough

2. Intestinal problems (colitis) that can lead to tears or holes in the intestine. Signs and symptoms of colitis may include:
- diarrhea or more bowel movements than usual
- stools that are black, tarry, sticky, or have blood or mucus
- severe stomach-area (abdomen) pain or tenderness

3. Liver problems (hepatitis). Signs and symptoms of hepatitis may include:
- yellowing of the skin or the whites of your eyes
- dark urine
- nausea or vomiting
- feeling less hungry than usual
- pain on the right side of your stomach area (abdomen)
- bleeding or bruising more easily than normal

4. Hormone gland problems (especially the thyroid, pituitary, and adrenal glands). Signs and symptoms that hormone glands are not working properly may include:
- rapid heart beat
- weight loss
- increased sweating
- weight gain
- hair loss
- feeling cold

- constipation
- voice gets deeper
- muscle aches
- dizziness or fainting
- headaches that will not go away or unusual headache

5. Kidney problems, including nephritis and kidney failure. Signs of kidney problems may include:
- change in the amount or color of urine.

6. Inflammation of the skin causing widespread peeling of the skin, itching, and skin redness. More severe skin reactions may involve the inside of the mouth, the surface of the eye and genital areas, and/or may cause the top layer of the skin to peel from all over the body which can cause severe infection. Rarely these reactions lead to death.

7. Inflammation of the middle layer of the heart wall (myocarditis) that may cause the heart to have difficulty pumping blood throughout the body, which can cause chest pain, shortness of breath and swelling of the legs. It is possible to experience a fast or irregular heartbeat that may cause dizziness or fainting. Sometimes this condition can lead to death

8. Problems in other organs. Signs of these problems may include:
- rash
- changes in eyesight
- severe or persistent muscle or joint pains
- severe muscle weakness

VERY COMMON Out of 100 people who receive pembrolizumab, 20 or more people may have the following:
▪ Itching of the skin ▪ Loose or watery stools ▪ Cough
COMMON Out of 100 people who receive pembrolizumab at least 5 but less than 20 people may have:
▪ Joint pain ▪ Rash ▪ Fever ▪ Back pain ▪ Pain in the belly ▪ Loss of skin color ▪ Not enough thyroid hormone so subjects may feel tired, gain weight, feel cold, have infrequent or hard stools (hypothyroidism) ▪ Low levels of salt in the blood that may cause subjects to feel tired, confused, have a headache, muscle cramps and/or feel sick to their stomach (hyponatremia)

UNCOMMON

Out of 100 people who receive pembrolizumab, at least 1 but less than 5 people may have the following:

- Too much thyroid hormone so subjects may feel anxious, angry, have trouble sleeping, feel weak, tremble, sweat, feel tired, have loose and watery stools (hyperthyroidism)
- Inflammation of the lungs so subjects may feel short of breath and cough. (pneumonitis)
- Infusion reaction, where subjects may feel dizzy or faint, flushed, get a rash, have a fever, feel short of breath, experience a decrease in blood pressure at the time of receiving their infusion (IV) or just after, or have pain at the site of infusion
- Inflammation of the bowels/gut which may cause severe pain in the belly with loose or watery stools and black, tarry, sticky stools or stools with blood or mucus (colitis)
- Inflammation of the skin so subjects may have peeling of the skin, itchiness, and/or skin redness. The skin inflammation (i.e. peeling, itching and redness) could also be widespread throughout the body. More severe skin reactions may involve the inside of the mouth, the surface of the eye and genital areas, and/or may cause the top layer of the skin to peel from all over thebody which can cause severe infection. (Severe skin reactions, including Stevens-Johnson syndrome or toxic epidermal necrolysis)

RARE, SOME MAY BE SERIOUS

Out of 100 people who receive pembrolizumab, less than 1 person may have the following:

- Inflammation of the liver that may make subjects feel sick to the stomach and vomit, feel like not eating, feel tired, have a mild fever, a pain in the right side of the belly, yellow eyes and skin, and dark urine (hepatitis)
- Inflammation of the pituitary gland (a gland in the head), which may cause you to feel sick to the stomach or have headaches, changes in behavior, double vision, few to no menstrual cycles, weakness, vomiting and dizziness or fainting. (hypophysitis)
- Adrenal glands (glands on top of the kidneys) that may not make enough hormone which could cause tiredness, weight loss, muscle weakness, feeling faint, having joint, muscle and belly aches, nausea, vomiting, loose or watery stools, fever, salt craving, and sometimes darkening of the skin like a suntan (adrenal insufficiency).
- Inflammation of the kidney so subjects may pass less urine or have cloudy or bloody urine, swelling and low back pain (nephritis)
- Inflammation of the muscles so subjects may feel weak or pain in the muscles(myositis)
- Inflammation of the pancreas, (a gland in the abdomen that controls sugar levels) so subjects may have severe pain in the top part of the belly that may move to the back, feel sick to the stomach, and vomiting that gets worse when subjects eat (pancreatitis)
- Inflammation of the eye so subjects may have eye redness, blurred vision, sensitivity to light, eye pain, see floaters or have headaches (uveitis)
- Type 1 Diabetes, a condition that can cause too much sugar in the blood, feeling thirstier than usual, frequent urination and weight loss. Subjects are likely to need regular insulin shots.

- Inflammation of the nerves that may cause pain, weakness or tingling in the hands and feet, and may spread to the legs, arms and upper body leading to severe muscle weakness and possibly temporary paralysis(Guillain-Barré syndrome) .
- Inflammation of the middle layer ofthe heart wall that may cause the heart to have difficulty pumping blood throughout the body, which can cause chest pain, shortness of breath and swelling of the legs. Subjects may experience a fast or irregular heartbeat that may cause dizziness or fainting . (myocarditis)
- Inflammation of the thyroid gland, an organ that makes and stores thyroid hormones. This condition may lead to change in heart rate, blood pressure, body temperature, and the rate at which food is converted into energy(thyroiditis) .
- A condition that may make subjects feel weak and tired and may cause drooping of the eyelids, blurred or double vision, difficulty swallowing, slurred speech, weakness in your arms and legs, or difficulty breathing (myasthenic syndrome/myasthenia gravis including exacerbation)
- The formation of small clusters of immune cells (called granulomas) in parts of the body such as the lymph nodes, eyes, skin, or lungs (sarcoidosis)
- Inflammation of the brain with confusion and fever. This may also include: disorientation, memory problems, seizures (fits), changes in personality and behavior, difficulty speaking, weakness or loss of movement in some parts of the body, and loss of consciousness (encephalitis)
- Inflammation of the spinal cord with pain, numbness, tingling, or weakness in the arms or legs, bladder or bowel problems including needing to urinate more frequently, urinary incontinence, difficulty urinating, and constipation (myelitis)
- Inflammation of the blood vessels (vasculitis)

Additionally, since pembrolizumab was approved in September 2014, the following side effects have been reported by people receiving pembrolizumab.

These side effects were voluntarily reported from a group of people of unknown size. It is not possible to estimate the frequency of these side effects:

- Inflammation of the joints which may include joint pain, stiffness and/or swelling (arthritis)
- Severe responses of the immune system that cause the body to attack its own blood cells, spleen, liver, lymph nodes, skin and brain. This may include fever, rash, inflammation of the liver, yellowing of the skin, an enlarged liver and spleen, low blood counts, and enlarged lymph nodes. The nervous system may also be affected and cause confusion, seizures, and even coma. (hemophagocytic lymphohistiocytosis)
- Changes in eyesight, eye pain, whitish patches on the skin and hearing loss (Vogt-Koyanagi-Harada syndrome)
- Inflammation and scarring of the bile ducts (tubes that carry digestive fluid that is made in the liver). This can cause symptoms similar to those seen with inflammation of the liver (hepatitis) such as pain in right side of your belly, yellow eyes and skin, feeling tired, and itching (sclerosing cholangitis).

In addition to the above, if subjects have had an allogeneic stem cell transplant (a procedure in which a person receives blood-forming stem cells from a donor), they may experience graft versus host disease (GvHD), which may include diarrhea, skin rashes, and liver damage, after receiving pembrolizumab. Sometimes this condition can lead to death.

If subjects have had a solid organ transplant (for example, received a kidney or heart transplant), subjects may experience rejection of the transplanted organ. The study doctor will monitor subjects and tell them what signs and symptoms they should report depending on the type of organ transplant that they have had.

Risks of Venipuncture/Intravenous Needle Insertion:

Occasional, some may be serious: Mild pain and discomfort at the injection or needle insertion site as well as possible infection, bleeding, bruising, and soreness.

Rare: Severe pain, swelling, infection from the actual injection, and fainting.

Reproductive risks: Patients should not get pregnant, or breastfeed while in this study. The drugs used in this study could be very damaging to an unborn baby. With regard to MK-3475, women of child bearing potential must agree to use adequate contraception (barrier method of birth control or abstinence) prior to study entry and for the duration of study participation through 120 days after receiving the last dose of MK-3473.

8.2 Carboplatin

More common

- Pain at place of injection
- Nausea and vomiting
- Unusual tiredness or weakness

Less common

- Black, tarry stools
- Blood in urine or stools
- Cough or hoarseness, accompanied by fever or chills
- Fever or chills
- Lower back or side pain, accompanied by fever or chills
- Numbness or tingling in fingers or toes
- Painful or difficult urination, accompanied by fever or chills
- Pinpoint red spots on skin
- Skin rash or itching
- Unusual bleeding or bruising
- Unusual tiredness or weakness
- Constipation or diarrhea
- Loss of appetite

Rare

- Blurred vision
- Ringing in ears
- Sores in mouth and on lips
- Wheezing

This medicine may cause a temporary loss of hair in some people. After treatment with carboplatin has ended, normal hair growth should return.

Hematologic

Hematologic side effects have been reported to include thrombocytopenia with platelet counts below 50,000/mm3 in 25% of patients and in 35% of previously treated ovarian cancer patients (PTOCP), neutropenia with granulocyte counts below 1,000/mm3 in 16% of patients (21% of PTOCP), and leukopenia with WBC counts below 2,000/mm3 in 15% of patients (26% of PTOCP).

Bone marrow suppression is the dose limiting toxicity of carboplatin. Marrow suppression is usually more severe in patients with impaired kidney function. Anemia with a hemoglobin count less than 11 g/dL has been observed in 71% of patients who started therapy with a baseline above that value. The incidence of anemia increases with increasing exposure. Bone marrow depression may be more severe when carboplatin is combined with other bone marrow suppressing drugs or with radiotherapy. One study has suggested that myelotoxicity could be minimized by the use of regimes based on the circadian rhythm of the bone marrow.

Gastrointestinal

Patients previously treated with emetogenic agents (especially cisplatin) have been more prone to vomiting. Nausea alone occurs in an additional 10% to 15% of patients. Prolonged administration of carboplatin (either by continuous 24 hour infusion or daily pulse doses given for 5 consecutive days) was associated with less severe vomiting than the single dose intermittent schedule.

Gastrointestinal side effects have included vomiting which occurred in 65% of patients and in 81% of PTOCP. In approximately one third of these patients, the vomiting was reported as severe. Other gastrointestinal side effects have included pain (17%), diarrhea (6%), constipation (6%), and stomatitis.

Nervous system

Nervous system side effects have included peripheral neuropathies which have been reported in 4% of patients and 6% of PTOCP, with mild paresthesias occurring most frequently. Patients older than 65 years of age or previously treated with cisplatin have been reported to have a 10% risk for peripheral neuropathies. Prolonged treatment, particularly in cisplatin-pretreated patients, may result in cumulative neurotoxicity.

Hepatic

Hepatic side effects have included abnormal liver function tests reported in patients with normal baseline values receiving standard dosages including total bilirubin (5%), SGOT (15%), and alkaline phosphatase (24%), and 5%, 19%, and 37% respectively in PTOCP. These abnormalities were mild and reversible in about one-half of the cases.

In patients receiving very high dosages of carboplatin and autologous bone marrow transplantation, severe abnormalities of liver function tests have been reported.

Renal

Renal side effects have included abnormalities in 6% of serum creatinine test results (10% for PTOCP) and 14% of blood urea nitrogen test results (22% for PTOCP). Most of these reported abnormalities have been mild and about one-half of them were reversible. There have been at least two case reports in the literature of patients with preexisting renal dysfunction deteriorating into renal failure due to intravenous carboplatin therapy. In one of the cases, renal failure followed high-dose therapy. In the other patient, acute renal failure was reversible. There have also been at least two reports in the literature of acute renal failure associated with the use of intraperitoneal carboplatin. Neither patient had a full return of renal function to baseline.

Creatinine clearance is the most sensitive measure of renal function in patients receiving carboplatin. Creatinine clearance also appears to be the most useful test for correlating drug clearance and bone marrow suppression.

Other

Other side effects have included abnormally decreased serum electrolyte values such as sodium (29%), magnesium (29%), calcium (22%), and potassium (20%), 47%, 43%, 31%, and 28% respectively in PTOCP. Electrolyte abnormalities were rarely associated with symptoms.

Ototoxicity has been reported with the use of high-dose carboplatin.

The most frequently reported miscellaneous side effects were pain and asthenia.

Hypersensitivity

One study has noted that approximately 40 instances of hypersensitivity have been reported. The study further notes that there is generally a slow development of hypersensitivity, with reactions evolving only after several cycles of therapy.

Allergic reactions have generally been manageable with standard epinephrine, corticosteroid, and antihistamine therapy.

Hypersensitivity side effects have been reported to include rash, urticaria, erythema, pruritus, and rarely bronchospasm and hypotension. Hypersensitivity reactions may be common in patients with gynecological malignancies.

Metabolic

Metabolic side effects have included dehydration.

Ocular

Ocular side effects including a case of blindness associated with the use of high dose carboplatin have been reported.

8.3 Nab-paclitaxel

More common

- Black or tarry stools
- Blurred vision
- Burning, numbness, tingling, or painful sensations
- Confusion
- Cough or hoarseness with fever or chills
- Dizziness, faintness, or lightheadedness when getting up suddenly from a lying or sitting position
- Feeling of warmth
- Fever or chills
- Lower back or side pain
- Painful or difficult urination
- Pale skin
- Redness of the face, neck, arms, and occasionally, upper chest
- Shortness of breath
- Skin rash or itching
- Sore throat
- Sweating
- Troubled breathing with exertion
- Ulcers, sores, or white spots in the mouth
- Unsteadiness
- Unusual bleeding or bruising
- Unusual tiredness or weakness
- Weakness in the arms, hands, legs, or feet
- Bleeding, blistering, burning, coldness, discoloration of the skin, feeling of pressure, hives, infection, inflammation, itching, lumps, numbness, pain, rash, redness, scarring, soreness, stinging, swelling, tenderness, tingling, ulceration, or warmth at the injection site
- Cracked lips
- Diarrhea
- Difficulty with swallowing

- Hair loss
- Nausea or vomiting
- Numbness, burning, or tingling in the hands or feet
- Pain in the joints or muscles, especially in the arms or legs
- Thinning of the hair

Less common
- Blood in the urine or stools
- Difficult or labored breathing
- Pinpoint red spots on the skin
- Shortness of breath (severe)
- Slow heartbeat
- Tightness in the chest
- Wheezing

Incidence not known
- Anxiety
- Blue lips, fingernails, or skin
- Difficult or troubled breathing
- Fainting
- Fast heartbeat
- Irregular, fast or slow, or shallow breathing
- Sudden shortness of breath

Hematologic

Hematologic side effects including bone marrow suppression have been the major dose-limiting toxicity. Neutropenia less than 2,000 cells/mm3 (90%) and less than 500 cells/mm3 (52%), is the most important hematological toxicity. Neutropenia has been both dose and schedule dependent, and generally rapidly reversible. The onset of neutropenia generally occurs after 8 to 10 days and recovery generally occurs after 15 to 21 days. Neutropenia does not appear to increase with cumulative exposure, nor to be more frequent or severe for patients previously treated with radiation therapy. Leukopenia less than 4,000 cells/mm3 (90%) and less than 1,000 cells/mm3 (17%), thrombocytopenia less than 100,000 cells/mm3 (20%) and less than 50,000 cells/mm3 (7%), and anemia less than 11 g/dl (78%) and less than 8 g/dl (16%) have been reported. Infections (30%), bleeding (14%), red cell transfusions (25%) and platelet transfusions (2%) have been reported. A case of paclitaxel-induced sickle cell crisis has also been reported.

Fever (12% of all treatment courses) has been reported. Fatal infectious episodes (1%) including sepsis, pneumonia and peritonitis have been reported.

Bleeding episodes (4% of all courses and 14% of all patients) have been reported. Most of the episodes were localized.

Hypersensitivity

The frequency and severity of hypersensitivity reactions were not affected by the dose or schedule of administration. Severe symptoms have primarily been reported to occur within the first hour of the infusion.

Single dose intravenous dexamethasone can be used in combination with appropriated ancillary medications to prevent paclitaxel-related hypersensitivity reactions.

Hypersensitivity side effects (41%) including severe reactions (2%) have been reported. The most frequent symptoms observed during the severe reactions were dyspnea, flushing, chest pain, and tachycardia. Minor hypersensitivity reactions consisted mostly of flushing (28%), rash (12%), hypotension (4%), dyspnea (2%), tachycardia (2%), and hypertension (1%). Three patients with transient pulmonary infiltrates caused by hypersensitivity reactions (after receiving treatment with paclitaxel and carboplatin) have been reported. A case of pneumonitis responsive to high-dose corticosteroids and a case of bullous fixed drug eruption have also been reported.

Cardiovascular

Cardiovascular side effects have included vital sign changes including bradycardia (3%) and hypotension (12%) during the first 3 hours of infusion as stated by the manufacturer. Significant cardiovascular events (1%) including syncope, rhythm abnormalities, hypertension and venous thrombosis have also been reported. A report from the Johns Hopkins oncology center stated that asymptomatic sinus bradycardia occurred in up to 29% of patients in phase 2 trails, and that other cardiac disturbances including atrioventricular conduction and bundle branch blocks, ventricular tachycardia, and possible ischemic manifestations had been reported (3%). A case of fatal myocardial infarction potentially induced by paclitaxel has also been reported.

The manufacturer further states that abnormal ECG readings have been reported in 23% of all patients receiving paclitaxel and in 14% of the patients with normal baseline ECGs. The most frequently reported ECG modifications were nonspecific repolarization abnormalities, sinus bradycardia, sinus tachycardia and premature beats.

Nervous system

Nervous system side effects including neurotoxicity, primarily including peripheral neurosensory manifestations (60%), have generally been mild to moderate in severity. However, severe symptoms (3%) have also been reported. Other serious neurologic events (less than 1%) have been reported including grand mal seizures, syncope, ataxia, neuroencephalopathy and autonomic neuropathy resulting in paralytic ileus. Disturbances of the optic nerve (19%) have also been reported.

The frequency and severity of neurologic manifestations have been dose dependent and cumulative. One study found that although the neurotoxicity was frequent, it remained mild or subclinical up to at least 1400 mg/m^2 administered over 8 cycles.

Peripheral neuropathy may appear within 24 to 72 hours when high doses are administered. The frequency of peripheral neuropathy also has been reported to have increased with cumulative dose. It usually presents as a "stocking-and-glove" numbness and paresthesia.

At least 3 cases of phantom limb pain associated with paclitaxel use have been reported.

Gastrointestinal

Gastrointestinal effects can generally be treated with standard antiemetic antidiarrheal therapy and dietary changes.
Mucositis occurs most frequently in patients receiving high doses. It is schedule-dependent, occurring more frequently with 24 and 96 hour infusions.

The author of one of the case reports of pancreatitis suggested that it was the companion agent, cremophor that was the cause, rather than the paclitaxel itself.

Gastrointestinal side effects including nausea and vomiting (52%), diarrhea (38%) and mucositis (31%) have been reported. Intestinal obstruction, intestinal perforation and ischemic colitis have been reported rarely. Three cases of pancreatitis have also been reported.

Hepatic

Hepatic side effects including elevations in bilirubin (7%), alkaline phosphatase (22%) and AST (SGOT) (19%) have been reported in patients with normal baseline levels. Hepatic necrosis and hepatic encephalopathy leading to death have been reported rarely. A case of fatal hepatic coma has also been reported.

Prolonged exposure to paclitaxel has not been associated with cumulative hepatic toxicity.

Renal

Renal side effects including edema have been reported in 21% of all patients receiving paclitaxel and 17% of patients without baseline edema. Severe edema has been reported in 1% of patients.

Dermatologic

Dermatologic side effects including transient skin changes due to hypersensitivity reactions and skin abnormalities related to radiation recall have been reported. Alopecia

(87%) and cumulative loss of body hair have also been reported. Some reports suggest that paclitaxel may cause vesicant reactions when extravasated. Nail changes including changes in pigmentation or discoloration of the nail bed have been reported (2%). Two cases of cutaneous lupus erythematosus and one case of systemic lupus erythematosus have been reported. Two cases of scleroderma-like reactions have been reported. A case of paclitaxel administration via a central vein producing a recall reaction at a site of prior paclitaxel extravasation has also been reported. A case of severe mucocutaneous toxicity and a case of cutaneous systemic sclerosis have been reported.

Alopecia usually begins 1 to 2 weeks after treatment and is usually reversible.

Respiratory

Respiratory side effects including radiation recall pneumonitis have been reported.

Musculoskeletal

Symptoms were usually transient, occurred two or three days after drug administration and resolved within five to seven days. Symptoms are more frequent and severe in patients receiving doses greater than 200 mg/m^2.

Musculoskeletal side effects including myalgia and/or arthralgia (60%), including severe symptoms (8%) have been reported.

Local

Injection site reactions, including reactions secondary to extravasation, were usually mild and consisted of erythema, tenderness, skin discoloration, or swelling at the injection site.

Local side effects have included injection site reactions. Phlebitis has been reported rarely.

Other

Other side effects including cellulitis have been reported rarely.

8.2 Definitions

8.2.1 Adverse Event

An **adverse event** (AE) is any unfavorable or unintended event, physical or psychological, associated with a research study, which causes harm or injury to a research participant as a result of the participant's involvement in a research study. The event can include abnormal laboratory findings, symptoms, or disease associated with the research study. The event does not necessarily have to have a causal relationship with the

research, any risk associated with the research, the research intervention, or the research assessments.

Adverse events may be the result of the interventions and interactions used in the research; the collection of identifiable private information in the research; an underlying disease, disorder, or condition of the subject; and/or other circumstances unrelated to the research or any underlying disease, disorder, or condition of the subject.

Progression of the cancer under study is not considered an adverse event.

8.2.2 Serious Adverse Events

A **serious adverse event** (SAE) is any adverse experience occurring at any dose that results in any of the following outcomes:

- Results in **death.**
- Is a **life-threatening** adverse experience. The term life-threatening in the definition of serious refers to an adverse event in which the subject was at risk of death at the time of the event. It does not refer to an adverse event which hypothetically might have caused death if it were more severe.
- Requires **inpatient hospitalization or prolongation of existing hospitalization**. Any adverse event leading to hospitalization or prolongation of hospitalization will be considered as Serious, UNLESS at least one of the following expectations is met:
    - The admission results in a hospital stay of less than 24 hours OR
    - The admission is pre-planned (e.g., elective or scheduled surgery arranged prior to the start of the study) OR
    - The admission is not associated with an adverse event (e.g., social hospitalization for purposes of respite care.

  However it should be noted that invasive treatment during any hospitalization may fulfill the criteria of "medically important" and as such may be reportable as a serious adverse event dependant on clinical judgment. In addition where local regulatory authorities specifically require a more stringent definition, the local regulation takes precedent.
- Results in **persistent or significant disability/incapacity**. The definition of disability is a substantial disruption of a person's ability to conduct normal life's functions.
- Is a **congenital anomaly/birth defect**.
- Is an **important medical event**. Important medical events that may not result death, be life-threatening, or require hospitalization may be considered a serious adverse experience when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood disease or disorders, or convulsions that do not result in inpatient hospitalization, or the development

of drug dependency or drug abuse. The development of a new cancer is always considered an important medical event.

8.2.3 Adverse Event Evaluation

The investigator or designee is responsible for ensuring that all adverse events (both serious and non-serious) observed by the clinical team or reported by the subject which occur after the subject has signed the informed consent are fully recorded in the subject's medical records. Source documentation must be available to support all adverse events.

A laboratory test abnormality considered clinically relevant (e.g., causing the subject to withdraw from the study, requiring treatment or causing apparent clinical manifestations, result in a delay or dose modification of study treatment, or judged relevant by the investigator), should be reported as an adverse event.

The investigator or sub-investigator (treating physician if applicable) will provide the following for all adverse events (both serious and non-serious):

- Event term (as per CTCAE)
- Description of the event
- Date of onset and resolution
- **Expectedness of the toxicity**
- **Grade of toxicity**
- **Attribution of relatedness to the investigational agent- (this must be assigned by an investigator, sub-investigator, or treating physician)**
- Action taken as a result of the event, including but not limited to; no changes, dose interrupted, reduced, discontinued, etc. or action taken with regard to the event, i.e. no action, received conmed or other intervention, etc.
- Outcome of event

Descriptions and **grading scales** found in the NCI Common Terminology Criteria for Adverse Events (CTCAE) version **4.0** will be utilized for AE reporting.
An expected adverse event is an event previously known or anticipated to result from participation in the research study or any underlying disease, disorder, or condition of the subject. The event is usually listed in the Investigator Brochure, consent form or research protocol.

An unexpected adverse event is an adverse event not previously known or anticipated to result from the research study or any underlying disease, disorder, or condition of the subject.

Attribution is the relationship between an adverse event or serious adverse event and the study drug. Attribution will be assigned as follows:

- Definite – The AE is clearly related to the study drug.
- Probable – The AE is likely related to the study drug.
- Possible – The AE may be related to the study drug.

- Unlikely – The AE is doubtfully related to the study drug.
- Unrelated – The AE is clearly NOT related to the study drug.

Protocol must specify if attribution is required for individual components of the treatment regimen or the treatment regimen as a whole.

8.3 SAE Report Form

SAEs will be recorded on the FDA Form 3500A (MedWatch) but should only be reported as instructed below. The electronic FDA SAE reporting forms should not be used.

8.4 Reporting Procedures for Serious Adverse Events

For the purposes of safety reporting, all adverse events will be reported that occur starting on Cycle 1 Day 1 through 30 days after the final dose of study drug. Adverse events, both serious and non-serious, and deaths that occur during this period will be recorded in the source documents. All SAEs should be monitored until they are resolved or are clearly determined to be due to a subject's stable or chronic condition or intercurrent illness(es). Related AEs will be followed until resolution to baseline or grade 1 or stabilization.

8.4.1 SAE Reporting Requirements

- Participating investigators (all sites) must report all serious adverse events to the Lead Site Principal Investigator (e.g. Sponsor-Investigator) within **24 hours** of discovery or notification of the event. The participating investigator must also provide follow-up information on the SAE until final resolution.
    - Joseph Baar, MD
- The Lead Site Principal Investigator will review the SAE and report the event to the FDA, external collaborator(s), and IRB as applicable.
- It is the Sponsor-Investigator's responsibility (e.g. lead site PI) to ensure that ALL serious adverse events that occur on the study (e.g. ALL SAEs that occur at each enrolling institution) are reported to all participating sites.

8.4.2 Merck Reporting Requirements

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 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 Sponsor and within 2 working days to Merck Global Safety.

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 Sponsor and to Merck.

SAE reports and any other relevant safety information are to be forwarded to the Merck Global Safety facsimile number: +1-215-993-1220

A copy of all 15 Day Reports and Annual Progress Reports is submitted as required by FDA, European Union (EU), Pharmaceutical and Medical Devices agency (PMDA) or other local regulators. Investigators will cross reference this submission according to local regulations 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.

All subjects with serious adverse events must be followed up for outcome.

Reporting of Pregnancy and Lactation to the Sponsor and 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) that occurs during the trial.

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

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

Such events 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).

8.4.3 Events of Clinical Interest

Selected non-serious and serious adverse events are also known as Events of Clinical Interest (ECI) and must be recorded as such on the Adverse Event case report forms/worksheets and reported within 24 hours to the Sponsor and within 2 working days

to Merck Global Safety. (Attn: Worldwide Product Safety; FAX 215 993-1220)Events of clinical interest for this trial include:

1. An overdose of Merck product, as defined in Section 7.2.1 - Definition of an 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. The trial site guidance for assessment and follow up of these criteria can be found in the Investigator Trial File Binder (or equivalent).

8.4.4 Definition of an Overdose for This Protocol and Reporting of Overdose to the Sponsor and to Merck

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 Sponsor and within 2 working days hours to Merck Global Safety. (Attn: Worldwide Product Safety; FAX 215 993-1220)

8.4.5 Institutional Review Board Reporting Requirements:

- Investigative sites will report adverse events to their respective IRB according to the local IRB's policies and procedures in reporting adverse events.

8.4.6 FDA Reporting:

The University Hospitals Principal Investigator, as holder of the IND, will be responsible for all communication with the FDA. In accordance with 21 CFR 312.32, the University Hospitals Principal Investigator is responsible for notifying the FDA of SAEs that are serious, unexpected (not listed in the Investigator Brochure) and judged to be related (i.e., possible, probable, definite) to the study drug. Events meeting the following criteria need to be submitted to the FDA as Expedited IND Safety Reports.

7 Calendar Day IND Safety Report
Any unexpected fatal or life-threatening suspected adverse event represent especially important safety information and, therefore, must be reported more rapidly to FDA (21 CFR 312.32(c)(2)). Any unexpected fatal or life-threatening suspected adverse event must be reported to FDA no later than 7 calendar days after the University Hospitals Principal Investigator initial receipt of the information (21 CFR 312.32(c)(2)). University Hospitals Principal Investigator will complete a Medwatch Form FDA 3500A and notify the FDA by telephone or facsimile transmission.

7 Calendar Day IND Safety Report
Any unexpected fatal or life-threatening suspected adverse event represent especially important safety information and, therefore, must be reported more rapidly to FDA (21 CFR 312.32(c)(2)). Any unexpected fatal or life-threatening suspected adverse event must be reported to FDA no later than 7 calendar days after the University Hospitals Principal Investigator initial receipt of the information (21 CFR 312.32(c)(2)). University Hospitals Principal Investigator will complete a Medwatch Form FDA 3500A and notify the FDA by telephone or facsimile transmission.

15 Calendar Day IND Safety Report
The timeframe for submitting an IND safety report to FDA and all participating investigators is no later than 15 calendar days after the University Hospitals Principal Investigator determines that the suspected adverse event or other information qualifies for reporting (21 CFR 312.32(c)(1)). This includes any serious, unexpected adverse events considered reasonably or possibly related to the investigational agent. University Hospitals Principal Investigator will complete a Medwatch Form FDA 3500A and notify the FDA by telephone or facsimile transmission. If FDA requests any additional data or information, the University Hospitals Principal Investigator must submit it to FDA as soon as possible, but no later than 15 calendar days after receiving the request (21 CFR 312.32(c)(1)(v)).

Follow-up IND Safety Report
Any relevant additional information that the University Hospitals Principal Investigator obtains that pertains to a previously submitted IND safety report must be submitted to FDA as a Follow-up IND Safety Report without delay, as soon as the information is available (21 CFR 312.32(d)(2)). The University Hospitals

Principal Investigator will maintain records of its efforts to obtain additional information.

Reporting Serious Problems to FDA
Medwatch Form FDA 3500A:
http://www.fda.gov/Safety/MedWatch/HowToReport/DownloadForms/default.htm
Telephone: 1-800-332-1088
Fax: 1-800-FDA-0178

8.5 SAEs and OnCore

- All SAEs will be entered into OnCore.
- A copy of the SAE form(s) submitted to the sponsor-investigator is also uploaded into Oncore.

8.6 Data Safety and Toxicity Committee

It is the responsibility of each site PI to ensure that ALL SAEs occurring on this trial (internal or external) are reported to the Case Comprehensive Cancer Center's Data and Safety Toxicity Committee. This submission is simultaneous with their submission to the sponsor and/or other regulatory bodies.

The sponsor-investigator is responsible for submitting an annual report to the DSTC as per CCCC Data and Safety Monitoring Plan.

8.7 Data and Safety Monitoring Plan (DSMP)

This protocol will adhere to the policies of the Case Comprehensive Cancer Center Data and Safety Monitoring Plan in accordance with NCI guidelines.

9.0 PHARMACEUTICAL INFORMATION

A list of the adverse events and potential risks associated with the investigational or commercial agents administered in this study can be found in Section 8.

9.1 Investigational Agent

9.1.1 Name of Agent Pembrolizumab

Other Names: MK-3475

Product description: Pembrolizumab is provided as a white to off white lyophilized powder (50 mg/vial) or as a liquid solution (100 mg/vial) in Type I glass vials intended for single use only.

Solution preparation: Pembrolizumab Powder for Solution for Infusion, 50 mg/vial, is reconstituted with sterile water for injection prior to use. The drug product is stored as a stable lyophilized powder or liquid solution under refrigerated conditions (2 to 8°C).

The lyophilized drug product after reconstitution with sterile water for injection, and the liquid drug product are a clear to opalescent solutions, essentially free of visible particles. The reconstituted lyophilized product and the liquid product are intended for IV administration.

The reconstituted drug product solution or the liquid drug product can be further diluted with normal saline or 5% dextrose in the concentration range of 1 to 10 mg/mL in intravenous (IV) containers made of polyvinyl chloride (PVC) or non-PVC material. Reconstituted vials should be immediately used to prepare the infusion solution in the IV bag and the infusion solution should be immediately administered.

Storage requirements: Diluted pembrolizumab solutions may be stored at room temperature for a cumulative time of up to 4 hours. This includes room temperature storage of admixture solutions in the IV bags and the duration of infusion. In addition, IV bags can be stored at 2 to 8°C for up to a cumulative time of 20 hours. This recommendation is based on up to 24 hours of room temperature and up to 24 hours of refrigerated stability data of diluted MK-3475 solutions in the IV bags.

Route of administration: 200 mg IV every 21 days (3 weeks)

Drug Procurement: Pembrolizumab will be supplied for this study by Merck.

Packaging and labeling: Clinical supplies will be affixed with a clinical label in accordance with regulatory requirements.

Drug Accountability: 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 institutional 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.

9.2 Commercial Agents

9.2.1 Carboplatin

Product description: Carboplatin is commercially available as a sterile lyophilized powder available in single-dose vials containing 50 mg, 150 mg and 450 mg of carboplatin. Each vial contains equal parts by weight of carboplatin and mannitol.
Refer to the package insert for further information.

Solution preparation: Immediately before use the content of each vial must be reconstituted with either sterile water for injection, USP, 5% dextrose in water, or 0.9% sodium chloride injection, USP according to the following schedule:

Vial Strength	Diluent Volume
50 mg	5 ml
150 mg	15 ml
450 mg	45 ml

These dilutions all produce a carboplatin concentration of 10 mg/ml. When prepared as directed carboplatin solutions are stable for eight hours at room temperature. Since no antibacterial preservative is contained in the formulation it is recommended that carboplatin solutions be discarded eight hours after dilution.

Note: Aluminum reacts with carboplatin causing precipitate formation and loss of potency; therefore, needles or intravenous sets containing aluminum parts that may come in contact with the drug must not be used for the preparation or administration of carboplatin.

Storage and Stability: Unopened vials of carboplatin are stable for the life indicated on the package when stored at controlled room temperature and protected from light.

Route of administration: AUC 4.5 IV on Day 1 of 21-day cycle.

Drug Procurement: Carboplatin must be obtained from commercial sources.

9.2.2 Nab-paclitaxel

Other Names: Abraxane

Product description: nab-Paclitaxel must be obtained commercially and is available in single-use vials in single count cartons. Each single-use 50 mL vial will contain paclitaxel (100 mg) and approximately 900 mg human albumin as a stabilizer.

Solution preparation: nab-Paclitaxel is supplied as a sterile, lyophilized powder for reconstitution before use.

Instructions for reconstitution:

1. Aseptically, reconstitute each vial by injecting 20mL of 0.9% sodium chloride injection.

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

Storage requirements: Un-reconstituted nab-paclitaxel should be stored in accordance with the product label.

Reconstituted nab-paclitaxel should be used immediately. If not used immediately, the vial of reconstituted nab-paclitaxel must be placed in its carton and be placed in a refrigerator at 2° to 8°C (36° to 46°F) for a maximum of 8 hours. Both forms should be stored in an area free of environmental extremes and must be accessible only to study personnel.

Route of administration: Short intravenous infusion over approximately 30-40 minutes.

Drug Procurement: Abraxane must be obtained by commercial sources.

10.0 EXPLORATORY or CORRELATIVE STUDIES

The following translational analyses will be coordinated by Shaveta Vinayak, MD.

We will correlate these independent measures with response to this chemo-immunotherapy combination: 1) pathology-based TIL scores (intratumoral and stromal) and quantitative computer-based TILs assessment; 2) gene expression-based TNBC subtypes; 3) gene expression-based immune signatures and immune cell subsets; and 4) immune cell subsets by multiplex IHC/IF in mTNBC. Lastly, we will integrate all four independent immune cell assessments, and correlate this integrative evaluation with response to the chemo-immunotherapy combination in mTNBC.

The following standard operating procedures (SOPs) are a guideline for collection of preoperative tissue core biopsies and of tissue at the time of surgery for these clinical trials. It is expected that minor differences in tissue handling may be necessary due to variation in institutional practice; however, it is important to adhere as closely as possible to these SOPs to maintain optimal conditions for tissue collection and processing. Where possible, options will be provided to allow flexibility in the SOP. Deviation from these SOPs MUST be recorded to allow for quality control and quality assurance.

The Translational Research and Pharmacology Core (TRPC) under the direction of John Pink Ph.D., will coordinate acquisition, processing and storage of correlative study specimens. Contact information for personnel responsible for these studies:

Patients enrolled at UH/CMC
Translational Research & Pharmacology Core
ATTN Erin Hohler
University Hospitals of Cleveland
11100 Euclid Avenue
Seidman Cancer Center, Room 3608
Cleveland, OH 44106
Telephone: 216-286-3889/216-386-3890
Pager: 33471
E-mail: emh14@case.edu

Patients enrolled at CCF:
Cleveland Clinic Central Biorepository: Department of Pathology L25
9500 Euclid Avenue
Cleveland, Ohio 44195
(216) 444-0047
tisscenterao@ccf.org

Biopsy Collection

- Coordination between the clinical team and the study personnel responsible for freezing the cores is essential in order to freeze the cores immediately after they've been taken.
- Core biopsies may be obtained by radiology or by surgery. It is STRONGLY RECOMMENDED that image guidance be used to localize the primary tumor for collection of core biopsy material. This can be achieved in the radiology suite, at the time of clip placement, sentinel node sampling or other procedure as a separate 'research only' biopsy and is typically performed under US guidance. MRI guidance is also acceptable. If the surgeon is taking the biopsy it can be done using a handheld ultrasound, or similar device. If such a device is not available then biopsies may be obtained without image guidance although the likelihood of collecting invasive cancer is reduced by 10-20% in this case.
- Four (4) 14-18 gauge cores of a metastatic tumor nodule should be obtained at each biopsy time point. If it is not possible to obtain four cores, as many as possible should be collected.

Specimen Processing:

Four (4) 14-18 gauge cores (prefer a 14-gauge needle but can use a smaller diameter needle to a minimum of 18 gauge) of a metastatic tumor nodule should be obtained at each biopsy time point if possible. If it is not possible to obtain four cores, as many as possible should be collected.

Processing should proceed in the following order for the 4 biopsies:

#1: Fixed in 10% Neutral Buffered Formalin (40ml container)
#2: Snap frozen in a sterile RNAse-free cryovial
#3: Frozen in OCT
#4: Snap frozen in a sterile RNAse-free cryovial

Timely processing of the specimens is critical, please contact TRPC or CCF Central Biorepository personnel prior to biopsy procedure to arrange for transportation and processing.

Specimens will be frozen over dry ice, or in liquid nitrogen (if available), and stored at -80˚C until processed.

Formalin fixed specimens will be transported within 1 day to the CaseCCC Tissue Resources Core, for completion of fixation processing and embedding. Once embedded they will be stored in the Tissue Resources Core until slides are cut and stained. Specimens from patients enrolled at CCF will be sent by courier at regular intervals (approximately every 3 months) for storage in the TRPC.

Frozen specimens will be stored in the TRPC until processed for RNA and/or DNA isolation.

10.1 Pathology-Based and Quantitative Computer-Based Tumor Infiltrating Lymphocyte (TIL) Assessment

Specimen to be used: Formalin-fixed tumor tissue from metastatic site.

10.1.1 Background

Pathology-based TIL scores (intratumoral and stromal) have been shown to be prognostic and predictive of therapy response in TNBC.

10.1.2 Rationale for Analysis

Pathology-based TIL scores (intratumoral and stromal) will be assessed prior to treatment and in the post-treatment biopsy in patients, if collected. International TILs working group guidelines by Salgado et al. will be used. Quantitative computer-based methodology has been developed by our Case collaborators (Dr. Madabhushi), which will be applied to this cohort of samples.

10.1.3 Collection of Specimens

FFPE slides will be cut and stained with H&E in batches upon request of the Principal Investigator in the Tissue Resources Core and TIL scores will be assessed by Hannah Gilmore MD. Slides will be digitized and quantitative TIL scores will be assessed.

10.2 Gene Expression Based TNBC subset Analysis

Specimen used: Snap frozen tumor tissue from the metastatic site.

10.2.1 Background

RNA and DNA will be extracted from tumor cores in the Translational Research and Pharmacology Core (TRPC) and Affymetrix Human Transcriptome Array (HTA) 2.0 will be used to generate whole genome gene expression data. After normalization and gene-level expression summarization, the Pietenpol molecular subytypes will be assessed TNBC using the online "TNBC type" tool (36).

10.2.2 Rationale for Analysis

Given the molecular heterogeneiety of TNBC, TNBC gene-expression subtypes will be determined and then response will be assessed within subtypes. TNBC subtyping tool as described previously will be applied. Tumor DNA will be used for other correlatives including neoantigen repertoire and T-cell receptor repertoire.

10.3 Gene expression-based immune signatures and immune cell subsets

Specimen used: Snap frozen tumor tissue from the metastatic site.

10.3.1 Background

Immune cell subsets will be determined based on gene expression profiling using established computational methodologies such as CIBERSORT. Nanostring may be used as well.

10.3.2 Rationale for Analysis

Pre-defined immune signatures and immune cell subset methodologies will be scored for each sample (38). These will be correlated with response.

10.4 Immune cell subsets by multiplex IHC/IF in mTNBC

Specimen to be used: Formalin-fixed tumor tissue from the metastatic sites. Samples for PD-L1 testing will be shipped in batches to the central lab, QualTek Molecular Labortories at:

QualTek Molecular Laboratories 300 Pheasant Run

Newtown, PA 18940
Phone: 215-504-7402
Fax: 805-830-6379
Email: info@qmlabs.com

10.4.1 Background

Multiplex IHC/IF will be used to assess immune cell subsets and checkpoints, including PD-L1. We will assess how these change with therapy and their correlation with response.

10.4.2 Rationale for Analysis

Tumor-based changes in immune cell subsets will be assessed in both pre-treatment and post-treatment biopsy, if available. Our pathology core has validated these immune markers by IHC already.

11.0 STUDY PARAMETERS AND CALENDAR

11.1 General Study Parameters

The following clinical laboratory tests will be performed:

Serum Chemistry: Comprehensive Panel (including glucose, sodium, potassium, chloride, bicarbonate, anion gap, nitrogen urea, creatinine, calcium, albumin, alkaline phosphatase (ALP), total protein, asparate aminotransferase (AST), total bilirubin, alanine aminotransferace (ALT), thyroid stimulating hormone (TSH), T4Thyroxine, T3 and magnesium.

*Note for serum chemistries: Tests for AST, ALT, ALP and total bilirubin must be conducted concurrently and assessed concurrently.

Hematology: Hematocrit, Hemoglobin, White cell count with differential count, Platelet count

Urinalysis (screening only): Macroscopic (including color, clarity, specific gravity, pH, leukocyte esterase, nitrite, ketones, protein, glucose, ketones, blood, bilirubin, urobilinogen)
Microscopic (including red blood cells, white blood cells, bacterial, epithelial cells, mucous, cast, crystal

Imaging: Imaging will be done every 3 cycles and a repeat brain CT/MRI will only be undertaken to check for brain metastases stability if patients had brain metastases at time of enrollment. MRI brain will only be done if there is either a history of prior brain mets or the patient presents with suspicious symptoms. Otherwise, the brain MRI will not be part of screening or follow up.

11.1.1 Screening Evaluation

Screening studies and evaluations will be used to determine the eligibility of each subject for study inclusion. All evaluations must be completed within 28 days prior to study entry.

Screening correlative biopsy will be obtained, preferably will obtain a fresh tissue biopsy. Urinalysis will be done at screening only.

11.1.2 Treatment Period

Treatment will be cycle-based.

C, Carboplatin, will be administered AUC 4.5 IV day 1 of 21-day cycle.
N, Nab-paclitaxel, will be administered 75 mg/m^2 IV days 1, 8 and 15 of 21-day cycle.
P, Pembrolizumab, will be administered 200 mg IV every 21 days .

Treatment on this regimen will continue until disease progression.

11.1.3 30 Day Follow-Up

For the purposes of safety reporting, all adverse events will be reported that occur starting on Cycle 1 Day 1 through 30 days after the final dose of study drug. Adverse events, both serious and non-serious, and deaths that occur during this period will be recorded in the source documents. All SAEs should be monitored until they are resolved or are clearly determined to be due to a subject's stable or chronic condition or intercurrent illness(es). Related AEs will be followed until resolution to baseline or grade 1 or stabilization.

11.1.4 Long Term Follow-Up

Patients will be followed for survival for at least 12 months after their post 30 day follow-up. A phone call is sufficient for this visit.

11.2 Calendar

A visit window of +/- **3** days is allowed for labs (hematology and chemistries including TSH, T3, T4 and HCG, vital signs, weight and performance status)
A visit window of +/- **1** day is allowed for treatment.
A visit window of +/- **7** days is allowed for 3 month follow-up visits.
A visit window of +/- **3** days is allowed for the 30 Day follow-up visit.

Study Days	**Screening**	**Cycles 1-n[1] Day 1**	**Cycles 1-n[1] Day 8**	**Cycles 1-n[1] Day 15**	**After completion of 3 cycles of treatment**	**30 Day Follow-Up**	**Long Term Follow-Up** (see section 11.1.4 for details)
REQUIRED ASSESSMENTS							
Informed Consent	X						
Demographics	X						
Medical History	X						
Height	X						
Weight and Body Surface Analysis	X	X	X	X	X	X	
Vitals including blood pressure	X	X	X	X	X	X	
Physical Examination	X	X			X	X	
Concomitant medication + allergy assessment	X	X	X	X	X	X	
ECOG PS	X	X	X	X	X	X	
Baseline Symptoms	X					X	
Adverse Event Assessment		X	X	X	X	X	X
CBC / diff / platelets	X	X	X	X	X	X	
Serum Chemistry	X	X	X	X	X	X	
Urinalysis	X						
TSH, T4 Thyroxine, T3[5]	X	X					
ß-HCG, women of childbearing potential (Cycle 1 only)	X	X					
DISEASE ASSESSMENT							
MRI Brain (see section 11.1 for details)	X	X			X	X	
CT Chest, Abdomen and Pelvis[3]	X				X		
Bone Scan	X				X		
TREATMENT							
Nab-paclitaxel[4]		X	X	X			
Carboplatin[4]		X					
Pembrolizumab[4]				X			
CORRELATIVE							
Biopsy	X				X (Optional after completion of 1st 3 cycles only)[2]		

[1] Patients may receive treatment for up to 24 months

[2]Biopsy must be completed before the initiation of cycle 4

[3]Cycle 3 assessment scans must be done at the conclusion of cycle 3 but before the initiation of cycle 4.

[4] Patients who discontinue carboplatin and/or nab-paclitaxel due to experiencing known toxicities to carboplatin and/or nab-paclitaxel will continue to follow the study calendar for all tests and procedures done on Day 1 of each consecutive cycle if they continue to

receive carboplatin or on Day1, 8 and 15 of each consecutive cycles if they continue to receive nab-paclitaxel. Patients receiving pembrolizumab only will follow the study calendar for all tests and procedures done on Day 15 of each consecutive cycle.
[5] Patients receiving pembrolizumab only will have thyroid testing done on Day 15 of each consecutive cycle.

12.0 MEASUREMENT OF EFFECT

Clinical response will be scored according to RECIST Criteria v1.1.
As an exploratory objective, we will score clinical response using irRECIST criteria [40].

13.0 DATA REPORTING / REGULATORY CONSIDERATIONS

Adverse event lists, guidelines, and instructions for AE reporting can be found in Section 8.0 (Adverse Events: List and Reporting Requirements).

13.1 Data Reporting

The OnCore® and Forte EDC Databases will be utilized, as required by the Case Comprehensive Cancer Center, to provide data collection for both accrual entry and trial data management. OnCore® is a Clinical Trials Management System housed on secure servers maintained at Case Western Reserve University. Forte EDC is an electronic data capture system which supports 21 CFR Part 11 compliance. Access to data through Forte EDC is restricted by user accounts and assigned roles. Once logged into the OnCore ® and Forte EDC systems with a user ID and password, defined roles for each user limit access to appropriate data. User information and password can be obtained by contacting the OnCore ®Administrator at OnCore-registration@case.edu.

OnCore® and Forte EDC are designed with the capability for study setup, activation, tracking, reporting, data monitoring and review, and eligibility verification. This study will utilize electronic Case Report Form completion in the Forte EDC database. A calendar of events and required forms are available in OnCore® and Forte EDC

13.2 Regulatory Considerations

The study will be conducted in compliance with ICH guidelines and with all applicable federal (including 21 CFR parts 56 & 50), state or local laws.

13.2.1 Written Informed Consent

Provision of written informed consent must be obtained prior to any study-related procedures. The Principal Investigator will ensure that the subject is given full and adequate oral and written information about the nature, purpose, possible risks and benefits of the study as well as the subject's financial responsibility. Subjects must also be notified that they are free to discontinue from the study at any time. The subject

should be given the opportunity to ask questions and be allowed time to consider the information provided.

The original, signed written Informed Consent Form must be kept with the Research Chart in conformance with the institution's standard operating procedures. A copy of the signed written Informed Consent Form must be given to the subject. Additionally, documentation of the consenting process should be located in the research chart.

13.2.2 Subject Data Protection

In accordance with the Health Information Portability and Accountability Act (HIPAA), a subject must sign an authorization to release medical information to the sponsor and/or allow the sponsor, a regulatory authority, or Institutional Review Board access to subject's medical information that includes all hospital records relevant to the study, including subjects' medical history.

13.2.3 Retention of Records

The Principal Investigator of The Case Comprehensive Cancer Center supervises the retention of all documentation of adverse events, records of study drug receipt and dispensation, and all IRB correspondence for as long as needed to comply with local, national and international regulations. No records will be destroyed until the Principal Investigator confirms destruction is permitted.

13.2.4 Audits and Inspections

Authorized representatives of the sponsor, a regulatory authority, an Independent Ethics Committee (IEC) or an Institutional Review Board (IRB) may visit the site to perform audits or inspections, including source data verification. The purpose of an audit or inspection is to systematically and independently examine all study-related activities and documents to determine whether these activities were conducted, and data were recorded, analysed, and accurately reported according to the protocol, Good Clinical Practice (GCP), guidelines of the International Conference on Harmonization (ICH), and any applicable regulatory requirements. For multi-center studies, participating sites must inform the sponsor-investigator of pending audits.

14.0 STATISTICAL CONSIDERATIONS

Aim 1. Determine ORR in patients treated with CNP.

Clinical response will be scored using Response Evaluation Criteria in Solid Tumors (RECIST 1.1) criteria. In order to determine the sample size of this study, a confidence interval approach was used. Under the proposed treatment, the expected clinical response is about 35%. With the precision of the 2-sided 95% confidence interval for the response rate set to 0.17 (the distance to the expected response rate of 35%), then the sample size required for the study is 30 patients. The true response rate of the therapy for this patient

population will be estimated based on the number of responses using a binomial distribution and its confidence intervals will be estimated using Wilson's method [41]. The same method will be used to estimate disease control rate. Safety/tolerability data will be summarized using descriptive statistics.

Aim 2. Determine PFS in patients treated with CNP.

The Kaplan-Meier method [42] will be used to estimate PFS. Factors including pathologic and genomic correlates that predict survival outcomes will be identified by Cox model [43] or extensions of Cox model [44].

Aim 3. Identify pathologic and genomic correlates of response to CNP.

The IHC, morphometric and genomic correlates will be assessed by comparing responders and non-responders with each specific marker as a continuous variable (TIL, Immune scores) or dichotomous variable (TNBC subtypes, Pathway analysis, IHC for PDL1). T-test and chi-square test will be used for the comparison of continuous variables and dichotomous variable, respectively. Furthermore, the pathologic and genomic predictors on overall response (CR+PR) and disease control (CR+PR+SD) will be identified using logistic regressions. With the limited the sample size, the analysis will be exploratory in nature.

15.0 REFERENCES

1. Perou CM, Sorlie T, Eisen MB, et al. Molecular portraits of human breast tumours. Nature 2000;406:747-752.
2. Sorlie T, Perou CM, Tibshirani R, et al. Gene expression patterns of breast carcinomas distinguish tumor subclasses with clinical implications. Proc Natl Acad Sci USA 2001;98:10869-10874.
3. Rakha EA, El-Sayed ME, Green AR, et al. Prognostic markers in triple-negative breast cancer. Cancer 2007;109:25-32.
4. Haffty BG, Yang Q, Reiss M, et al. Locoregional relapse and distant metastasis in conservatively managed triple negative early-stage breast cancer. J Clin Oncol 2006;24:5652-5657.
5. Bertucci F, Finetti P, Cervera N, et al. How basal are triple-negative breast cancers? Int J Cancer 2008; 123:236-240.
6. Sorlie T, Tibshirani R, Parker J, et al. Repeated observation of breast tumor subtypes in independent gene expression data sets. Proc Natl Acad Sci USA 2003; 100:8418-8423.

7. Von Minckwitz G, Jonat W, Fasching P, et al. A multicentre phase II study on gefitinib in taxane- and anthracycline-pretreated metastatic breast cancer. Breast Cancer Res Treat. 2005;89:165-172.

8. Green MD, Francis PA, Gebski V, et al. Gefitinib treatment in hormone-resistant and hormone receptor negative advanced breast cancer. Ann Oncol 2009;20:1813-1817.

9. O'Shaughnessy J, Schwartzberg LS, Danso MA, et al. A randomized phase III study of iniparib (BSI-201) in combination with gemcitabine/carboplatin (G/C) in metastatic triple-negative breast cancer (TNBC). J Clin Oncol 2011;29 Suppl:1007.

10. Liu S, Lachapelle J, Leung S, Gao D, Foulkes WD, Nielsen TO. CD8+ lymphocyte infiltration is an independent favorable prognostic indicator in basal-like breast cancer. Breast Cancer Res. 2012 Mar 15;14(2):R48.

11. Loi S. Tumor-infiltrating lymphocytes, breast cancer subtypes and therapeutic efficacy. Oncoimmunology. 2013 Jul 1;2(7).

12. Loi S, Sirtaine N, Piette F, Salgado R, Viale G, Van Eenoo F, Rouas G, Francis P, Crown JP, Hitre E, de Azambuja E, Quinaux E, Di Leo A, Michiels S, Piccart MJ, Sotiriou C. Prognostic and predictive value of tumor-infiltrating lymphocytes in a phase III randomized adjuvant breast cancer trial in node-positive breast cancer comparing the addition of docetaxel to doxorubicin with doxorubicin-based chemotherapy: BIG 02-98. J Clin Oncol. 2013 Mar 1;31(7):860-7.

13. Denkert C, Loibl S, Noske A, Roller M, Müller BM, Komor M, Budczies J, Darb-Esfahani S, Kronenwett R, Hanusch C, von Törne C, Weichert W, Engels K, Solbach C, Schrader I, Dietel M, von Minckwitz G. Tumor-associated lymphocytes as an independent predictor of response to neoadjuvant chemotherapy in breast cancer. J Clin Oncol. 2010 Jan 1;28(1):105-13.

14. Denkert C, von Minckwitz G, Brase JC, Sinn BV, Gade S, Kronenwett R, Pfitzner BM, Salat C, Loi S, Schmitt WD, Schem C, Fisch K, Darb-Esfahani S, Mehta K, Sotiriou C, Wienert S, Klare P, André F2 Klauschen F, Blohmer JU, Krappmann K, Schmidt M, Tesch H, Kümmel S, Sinn P, Jackisch C, Dietel M, Reimer T, Untch M, Loibl S. Tumor-Infiltrating Lymphocytes and Response to Neoadjuvant Chemotherapy With or Without Carboplatin in Human Epidermal Growth Factor Receptor 2-Positive and Triple-Negative Primary Breast Cancers. J Clin Oncol. 2014 Dec 22 [Epub ahead of print]

15. Menetrier-Caux C, Gobert M, Caux C. Differences in tumor regulatory T-cell localization and activation status impact patient outcome.CancerRes2009;69:7895–8.

16. Gabrilovich DI, Nagaraj S. Myeloid-derived suppressor cells as regulators of the immune system. Nat Rev Immunol 2009; 9: 162–74.

17. Liu F, Lang R, Zhao J, Zhang X, Pringle GA, Fan Y, Yin D, Gu F, Yao Z, Fu L. CD8(+) cytotoxic T cell and FOXP3(+) regulatory T cell infiltration in relation to breast cancer survival and molecular subtypes. Breast Cancer Res Treat. 2011 Jun 30.

18. Xu L, Xu W, Qiu S, Xiong S. Enrichment of CCR6+Foxp3+ regulatory T cells in the tumor mass correlates with impaired CD8+ T cell function and poor prognosis of breast cancer. Clin Immunol. 2010 Jun;135(3):466-75.

19. Gobert M, Treilleux I, Bendriss-Vermare N, Bachelot T, Goddard-Leon S, Arfi V, Biota C, Doffin AC, Durand I, Olive D, Perez S, Pasqual N, Faure C, Ray-Coquard I, Puisieux A, Caux C, Blay JY, Ménétrier-Caux C. Regulatory T cells recruited through CCL2/CCR4 are selectively activated in lymphoid infiltrates surrounding primary breast tumors and lead to an adverse clinical outcome. Cancer Res. 2009 Mar 1;69(5):2000-9.

20. Diaz-Montero CM, Salem ML, Nishimura MI, Garrett-Mayer E, Cole DJ, Montero AJ. Increased circulating myeloid-derived suppressor cells correlate with clinical cancer stage, metastatic tumor burden, and doxorubicin-cyclophosphamide chemotherapy. Cancer Immunol Immunother. 2009 Jan;58(1):49-59.

21. Janakiram M, Abadi YM, Sparano JA, Zang X. T cell coinhibition and immunotherapy in human breast cancer. Discov Med. 2012 Oct;14(77):229-36.

22. Muenst S, Soysal SD, Gao F, Obermann EC, Oertli D, Gillanders WE. The presence of programmed death 1 (PD-1)-positive tumor-infiltrating lymphocytes is associated with poor prognosis in human breast cancer. Breast Cancer Res Treat. 2013 Jun;139(3):667-76.

23. Mittendorf EA, Philips AV, Meric-Bernstam F, Qiao N, Wu Y, Harrington S, Su X, Wang Y, Gonzalez-Angulo AM, Akcakanat A, Chawla A, Curran M, Hwu P, Sharma P, Litton JK, Molldrem JJ, Alatrash G. PD-L1 expression in triple-negative breast cancer. Cancer Immunol Res. 2:361-70, 2014.

24. Nanda R, Chow LQ, Dees EC, Berger R, Gupta S, Geva R, Pusztai L, Dolled-Filhart M, Emancipator K, Gonzalez EJ, Houp J, Pathiraja K, Karantza V, Iannone R, Gause CK, Cheng JD, Buisseret L. A phase Ib study of pembrolizumab (MK-3475) in patients with advanced triple-negative breast cancer. 2014. Abstract S1-09; San Antonio Breast Cancer Symposium.

25. Hamilton E, Kimmick G, Hopkins J, Marcom PK, Rocha G, Welch R, Broadwater G, Blackwell K. Nab-paclitaxel/bevacizumab/carboplatin chemotherapy in first-line triple negative metastatic breast cancer. Clin Breast Cancer. 2013 Dec;13(6):416-20.

26. Conlin AK, Seidman AD, Bach A, Lake D, Dickler M, D'Andrea G, Traina T, Danso M, Brufsky AM, Saleh M, Clawson A, Hudis CA. Phase II trial of weekly nanoparticle albumin-bound paclitaxel with carboplatin and trastuzumab as first-line therapy for women with HER2-overexpressing metastatic breast cancer. Clin Breast Cancer. 2010 Aug 1;10(4):281-7.

27. Michaud M, Martins I, Sukkurwala AQ, Adjemian S, Ma Y, Pellegatti P, Shen S, Kepp O, Scoazec M, Mignot G, Rello-Varona S, Tailler M, Menger L, Vacchelli E, Galluzzi L, Ghiringhelli F, di Virgilio F, Zitvogel L, Kroemer G. Autophagy-dependent anticancer immune responses induced by chemotherapeutic agents in mice. Science. 2011;334:1573-7.

28. Diaz Y, Tundidor Y, Lopez A, Leon K. Concomitant combination of active immunotherapy and carboplatin- or paclitaxel-based chemotherapy improves anti-tumor response. Cancer Immunol Immunother. 2013 Mar;62(3):455-69.

29. Chang CL, Hsu YT, Wu CC, Lai YZ, Wang C, Yang YC, Wu TC, Hung CF. Dose-dense chemotherapy improves mechanisms of antitumor immune response. Cancer Res. 2013 Jan 1;73(1):119-27.

30. Zhang H, Wang Y, Liu C, Zhang L, Xia Q, Zhang Y, Wu J, Jiang C, Chen Y, Wu Y, Zha X, Yu X, Kong W. DNA and adenovirus tumor vaccine expressing truncated survivin generates specific immune responses and anti-tumor effects in a murine melanoma model. Cancer Immunol Immunother. 2012 Oct;61(10):1857-67.

31. Liu H, Zhang T, Ye J, Li H, Huang J, Li X, Wu B, Huang X, Hou J. Tumor-infiltrating lymphocytes predict response to chemotherapy in patients with advance non-small cell lung cancer. Cancer Immunol Immunother. 2012 Oct;61(10):1849-56.

32. Braly P, Nicodemus CF, Chu C, Collins Y, Edwards R, Gordon A, McGuire W, Schoonmaker C, Whiteside T, Smith LM, Method M. The Immune adjuvant properties of front-line carboplatin-paclitaxel: a randomized phase 2 study of alternative schedules of intravenous oregovomab chemoimmunotherapy in advanced ovarian cancer. J Immunother. 2009 Jan;32(1):54-65.

33. Liu WM, Fowler DW, Smith P, Dalgleish AG. Pre-treatment with chemotherapy can enhance the antigenicity and immunogenicity of tumours by promoting adaptive immune responses. Br J Cancer. 2010 Jan 5;102(1):115-23.

34. von Minckwitz G, Schneeweiss A, Loibl S, Salat C, Denkert C, Rezai M, Blohmer JU, Jackisch C, Paepke S, Gerber B, Zahm DM, Kümmel S, Eidtmann H, Klare P, Huober J, Costa S, Tesch H, Hanusch C, Hilfrich J, Khandan F, Fasching PA, Sinn BV, Engels K, Mehta K, Nekljudova V, Untch M. Neoadjuvant carboplatin in patients with triple-negative and HER2-positive early breast cancer (GeparSixto; GBG 66): a randomised phase 2 trial. Lancet Oncol. 2014 Jun;15(7):747-56.

35. Karasar P, Esendagli G. T helper responses are maintained by basal-like breast cancer cells and confer to immune modulation via upregulation of PD-1 ligands. Breast Cancer Res Treat. 2014; 145:605-14.

36. Xi Chen, Jiang Li, William H. Gray, Brian D. Lehmann, Joshua A. Bauer, Yu Shyr and Jennifer A. Pietenpol. TNBCtype: A Subtyping Tool for Triple-Negative Breast Cancer. Cancer Informatics 2012:11 147–156.

37. Burstein MD, Tsimelzon A, Poage GM, Covington KR, Contreras A, Fuqua S, Savage M, Osborne CK, Hilsenbeck SG, Chang JC, Mills GB,Lau CC, Brown PH. Comprehensive Genomic Analysis Identifies Novel Subtypes and Targets of Triple-negative Breast Cancer.Clin Cancer Res. 2014 Sep 10.

38. Yoshihara K, Shahmoradgoli M, Martínez E, Vegesna R, Kim H, Torres-Garcia W, Treviño V, Shen H, Laird PW, Levine DA, Carter SL, Getz G, Stemke-Hale K, Mills GB, Verhaak RG. Inferring tumour purity and stromal and immune cell admixture from expression data. Nat Commun. 2013;4:2612.

39. Socinski MA1, Okamoto I, Hon JK, Hirsh V, Dakhil SR, Page RD, Orsini J, Yamamoto N, Zhang H, Renschler MF. Safety and efficacy analysis by histology of weekly nab-paclitaxel in combination with carboplatin as first-line therapy in

patients with advanced non-small-cell lung cancer.Ann Oncol. 2013 Sep;24(9):2390-6.

40. Hoos A1, Eggermont AM, Janetzki S, Hodi FS, Ibrahim R, Anderson A, Humphrey R, Blumenstein B, Old L, Wolchok. Improved endpoints for cancer immunotherapy trials. J Natl Cancer Inst. 2010 Sep 22;102(18):1388-97.
41. J.Brown, L.D., et al., Interval estimation for a binomial proportion - Comment - Rejoinder. Statistical Science, 2001. 16(2): p. 101-133.
42. Kaplan, E.L. and P. Meier. Nonparametric Estimation from Incomplete Observations. Journal of the American Statistical Association. 1958. 53(282): p. 457-481.
43. Cox, D.R. Regression Models and Life Tables. Journal of the Royal Statistical Society Series B-Statistical Methodology, 1972. 34(2): p.187.
44. Therneau, T.M. and P.M. Grambsch, Modeling survival data : extending the Cox model. Statistics for biology and health. 2000, New York: Springer. xiii, 350 p.

APPENDIX I

PERFORMANCE STATUS CRITERIA

ECOG Performance Status Scale	
Grade	Description
0	Normal activity. Full 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. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% if 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.

APPENDIX II
Immune-mediated Adverse Reactions

Immune-mediated Adverse Reactions

	KEYTRUDA 2 mg/kg every 3 weeks or 10 mg/kg every 2 or 3 weeks n=1562				
Adverse Reaction	All Grades (%)	Grade 2 (%)	Grade 3 (%)	Grade 4 (%)	Grade 5 (%)
Hypothyroidism	7.2	0	0.1	0	0
Pneumonitis	2.9*	1.0	0.8	0.1†	0.1†
Hyperthyroidism	2.2	0.5	0.2	0	0
Colitis	1.3	0.4	0.8	0	0
Hypophysitis	0.7	0.3	0.3	0.1	0
Hepatitis	0.5	0.1	0.3	0.1	0
Nephritis	0.3	0.1	0.1	0.1	0
Diabetes Mellitus	0.1	0.1	0	0	0
* Incidence was 3.5% in subjects with NSCLC. † These events were reported in subjects with NSCLC.					

Endocrinopathies: The median time to onset of hypophysitis was 1.7 months (range 1 day to 6.5 months). The median duration was 3.3 months (range 0.8 months to 12.7 months). Hypophysitis led to discontinuation of KEYTRUDA in 4 (0.3%) subjects. Hypophysitis resolved in 5 subjects. The median time to onset of hyperthyroidism was 1.4 months (range 1 day to 21.9 months). The median duration was 2.8 months (range 1.4 weeks to 12.8 months). Hyperthyroidism led to discontinuation of KEYTRUDA in 2 (0.1%) subjects.

Hyperthyroidism resolved in 25 subjects. The median time to onset of hypothyroidism was 3.5 months (range 5 days to 18.9 months). The median duration was 6.4 months (range 0.9 weeks to 24.3 months). No subjects discontinued KEYTRUDA due to hypothyroidism.
Pneumonitis: The median time to onset of pneumonitis was 3.1 months (range 2 days to 19.3 months). The median duration was 1.7 months (range 0.3 weeks to 15.1 months).

Pneumonitis led to discontinuation of KEYTRUDA in 20 (1.3%) subjects. Pneumonitis resolved in 28 subjects.

Colitis: The median time to onset of colitis was 3.4 months (range 1.3 weeks to 9.7 months). The median duration was 1.2 months (range 0.6 weeks to 7.2 months). Colitis led to discontinuation of KEYTRUDA in 7 (0.4%) subjects. Colitis resolved in 19 subjects.

Hepatitis: The median time to onset of hepatitis was 3.1 weeks (range 1.1 weeks to 21.4 months). The median duration was 1.3 months (range 1.1 weeks to 2.2 months). Hepatitis led to discontinuation of KEYTRUDA in 2 (0.1%) subjects. Hepatitis resolved in 6 subjects.

Nephritis: The median time to onset of nephritis was 6.8 months (range 1.7 weeks to 12.8 months). The median duration was 1.1 months (range 2.1 weeks to 3.3 months). Nephritis led to discontinuation of KEYTRUDA in 1 (0.1%) subject. Nephritis resolved in 3 subjects.