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Title: Phase II Study of Pembrolizumab and Nab-paclitaxel in HER-2 Negative Metastatic Breast Cancer

CONFIDENTIAL

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1.0 TRIAL SUMMARY

Abbreviated Title	Pembrolizumab and nab-paclitaxel in metastatic breast cancer
Trial Phase	II
Clinical Indication	Metastatic HER2-negative breast cancer
Trial Type	Single-arm open-label multi-cohort
Type of control	N/A
Route of administration	Intravenous (IV)
Trial Blinding	No
Treatment Groups	All cohorts receive pembrolizumab and nab-paclitaxel
Number of trial subjects	70
Estimated enrollment period	4 years
Estimated duration of trial	9/2015-12/2019
Duration of Participation	9/2015-12/2019

This document is a protocol for a human research study. This study is to be conducted in accordance with US government research regulations, and applicable international standards of Good Clinical Practice, and institutional research policies and procedures.

2.0 TRIAL DESIGN

2.1 Trial Design

This is a single-arm open-label multi-cohort Phase II study evaluating the safety/tolerability and clinical activity of the combination of nab-paclitaxel and the antibody against programmed cell death 1 (PD-1), pembrolizumab, in patients with human epidermal growth factor receptor (HER-2) negative metastatic breast cancer (n=50). There will be two cohorts of patients consisting of a triple negative breast cancer (TNBC) cohort with 30 subjects and a hormone receptor (HR)-positive cohort with 20 subjects. There will be an initial safety run-in with 12 subjects (patients from both, TNBC and HR-positive cohort are eligible, we expect approximately 6 patients from each cohort). If no unexpected toxicity is observed (as defined in the study protocol), then enrollment will continue to complete both cohorts (30 total TNBC, 20 total in HR positive cohort). The subjects from the run in safety part will be included in the Phase II analysis. Tumor expression of programmed cell death ligand 1 (PD-L1) is not required for enrollment in the study, but will be assessed as possible predictive marker.

Amendment 2/2019: addition of a 20 patient TNBC cohort, who will be receive a pembrolizumab-run in cycle (cycle 1) before starting the combination of pembrolizumab/nab-paclitaxel with cycle 2 (rationale discussed in section 4.3.5). This cohort is labeled as immunotherapy-run in cohort (**iTNBC**). The TNBC cohort in the initial trial is labeled as chemotherapy-run in cohort (**cTNBC**).

2.1.1 Primary Study Endpoints

The primary endpoint for the safety run-in group is safety and tolerability of the combination of nab-paclitaxel and pembrolizumab (anti PD-1 antibody). A prior study in TNBC of the combination of nab-paclitaxel and atezolizumab (an anti-PD-L1 antibody) showed tolerability of the treatment in 32 women with metastatic disease with no increase in toxicity beyond what has been observed for either single agent (Adams S, et al. Presented at: San Antonio Breast Cancer Symposium; December 8-12, 2015; San Antonio, TX. Abstract P2-11-06).

Safety success is defined as avoidance of excess toxicity with the combination compared to known single agent toxicity.

The primary endpoint for Phase II is best overall response rate (BORR) based on Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 in the cTNBC cohort who will be treated with the combination regimen as either first, second, or third line therapy for metastatic disease.

2.1.2 Secondary Study Endpoints

The BORR will also be estimated based on RECIST 1.1 in the iTNBC cohort who will be treated with the combination regimen as either first, second, or third line therapy for metastatic disease.

For the TNBC cohorts (iTNBC and cTNBC), BORR will also be evaluated using immune-related RECIST criteria; see Appendix (Section 10.4) for criteria details. Progression-free survival (PFS), overall survival (OS), disease control rate (DCR), and duration of response (DOR) using RECIST 1.1 as well as immune-related RECIST criteria will be used in this cohort. In addition, the subset of patients with confirmed PD-L1 expression in both the TNBC and HR-positive cohorts will be analyzed for efficacy. It is anticipated that efficacy will be highest in the PD-L1 expressors, regardless of HR status. However, efficacy will also be assessed preliminarily in PD-L1 expressors by HR subgroup (although there will be limited power in the HR-positive group).

2.1.3 Exploratory Endpoints

In the HR-positive cohort, BORR using RECIST 1.1 as well as immune-related RECIST criteria will be evaluated in women with metastatic breast cancer previously treated with 0-2 lines of chemotherapy in the metastatic setting.

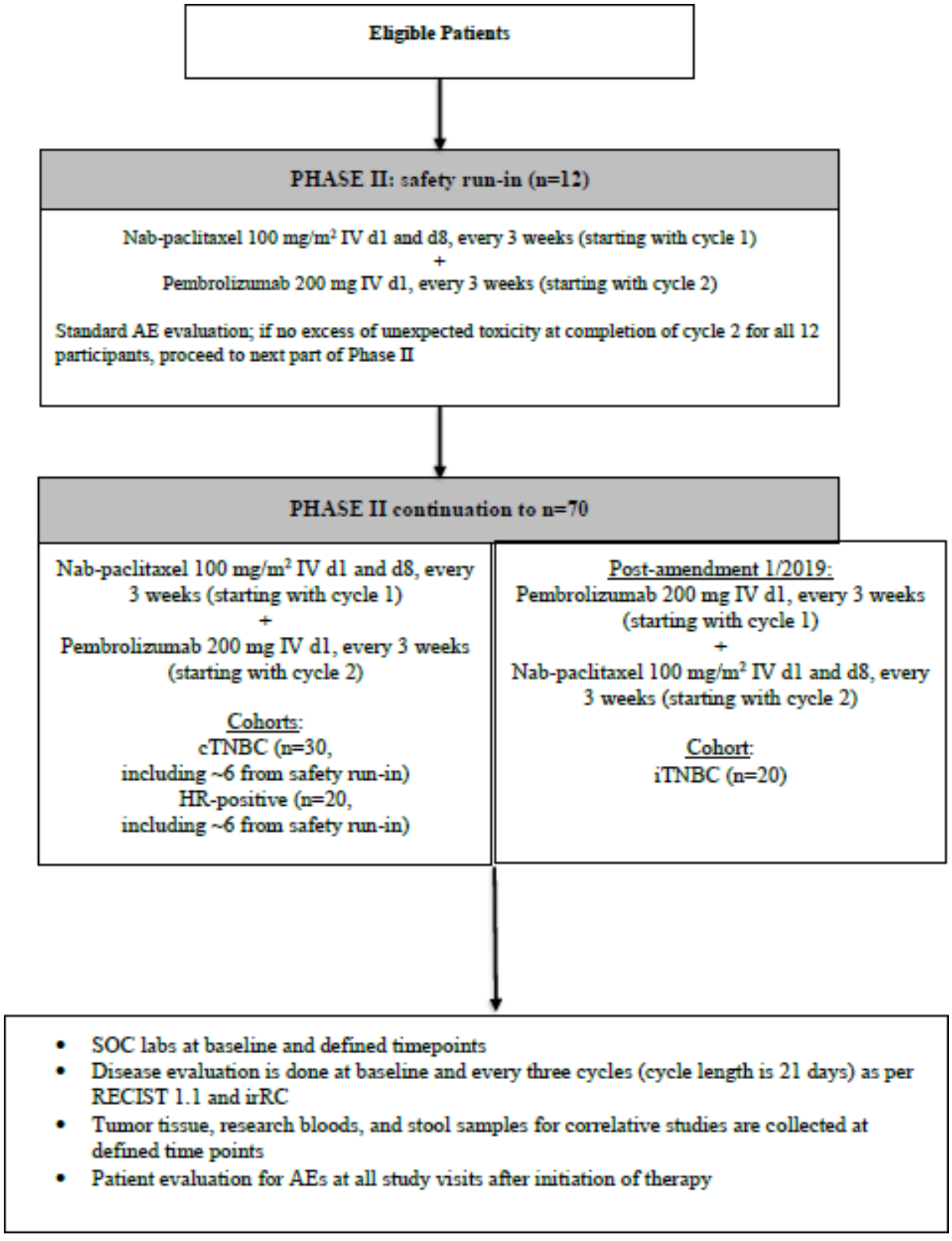
Predictive markers of response including PD-1 expression on peripheral leukocytes, TILs by histopathological assessment, TCR by immunosequencing, immune gene profiles in tumors and the gut microbiome composition and abundance by 16S ribosomal RNA sequencing will be explored. Nab-paclitaxel induced changes in tumoral PD-L1 expression and immune infiltrates in TNBC and HR-positive tumors will be assessed.

Pembrolizumab induced changes in tumoral PD-L1 expression and immune infiltrates in TNBC will be assessed (iTNBC + cTNBC)

Mutational and neoantigen load in TNBC will be evaluated for frequency and as predictive marker of response (iTNBC + cTNBC)

Efficacy (BORR, PFS and OS) will be explored in each of the iTNBC and cTNBC cohorts.

2.2 Trial Diagram



3.0 OBJECTIVES & HYPOTHESES

3.1 Primary Objectives & Hypotheses

(1) Objectives:

a) Phase II-safety run-in: To evaluate the safety and tolerability of the combination of nab-paclitaxel and pembrolizumab in women with metastatic HER2-negative breast cancer.

b) Phase II: In the cTNBC cohort, to evaluate the best overall response rate (BORR) using RECIST 1.1 of nab-paclitaxel with pembrolizumab in women with breast cancer treated with 0-2 lines of chemotherapy in the metastatic setting.

Hypotheses:

a) Treatment with the combination of nab-paclitaxel and pembrolizumab is safe and tolerable.

b) Phase II study will show for the cTNBC cohort that the combination of nab-paclitaxel and pembrolizumab as 1st to 3rd line of therapy for women with metastatic breast cancer will result in a clinically significant BORR, greater than 30% based on RECIST 1.1.

3.2 Secondary Objectives

(1) **Objectives**:

a) In the TNBC cohorts, to evaluate BORR using immune-related RECIST criteria.

b) In the TNBC cohorts, to evaluate progression-free survival (PFS), disease control rate (DCR), and duration of response (DOR) using RECIST 1.1 as well as immune-modified response criteria. Overall survival (OS) will be evaluated.

c) To evaluate efficacy in the subset defined by PD-L1 expression in subjects with TNBC and HR-positive tumors.

3.3 Exploratory Objectives

(1) Objectives:

a) In the HR-positive cohort, to evaluate BORR using RECIST 1.1 as well as immune-related RECIST criteria in women with metastatic breast cancer previously treated with 0-2 lines of chemotherapy in the metastatic setting.

b) To explore predictive markers of response including PD-1 expression on peripheral leukocytes, TILs by histopathological assessment, TCR by immunosequencing, and immune gene profiles in tumors.

c) To assess nab-paclitaxel induced changes in tumoral PD-L1 expression and immune infiltrates in cTNBC and HR-positive tumors.

d) To assess pembrolizumab induced changes in tumoral PD-L1 expression and immune infiltrates in iTNBC.

e) To assess the frequency of mutational and neoantigen load in TNBC (discussed in Section 4.3.6)

f) To explore mutational and neoantigen load as predictive markers of response in TNBC.

g) To explore the relationship between the gut bacterial microbiome and antitumor response with anti-PD-1 therapy by evaluating bacterial composition by 16S ribosomal RNA sequencing.

h) To explore differences in efficacy (BORR, PFS and OS) in TNBC patients between the iTNBC and cTNBC cohorts.

4.0 BACKGROUND & RATIONALE

4.1 MK-3475 (pembrolizumab)

4.1.1. Background: (Drug information provided by Merck)

Refer to the Investigator's Brochure (IB)/approved labeling for detailed background information on MK-3475 (pembrolizumab).

4.1.2. Pharmaceutical and Therapeutic Background—Immune surveillance and PD1-PDL1 axis

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

The PD-1 receptor-ligand interaction is a major pathway hijacked by tumors to suppress immune control. The normal function of PD-1, expressed on the cell surface of activated T-cells under healthy conditions, is to down-modulate unwanted or excessive immune responses, including autoimmune reactions. PD-1 (encoded by the gene Pdcd1) is an Ig superfamily

member related to CD28 and CTLA-4 which has been shown to negatively regulate antigen receptor signaling upon engagement of its ligands (PD-L1 and/or PD-L2). The structure of murine PD-1 has been resolved. PD-1 and family members are type I transmembrane glycoproteins containing an Ig Variable-type (V-type) domain responsible for ligand binding and a cytoplasmic tail which is responsible for the binding of signaling molecules. The cytoplasmic tail of PD-1 contains 2 tyrosine-based signaling motifs, an immunoreceptor tyrosine-based inhibition motif (ITIM) and an immunoreceptor tyrosine-based switch motif (ITSM). Following T-cell stimulation, PD-1 recruits the tyrosine phosphatases SHP-1 and SHP-2 to the ITSM motif within its cytoplasmic tail, leading to the dephosphorylation of effector molecules such as CD3ζ, PKCθ and ZAP70 which are involved in the CD3 T-cell signaling cascade. The mechanism by which PD-1 down modulates T-cell responses is similar to, but distinct from that of CTLA-4 as both molecules regulate an overlapping set of signaling proteins. PD-1 was shown to be expressed on activated lymphocytes including peripheral CD4+ and CD8+ T-cells, B-cells, T regs and Natural Killer cells. Expression has also been shown during thymic development on CD4-CD8- (double negative) T-cells as well as subsets of macrophages and dendritic cells. The ligands for PD-1 (PD-L1 and PD-L2) are constitutively expressed or can be induced in a variety of cell types, including non-hematopoietic tissues as well as in various tumors . Both ligands are type I transmembrane receptors containing both IgV- and IgC-like domains in the extracellular region and contain short cytoplasmic regions with no known signaling motifs. Binding of either PD-1 ligand to PD-1 inhibits T-cell activation triggered through the T-cell receptor. PD-L1 is expressed at low levels on various non-hematopoietic tissues, most notably on vascular endothelium, whereas PD-L2 protein is only detectably expressed on antigen-presenting cells found in lymphoid tissue or chronic inflammatory environments. PD-L2 is thought to control immune T-cell activation in lymphoid organs, whereas PD-L1 serves to dampen unwarranted T-cell function in peripheral tissues. Although healthy organs express little (if any) PD-L1, a variety of cancers were demonstrated to express abundant levels of this T-cell inhibitor. PD-1 has been suggested to regulate tumor-specific T-cell expansion in subjects with melanoma (MEL). This suggests that the PD-1/PD-L1 pathway plays a critical role in tumor immune evasion and should be considered as an attractive target for therapeutic intervention.

Pembrolizumab is a potent and highly selective humanized monoclonal antibody (mAb) of the IgG4/kappa isotype designed to directly block the interaction between PD-1 and its ligands, PD-L1 and PD-L2. Keytruda™ (pembrolizumab) has recently been approved in the United Stated for the treatment of patients with unresectable or metastatic melanoma and disease progression following ipilumumab and, if BRAF V600 mutation positive, a BRAF inhibitor.

4.1.3 Preclinical and Clinical Trial Data

Refer to the Investigator's Brochure for Preclinical and Clinical data.

4.2 Taxane-based chemotherapy in metastatic breast cancer

4.2.1. Background

Refer to the package insert/approved labeling for detailed background information on nab-paclitaxel.

4.2.2. Nab-paclitaxel and Taxanes in Metastatic Breast Cancer

Taxane-based chemotherapy is a first-line standard of care in metastatic breast cancer[1]. Paclitaxel has been well studied, and response rates is about 25 percent for single agent paclitaxel in patients with metastatic breast cancer as first-line treatment[2-4]. Nanoparticle albumin-bound-paclitaxel is an albumin-bound formation of paclitaxel that was developed to avoid toxicities associated with intravenous administration of solvent-based (sb)-paclitaxel (polyethylated castor oil and polysorbate 80). Nab-paclitaxel has been shown to have a 33% higher uptake in the tumor in preclinical models compared to paclitaxel. It also has a shorter infusion time than paclitaxel and can be administered without steroid premedication.

4.3. Rationale for the Trial and Selected Subject Population

4.3.1. Metastatic Breast Cancer

Breast cancer is the most common cancer among women, affecting 1 in 8 women, and is the second leading cause of mortality from cancer[5]. The majority of breast cancer-related deaths are a result of complications from recurrent or metastatic disease. Metastatic breast cancer is uncommon as an initial presentation, occurring in less than 10% of newly diagnosed cases. However, up to 30% of women who are initially diagnosed with early stage breast cancer will develop recurrent or metastatic disease. In the metastatic setting, general treatment goals are to prolong life, control symptoms, and maintain quality of life.

4.3.2 Triple Negative Breast Cancer (TNBC)

Triple negative breast cancer (TNBC) is characterized by lack of estrogen receptor (ER), progesterone receptor (PR), and HER-2 and occurs in approximately 20% of all patients with breast cancer[6]. Of the three subtypes of breast cancer (HR-positive, HER-2 positive, and TNBC), TNBC carries the worse prognosis. TNBC is characterized by a more aggressive biological behavior that includes higher-grade tumors and visceral and distant metastases including brain metastases[7,8]. Patients with metastatic TNBC typically exhibit rapid disease progression and a median overall survival (OS) of less than 1.5 years[9]. Patients with TNBC derive no benefit from endocrine therapy or trastuzumab (monoclonal antibody against HER-2 receptor) and are primarily treated with systemic chemotherapy. Although TNBC may initially respond to chemotherapy (response rate to chemotherapy combinations or single agents is less than 40%), including taxanes, there are no approved targeted therapies and responses to chemotherapy are short lasting[10]. There is therefore an important and unmet need for novel therapeutic approaches to TNBC. In addition, in 2010, the American Society of Clinical Oncology (ASCO) and College of American Pathologists[11] lowered the immunohistochemistry (IHC) threshold for determining ER positivity from the previous value of 10% to 1% of stained cells[12]. This has led to a subclass of low-ER positive (1-9%) breast tumors (formerly classified as TNBC), of which the majority tends to behave like TNBC as compared to HR-positive cancers[13].

4.3.3 Anti-PD-1 Immunotherapeutics in metastatic TNBC (as single agent)

Evading anti-tumor immunity is a hallmark for the development and progression of cancer[14]. Tumors may use various mechanisms to avoid recognition by the host immune system including expression of PD-1. Immunotherapies, especially checkpoint inhibitors, have demonstrated durable responses in several immunogenic advanced solid tumors including melanoma, renal cell carcinoma, and non small cell lung cancer (NSCLC)[15] and have shown preliminary efficacy in TNBC as single agents (anti-PD-1 and anti-PD-L1)[16-18]. A phase Ib study that was presented at San Antonio Breast Cancer Symposium (SABC) in 2014 showed that pembrolizumab (MK-3475) as a single agent (at 10mg/kg IV every 2 weeks) achieved a long-lasting response rate of 18% in a phase Ib trial of women (n=32) with heavily pretreated metastatic TNBC with PD-L1 expression[16]. One patient had a complete response (CR) and four had partial response (PR) to treatment which were durable. An additional seven had stable disease. Another study reported that atezolizumab (MPDL3280A), an investigational monoclonal antibody against PD-L1, had a similar overall response rate of 19% among 21 patients with metastatic TNBC in a phase Ia trial[17,18]. This included two CRs in subjects with high PD-L1 expression (at least 5%) and three with PR; three of the four responses are ongoing. These results suggest that immunotherapy may have a durable therapeutic role in the management of patients with TNBC by targeting the PD-1/PDL-1 axis.

TNBC is the most immunogenic breast cancer subtype with higher PD-L1 expression levels and more tumor-infiltrating lymphocytes (TILs). Ghebeh et al. identified PD-L1 expression in 22 (50%) of 44 tumors evaluated; in 18 tumors (41%), it was identified in TILs and in 15 (34%) it was found in the tumor epithelium[19]. Intramural expression of PD-L1 was also associated with high histological grade and negative hormone receptor status. Studies by our group and others have provided level I evidence that pre-existing TILs in TNBC, indicative of an endogenous adaptive anti-tumor response, significantly and independently predicts and influences disease-free survival (DFS), distant recurrence-free interval (DRFI), and overall survival (OS)[20,21]. However, tumor upregulation of PD-L1 expression is often induced by the release of interferon (IFN)-gamma(γ) from TILs which can inactivate T-cells expressing PD-1 receptor and block the anti-tumor response[22]. This is a mechanism in which tumor cells evade the antitumor immune response of tumor-specific T cells. In breast cancer, PD-1 expression on TILs is highest in basal-like tumors as is constitutive PD-L1 expression in TNBC (linked to the degree of lymphocytic infiltrate)[23-26]. Assay methods for protein and gene expression for either target vary widely as do cut-offs for positivity, therefore making a comparison across studies difficult. Proprietary PD-L1 assays used at Merck have demonstrated 58% positivity for TNBC[16] and 17% positivity for HR-positive tumors (unpublished data). Predictor of response in early clinical trials utilizing PD-1 and PD-L1 inhibitors involved tumoral PD-L1 expression, however responses (albeit lower) were also observed without target expression[17,18].

4.3.4 Rationale for Combination Therapy of anti-PD-1 antibody pembrolizumab with Nab-paclitaxel in this Protocol

While the observed single agent activity of pembrolizumab in TNBC has been encouraging, efficacy may be enhanced by the addition of chemotherapy for several reasons:

1) Cytotoxic chemotherapy can maintain clinical stability in these highly aggressive tumors until responses can be induced by immunotherapy (median time to response in TNBC with pembrolizumab was 18 weeks)[16].

2) Cytotoxic chemotherapy can be used to lower the tumor burden, which is a known predictive factor for success with immunotherapy.

3) Immune effects of chemotherapy can be harnessed. For example, paclitaxel-based neoadjuvant chemotherapy has been shown to increase TILs in breast cancer, and more so in patients who respond to chemotherapy[27]. It enhances the antigenicity of tumor cells by increasing the expression of major histocompatibility complex (MHC) class I molecules and has been shown to sensitize mouse cancer cell lines to the cytotoxic functions of cytotoxic T lymphocytes (CTLs) by increasing the expression of mannose-6-phosphate receptor (M6PR) on the cell surface[28]. M6PR augments the permeability of the plasma membrane to granzyme B, one of the main CTL effector molecules and leads to tumor cell killing by CTLs, independent from perforin.

4) Taxanes may reduce local immunosuppressive mechanisms such as intratumoral myeloid-derived suppressor cells (MDSCs), transforming growth factor-ß (TGF-ß), interleukin (IL)-10, and regulatory T cells (Tregs)[29].

5) PD-L1 expression has been shown to be induced by chemotherapeutics including taxanes[30].

6) Nab-paclitaxel is specifically chosen as a combination partner with pembrolizumab as it is FDA approved for the treatment of metastatic breast cancer and does not require steroid premedication, which could dampen the immune response.

Very high response rates were observed in a recently presented study evaluating the combination of nab-paclitaxel with another checkpoint inhibitor (atezolizumab, anti PD-L1) in metastatic TNBC (Adams S, et al. Presented at: San Antonio Breast Cancer Symposium; December 8-12, 2015; San Antonio, TX. Abstract P2-11-06). In 24 patients evaluable for response, the ORR was 70.8% (confirmed ORR at time of presentation 41.7%), far exceeding responses observed with taxanes or checkpoint inhibitors as single agents in TNBC. Importantly, responses were also observed in patients with PD-L1 negative tumors, highlighting the promising potential for combination of immunotherapy with chemotherapies as well as the need to develop additional predictive biomarkers.

4.3.5 Rationale for Dose Selection/Regimen/Modification

Pembrolizumab (drug information provided by Merck)

An open-label Phase I trial (Protocol 001) is being conducted to evaluate the safety and clinical activity of single agent MK-3475. The dose escalation portion of this trial evaluated three dose levels, 1 mg/kg, 3 mg/kg, and 10 mg/kg, administered every 2 weeks (Q2W) in subjects with advanced solid tumors. All three dose levels were well tolerated and no dose-limiting toxicities were observed. This first in human study of MK-3475 showed evidence of target engagement and objective evidence of tumor size reduction at all dose levels (1 mg/kg, 3 mg/kg and 10 mg/kg Q2W). No MTD has been identified to date. 10.0 mg/kg Q2W, the highest dose tested in PN001, will be the dose and schedule utilized in Cohorts A, B, C and D of this protocol to test for initial tumor activity. Recent data from other clinical studies within the MK-3475 program has shown that a lower dose of MK-3475 and a less frequent schedule may be sufficient for target engagement and clinical activity.

PK data analysis of MK-3475 administered Q2W and Q3W showed slow systemic clearance, limited volume of distribution, and a long half-life (refer to IB). Pharmacodynamic data (IL-2 release assay) suggested that peripheral target engagement is durable (>21 days). This early PK and pharmacodynamic data provides scientific rationale for testing a Q2W and Q3W dosing schedule.

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.

The planned dose of pembrolizumab for this study is 200 mg every 3 weeks (Q3W). Based on the totality of data generated in the Keytruda development program, 200 mg Q3W is the appropriate dose of pembrolizumab for adults across all indications and regardless of tumor type. As outlined below, this dose is justified by:

- Clinical data from 8 randomized studies in melanoma and NSCLC indications demonstrating flat dose- and exposure-efficacy relationships from 2 mg/kg Q3W to 10 mg/kg Q2W, representing an approximate 5- to 7.5-fold exposure range (refer to IB, Section 5.2.2)
- Population PK analysis showing that both fixed dosing and weight-based dosing provides similar control of PK variability with considerable overlap in the distributions of exposures, supporting suitability of 200 mg Q3W
- Pharmacology data showing full target saturation in both systemic circulation (inferred from pharmacokinetic [PK] data) and tumor (inferred from physiologically-based PK [PBPK] analysis) at 200 mg Q3W

Nab-paclitaxel (drug information provided by Celgene)

Nab-paclitaxel (ABRAXANE® for Injectable Suspension [Abraxis BioScience, LLC, a wholly

owned subsidiary of Celgene Corporation, Summit, New Jersey, United States; hereafter referred to as "Celgene"], ABI-007) is a proprietary solvent-free, protein-stabilized formulation of paclitaxel comprised of paclitaxel in a noncrystalline amorphous state and human albumin with a mean particle size of approximately 130 nanometers. *nab*-Paclitaxel has been developed to improve the therapeutic index of paclitaxel, also reducing the toxicities associated with Taxol and the CrEL and ethanol vehicle. This may be achieved in part by taking advantage of endogenous transport pathways to deliver higher doses of paclitaxel to the tumor. Because *nab*-paclitaxel does not contain a solvent vehicle, micellar entrapment observed with Taxol does not occur[31-33]. *nab*-Paclitaxel displays linear pharmacokinetic (PK) characteristics. The novel albumin-bound particle formulation of paclitaxel in *nab*-paclitaxel conferred the ability to achieve a higher maximum tolerated dose (MTD) based on every 3- weeks dosing: 300 mg/m$_2$ for *nab*-paclitaxel (Study DM97-123) versus 175 mg/m$_2$ for Taxol[34]. The use of albumin-bound paclitaxel also enables *nab*-paclitaxel to be given in a shorter, more convenient infusion time of 30 - 40 minutes compared with 3 hours to 24 hours with Taxol. Due to its distinct pharmacological and PK properties and therapeutic index, *nab*-paclitaxel has been approved by regulatory authorities worldwide in over 40 countries/regions as a new product, rather than as a generic formulation of Taxol. *nab*-Paclitaxel may be given without steroid and anti-histamine premedication, which is required for Taxol to prevent solvent- related HSRs[35]. Cremophor EL has been shown to leach plasticizers, specifically di(2-

ethylhexyl)phthalate (DEHP), from polyvinyl chloride (PVC) bags and polyethylene-lined tubing[36-41]. Although no controlled epidemiologic toxicity studies have been conducted in humans exposed to DEHP, severe effects (eg, carcinogenicity, cardiopulmonary toxicity, hepatotoxicity, and nephrotoxicity) have been observed in experimental models. The Taxol prescribing information instructs users to prepare, store, and administer solutions in glass, polypropylene, or polyolefin containers; non-PVC-containing infusion sets (eg, those with polyethylene lining) should be used (Taxol US prescribing information). By comparison, standard tubing and intravenous (IV) bags may be used for the IV administration of *nab*-paclitaxel[31,34].

As of October 2014, *nab*-paclitaxel is approved under the trade name of ABRAXANE® in 51 countries worldwide for the treatment of patients with metastatic breast cancer. ABRAXANE® is also approved in 8 countries worldwide for the first-line treatment of locally advanced or metastatic non-small cell lung cancer (NSCLC), and in 40 countries for the first-line treatment of metastatic adenocarcinoma of the pancreas, and it is approved in Japan for treatment of advanced gastric cancer.

Based upon an important randomized phased III trial,[42] nab-paclitaxel was approved for the treatment of metastatic breast cancer. In this study, patients received either nab-paclitaxel at 260 mg/m^2 (n=229) or paclitaxel at 175 mg/m^2 (n=225) given every three weeks[42]. Enrolled patients had not received a prior taxane for metastatic disease or had not relapsed less than twelve months after receiving a taxane for adjuvant treatment. Patients who received nab-paclitaxel had a higher response rate compared to paclitaxel (33% versus 19%, respectively, p=0.001). The median time to disease progression was longer for the nab-paclitaxel group compared to the control group (23.0 versus 16.9 weeks, respectively, HR=0.75, p=0.006). In terms of adverse events, the incidence of grade 4 neutropenia was lower for nab-paclitaxel compared to paclitaxel (9% versus 22%, p<0.001). No hypersensitivity reactions occurred with nab-paclitaxel despite a shorter infusion time and absence of premedications (which were given with paclitaxel). Grade 3 sensory neuropathy was more common with the nab-paclitaxel group (10% versus 2%, p<0.001), but was easily manageable with dose reduction or treatment interruption.

The dosing of nab-paclitaxel at 260 mg/m^2 every three weeks in the FDA label established from the above study[42] is not generally used in clinical practice. Instead, weekly dosing of nab-paclitaxel is the most commonly utilized schedule due to better tolerability and the suggestion of increased efficacy of weekly dosing compared to every three week dosing. The superiority of the weekly regimen of nab-paclitaxel was shown in a randomized Phase II study of previously untreated patients with metastatic breast cancer (n=302) who received either nab- paclitaxel 300 mg/m^2 q3w, 100 mg/m^2 weekly, or 150 mg/m^2 weekly or docetaxel 100 mg/m^2 q3 weeks[43]. In the four arms of this study, the overall response rates (ORRs) were 37% with q3w nab-paclitaxel, 45% with weekly nab-paclitaxel 100 mg/m2 (3-weeks-on and 1-week- off), 49% with weekly nab-paclitaxel 150 mg/m2 (3-weeks-on and 1 week off), and 35% with q3w docetaxel 100 mg/m^2. Progression free survival (PFS) was 11.0 months, 12.8 months, 12.9 months and 7.5 months, respectively. The difference in PFS and ORR between the 100 and 150 mg/m^2 weekly dose levels of nab-paclitaxel was not statistically significant, however

patients receiving the higher dose experienced a greater incidence of Grade 3 or 4 neutropenia (44% vs. 25%) and Grade 3 sensory neuropathy (14% vs. 8%).

Another phase III trial (CALGB 40502) enrolled patients with HER2-negative metastatic breast cancer and no prior chemotherapy[44]. Patients (n=799) were randomized to one of either three arms: paclitaxel 90 mg/m2, nab-paclitaxel 150 mg/m2, or ixabepilone 16 mg/m2, on a 3-week-on/1-week-off schedule. All agents were given in combination with bevacizumab. Median PFS for paclitaxel was 11 months and 7.4 months for ixabepilone (hazard ratio, 1.59; 95% CI, 1.31 to 1.93; P <0.001). Nab-paclitaxel was not superior to paclitaxel (PFS, 9.3 months; hazard ratio, 1.20; 95% CI, 1.00 to 1.45; P = 0.054). Hematologic and non-hematologic toxicities were increased with nab-paclitaxel, leading to frequent dose reductions.

At this time, 100 mg/m^2 of weekly nab-paclitaxel has been shown to be well tolerated with suggestion of improved efficacy and decreased toxicity compared with the higher weekly dosing at 150 mg/m^2 or the every three week dosing at 260 mg/m^2. The patients enrolled in this study will therefore receive nab-paclitaxel 100 mg/m^2 on Days 1 and 8 of every 21 day cycle (Day 15 will be omitted because each cycle length will be 21 days instead of a 28 day cycle, and pembrolizumab is also given on Day 1 of every 21 day cycle).

Pembrolizumab Immunotherapy run-in: rationale

The rationale for combining anti PD-1 or PD-L1 antibodies with chemotherapy is outlined in section 4.3.4. The current protocol with the chemotherapy-run in was amended to include a cohort of patients who will be treated with a immunotherapy run-in after results from the GeparNuevo trial were presented. GeparNuevo showed an increase of pCR rates when anti-PD-L1 antibodies were administered before initiation of chemotherapy. The GeparNuevo is a randomized phase II study examining the addition of durvalumab, an antibody against PD-L1, to standard neoadjuvant chemotherapy with *nab*-paclitaxel followed by epirubicin and cyclophosphamide (NCT02685059) in patients with early TNCB. In the subgroup of patients starting with durvalumab prior to chemotherapy the pCR rate in the exploratory analysis was significantly higher compared to the subgroup receiving placebo prior to chemotherapy (61.0 % vs. 41.4 %) [45]. This was an unexpected finding as it was thought that the immunogenic effects of chemotherapy would stimulate an initial immune response, but as we recently published from a phase 1 trial nab-paclitaxel does not induce changes in the tumor microenvironment consistent with strong T-cell priming[46]. It is possible that by administering chemotherapy before or with the first cycle of immunotherapy, the immune response could be dampened. By including an initiation boost with pembrolizumab monotherapy prior to chemotherapy, activation of anti-tumor immune response may be increased due to the immune modulating effects of pembrolizumab. This study seeks to preliminarily assess whether a window for an initiation boost with pembrolizumab could improve response rates, biomarkers of response will be assessed in serial biospecimens for this iTNBC cohort as planned in the cTNBC cohort.

4.3.6 Rationale for Identifying Mutated Tumor Antigens

Mutation-derived tumor antigens may play a key role in the anti-tumor immune responses achieved with immune checkpoint blockade.

The precise mechanism of action leading to tumor regression in response to treatment with immune checkpoint blockade is not fully understood. There is evidence that these agents may unmask the endogenous adaptive response to specific tumor antigens[47-50]. However, little is known about the identity of the tumor antigens that function as the targets of T cells activated by immune checkpoint blockade. Such knowledge may be critical, however, to optimizing existing immunotherapies and to generating "personalized" vaccines that are highly tumor-specific. Emerging evidence suggests that **mutation-derived tumor antigens (MTA)** may predominate in this regard[51,52]. Rammensee et al.[53] combined whole-exome and transcriptome sequencing analysis with mass spectrometry, followed by structural modeling to identify immunogenic neo-epitopes that were accessible to T-cell antigen receptors and which were therapeutically effective in animal models of cancer. Gubin et al. used genomics and bioinformatics approaches to identify MTAs as a major class of T-cell rejection antigens following immune checkpoint blockade therapy in tumor-bearing mice and subsequently showed that these mutant epitopes (i.e., "MTA-vaccines") induce tumor rejection comparably to immune checkpoint blockade[54]. Synder et al.[45] and Rizvi et al.[55] applied a similar approach to identify MTAs in a cohort of patients with metastatic melanoma or lung cancer, respectively, treated with CTLA-4 blockade (ipilimumab) or PD-1 blockade (pembrolizumab). These investigators demonstrated that higher mutational load was associated with a higher likelihood of clinical benefit with CTLA-4 blockade and that a MTA signature could be used to predict patient benefit. Importantly, work from The Cancer Genome Atlas Project has shown that TNBC harbors significant mutational loads and recent studies have shown that PD-L1 blockade can lead to clinical activity in patients with metastatic disease[56,57]. The proposed trial will assess, in a similar manner, whether mutational load (nonsynonymous mutation burden), and more specifically, patient specific neoantigen load, associates with clinical benefit. This approach will be used to identify the range and median number of nonsynonymous mutations per sample. Higher somatic nonsynonymous mutation burden (> median burden) will be associated with clinical efficacy of pembrolizumab using the Mann-Whitney test.

Computational biology approaches can be used to identify patient specific mutated antigens that may serve as the basis for personalized MTA-based vaccines.

The *major histocompatibility complex* (MHC) is responsible for the presentation of peptide antigens to the cellular arm of the adaptive immune system. The cell-mediated adaptive immune response to peptide antigens is determined by the physical interaction between the *T cell receptor* (TCR) which is used to scan the surface of the combined peptide-MHC molecule (pMHC)[47]. Recognizing the importance of this process, a great deal of effort has gone into characterizing the peptide-MHC binding event[48]. Rammensee et al. identified distinct patterns in the frequency with which amino acids are represented at specific positions in MHC-I ligands[49,50,51]. This discovery was evidence that the process of binding to the MHC-I molecule is a deterministic event predictable based on amino acid sequence information. Subsequently hundreds of thousands of independent peptide-MHC binding affinity measurements have been performed for both human and murine MHC-I molecules, and the results made publicly

available by repositories such as SYFPETHI and the Immune Epitope Database[52,56,57]. Based on this data investigators have created statistical models which are designed to distinguish between amino acid sequences which will (ligands) and will not (non-ligands) bind to a given MHC-I molecule[58-60]. The work of multiple authors has demonstrated that MTA may be identified through the sequential use of whole exome sequencing (WES) followed by peptide-MHC binding affinity prediction[61-63]. Subsequently the sensitivity of this approach has been formally assessed by Fritsch et al. and Rajasagi et al[64,65]. We have now applied NetMHCcons v1.1 to correctly define 46 of 54 known MTA as MHC-I ligands, for a combined sensitivity across all tested MHC-1 molecules of 0.852. This analysis demonstrates that NetMHCcons v1.1 can be correctly used to identify MHC-1 ligands arising from novel amino acid sequences and is the approach that will be used to determine patient specific neoantigens.

4.3.7 Role of the Gut Microbiome as a Possible Modulator of Antitumor Immunity

The gut microbiome has been shown to play an important role in modulating the immune response. In particular, commensal bacterial microbiota may influence the anti-tumor effects of checkpoint blockade with anti-PD-1/anti-PDL-1 and anti-CTLA-4 antibodies[66]. Sivan et al. studied the gut bacterial microbiome in a murine model of melanoma and found that there were differences in anti-tumor immunity among mice with distinct commensal microbiota[67]. An anti-tumor effect was associated with the presence of *Bifidobacterium* (identified by bacterial 16S ribosomal RNA gene sequencing). When a cocktail of *Bifidobacterium* species was administered orally to mice with tumors, these mice displayed improved anti-tumor control in comparison to those not treated with *Bifidobacterium*. Interestingly, the treated mice had improved tumor control similar to treatment with anti-PD-L1 therapy, and those mice that received the combination had nearly completely resolution of tumor growth. This effect was mediated by the modulation of dendritic cell function leading to improved effector function of $CD8^+$ T cells and accumulation in the tumor microenvironment. Similarly, Vétizou et al. showed that in both mice and patients with melanoma, *Bacteroides* played a role in the efficacy of antibodies against CTLA-4[68]. These results show that gut bacterial microbial composition may potentially influence anti-tumor immunity as well as response to immunotherapy with checkpoint blockade.

4.3.8 Rationale for Endpoints

4.3.8.1 Efficacy Endpoints

The gold standard for evaluating tumor response is the response rate and best overall response rate (BORR) will be determined byRECIST 1.1 criteria (see Appendix, Section 10.3). Immune-related RECIST criteria is also important for the evaluation of immune therapy activity in solid tumors and will also be used as a secondary endpoint (see Appendix, Section 10.4). Progression-free and overall survival will also be assessed in each cohort.

4.3.8.2 Biomarker Research

The most promising correlatives for monitoring effects of PD-1 blockade are changes in the tumor microenvironment, therefore sequential sampling of tumors is proposed (3 time points:

at baseline, after nab-paclitaxel alone in HR+ breast cancer and cTNBC or pembrolizumab alone in iTNBC (Cycle 1), and after nab-paclitaxel and pembrolizumab (Cycle 2). Associations of correlative biomarkers with BORR and other efficacy parameters will be explored within each cohort. Biomarkers in circulating leukocytes will be simultaneously evaluated to correlate with in situ changes and to assess for predictive association. The impact of nab-paclitaxel on tumoral PD-L1 expression will also be explored.

4.3.8.3. Study Calendars

4.3.8.3.1 Treatment Phase

	Baseline	**Cycle 1[a] (21 days)**			**Cycle 2[a] (21 Days)**			**Cycle ≥ 3[a] (21 days)**		**Every 3 cycles [a]**	**End of Treatment [a,r]**	**Follow up[q]**
	Days -30 to -1	Day 1	Day 8[t]	Day 15	Day 1	Day 8[u]	Day 15	Day 1	Day 8[u]			
Signed informed consent form	X											
Medical, surgical, cancer, prior therapy histories	X											
Full physical exam	X	X			X			X			X	
ECOG PS	X	X			X			X			X	
Hematology[b, c]	X	X	X		X	X		X	X		X	
Chemistry[b, d]	X	X	X		X	X		X	X		X	
Coagulation panel (aPTT, PT/INR)	X											
Hepatitis serology[e]	X											
Serum or urine pregnancy test[f]	X	X[f]			X[f]			X[f]				
Urinalysis	X	X			X			X			X	
TSH, total T3, free T4	X							X		X	X	
EKG[g]	X											
Adverse event and concomitant medication assessment	X	X	X		X	X		X	X		X[r, s]	X[s]
Vital signs, height, weight[p]	X	X	X		X	X		X	X		X	
BEFORE 2/2019 for TNBC and BEFORE+AFTER 2/2019 for HR+BC: Nab-paclitaxel[h]		X[i]	X[i]		X[i]	X[i]		X[i]	X[i]			
BEFORE 2/2019 for TNBC and BEFORE+AFTER 2/2019 for HR+BC: Pembrolizumab[j]		--	--		X[i]			X[i]				
AFTER 2/2019 for TNBC only: Pembrolizumab[j]		X[i]	--		X[i]			X[i]				
AFTER 2/2019 FOR TNBC only: Nab-paclitaxel[h]		--	--		X[i]	X[i]		X[i]	X[i]			

Tumor assessment[k]	X	Every 9 weeks from date of allocation (=/- 7 days) for the first 12 months (minimum of 5 scans), then every 12 weeks thereafter until disease progression X									X	
Newly obtained or archival tissue for correlative studies[l]	X			X[m]			X[m]				X[m]	
Blood for correlative studies[n]	X				X			X C3,4&C6 only				
Stool for microbiome analysis[o]	X	X[o]			X			X, C4&C6 only				
Survival status[q]												X

[a] Unless noted otherwise, all procedures can be performed within a +/- 4 day window if there is no safety concern in the opinion of the investigator.

[b.] About 15 cc of blood will be collected at each visit while the patient is receiving study drug. Results for clinically significant laboratory values (ANC, hemoglobin, platelet count, creatinine, bilirubin, AST and ALT) must be reviewed by the investigator or qualified designee and found to be acceptable prior to each dose of trial treatment.

[c.] Hematology consists of hematocrit, hemoglobin, platelet count, white blood cell count (total and differential), red blood cell count, absolute neutrophil count, absolute lymphocyte count.

[d.] Chemistry consists of albumin, alkaline phosphatase, alanine aminotransferase (ALT), aspartate aminotransferase (AST), bicarbonate or CO_2, calcium, chloride, creatinine, glucose, lactate dehydrogenase (LDH), potassium, sodium, total bilirubin, total protein, blood urea nitrogen (BUN). LDH is only required on day 1 of each treatment cycle.

[e.] Hepatitis testing will be required at screening: Hepatitis B (HBsAg, HBsAB and HBcAB) and Hepatitis C (HCV AB, if positive reflex to HBV-RNA [qualitative]).

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

[g.] 5-min resting, single 12-lead EKG

[h.] Nab-paclitaxel will be given for a minimum of 4 cycles, after which the investigator will determine whether to continue the drug based on safety profile and clinical judgment. If the nab-paclitaxel is stopped for any reason, pembrolizumab may be continued.

[i.] Trial treatment may be administered up to 3 days before or after the scheduled Day 1/8 of each cycle due to administrative reasons. Dosing interruptions are permitted in the case of medical / surgical events or logistical reasons not related to study therapy (e.g., elective surgery, unrelated medical events, patient vacation, and/or holidays). Subjects should be placed back on study therapy within 3 weeks of the scheduled interruption, unless otherwise discussed with the Medical monitor or PI. The reason for interruption should be documented in the patient's studyrecord.

[j.] **BEFORE 2/2019 for TNBC and BEFORE+AFTER 2/2019 for all HR+ BC**: Pembrolizumab is not given during cycle 1. The first dose of pembrolizumab will be given on cycle 2, day 1, then on day 1 of every cycle thereafter.

AFTER 2/2019 for TNBC only: Nab-paclitaxel is not given during cycle 1. The first dose of nab-paclitaxel will be given on cycle 2, day 1, then on day 8, and d1/8 of every cycle thereafter. Pembrolizumab will be given for 24 months of uninterrupted treatment or 35 administrations of study medication, whichever is later.

[k.] CT of the chest and abdomen/ pelvis with IV contrast will be used, and per investigator discretion, PET CT can be substituted. If IV contrast is contraindicated, a non-contrast CT chest/abdomen/pelvis is acceptable. Bone scans may be used if clinically indicated. MRI brain or CT brain with IV contrast is required at baseline and as clinically indicated thereafter. The same imaging methods should be used throughout the trial. Baseline imaging can be obtained within 42 days of day 1. A 7-day window will be allowed around post-baseline imaging scans (i.e. should be obtained every 9 weeks from the date of allocation (+/- 7 days)). Imaging studies will be obtained every 12 weeks (+/- 7 days) after 12 months on study treatment (a minimum of 5 scans). Tumor assessment dates are fixed and should not be adjusted for dose interruptions, delays, or modifications.

[l.] Refer to section 6.6.1. Newly obtained tissue biopsies are mandatory at baseline. Newly-obtained is defined as a specimen obtained up to 6 weeks (42 days) prior to initiation of treatment on Day 1. Subjects for whom newly-obtained samples cannot be provided (e.g. inaccessible or subject safety concern) may submit an archived specimen only upon agreement from the PI. Whenever possible, the baseline biopsy should be taken from a lesion amenable to serial biopsies and should not be the sole measurable lesion per RECIST 1.1 criteria. A minimum of 2 cores are required at each time point. Soft tissue and bone lesions are acceptable. Subsequent biopsies should be taken from the same lesion, if feasible.. At time of progression, however, sample collection is optional and patients will be asked if they would be willing to undergo a tumor biopsy for correlative immune studies (if clinically feasible).

[m.] Fresh tissue biopsies to be collected between days 15-21 of cycles 1 and 2. Biopsies may be done prior to treatment on C2D1 and C3D1, if needed.

[n.] About 60 cc of blood will be collected at baseline, C2D1, C3D1, C4D1 and C6D1.

[o.] Patients will be given a stool collection kit with specific instructions at baseline. In the event a stool specimen cannot be obtained between days -30 and treatment start, a pre-dose specimen is acceptable on cycle 1, day 1. Refer to section 6.6.5. +/- 1 week window for stool collection

[p.] Vital signs are defined as blood pressure, pulse, oxygen saturation, respiration rate, and temperature. Height is required at baseline only. Weight is required prior to treatment on day 1 of every cycle.

[q] Following study completion, patients will enter routine follow-up with their primary oncologist, who may be contacted to provide follow-up information on the patient's clinical and disease status until death or withdrawal of consent, whichever occurs first.
[r] The mandatory Safety Follow-Up Visit should be conducted approximately 30 days after the last dose of trial treatment or before the initiation of a new anti-cancer treatment, whichever comes first. All AEs that occur prior to the Safety Follow-Up Visit should be recorded.
[s] After the end of treatment, each subject will be followed for 30 days for adverse event monitoring (serious adverse events will be collected for 90 days after the end of treatment as described in Section 6.11.1). SAEs that occur within 90 days of the end of treatment or before initiation of a new anti-cancer treatment should also be followed and recorded.
[t] AFTER 1/2019 amendment: the cycle 1 day 8 visit will be eliminated (as no treatment), therefore no blood draw, vitals and concomitant medications will be assessed. AE assessment will be performed by telephone by research personnel.
[u] If day 8 treatment is planned to be held per the investigator, the clinic visit, lab assessments and exam/vitals are optional if considered safe and, to diminish burden for the patient (for instance for patients who come to the clinic from out of state). AEs can be collected via phone call by research personnel.

5 METHODOLOGY

5.1 Entry Criteria

5.1.1 Diagnosis/Condition for Entry into the Trial

Subjects with histologically confirmed metastatic breast cancer that is either TNBC or HR-positive (see inclusion and exclusion criteria below).

5.1.2 Subject Inclusion Criteria

In order to be eligible for participation in this trial, the subject must:

1. Have histologically confirmed adenocarcinoma of the breast that is either TNBC or HR positive/HER-2 negative. TNBC is defined as: ER/PR <1% and HER-2 negative disease (IHC 0-1+ or 2+ with HER2/17 ratio on FISH ≤1.8) according to ASCO/CAP guidelines[11,69]. HR positive is defined as: ER/PR >= 1% and HER-2 negative as per ASCO/CAP guidelines. Subjects with tumors expressing ER/PR1-4% are eligible if the investigator is not planning endocrine therapy.

2. Have received 0-2 lines of cytotoxic chemotherapy for metastatic breast cancer. Prior endocrine therapy and/or targeted therapy is allowed.

3. Be willing and able to provide written informed consent/assent for the trial.

4. Be ≥ 18 years of age on day of signing informed consent.

5. Have measurable disease based on RECIST 1.1.

6. Be willing to provide tissue from a newly obtained core or excisional biopsy of a tumor lesion. *Newly-obtained is defined as a specimen obtained up to 6 weeks (42 days) prior to initiation of treatment on Day 1. Subjects for whom newly-obtained samples cannot be provided (e.g. inaccessible or subject safety concern) may submit an archived specimen only upon agreement from the PI or designee.*

7. Have a performance status of 0 or 1 on the ECOG Performance Scale.

8. Be willing to undergo tissue biopsies as mandatory as per protocol for patients with biopsy accessible disease.

9. Must have </= Grade 1 pre-existing peripheral neuropathy (as per CTCAE).

10. Demonstrate adequate organ function as defined in Table 1all screening labs should be performed within 14 days of treatment initiation.

Table 1 Adequate Organ Function Laboratory Values

System	Laboratory Value
Hematological	
Absolute neutrophil count (ANC)	≥1,500 /mcL
Platelets	≥100,000 /mcL (transfusion independent, defined as not receiving platelet transfusions within 7 days prior to laboratory sample)
Hemoglobin	≥9 g/dL or ≥5.6 mmol/L without transfusion or EPO dependency (within 7 days of assessment)
Renal	
Serum creatinine **OR** Measured or calculated[a] creatinine clearance (GFR can also be used in place of creatinine or CrCl)	≤1.5 X upper limit of normal (ULN) **OR** ≥60 mL/min for subject with creatinine levels > 1.5 X institutional ULN
Hepatic	

Serum total bilirubin	≤ 1.5 X ULN **OR**
	Direct bilirubin ≤ ULN for subjects with total bilirubin levels > 1.5 ULN
AST (SGOT) and ALT (SGPT)	≤ 2.5 X ULN **OR** ≤ 5 X ULN for subjects with liver metastases
Albumin	>2.5 mg/dL
Alkaline phosphatase	≤ 2.5 X ULN, unless bone metastasis is present (<5 X ULN) in the absence of liver metastasis.
Coagulation	
International Normalized Ratio (INR) or Prothrombin Time (PT) Activated Partial Thromboplastin Time (aPTT)	≤1.5 X ULN unless subject is receiving anticoagulant therapy as long as PT or PTT is within therapeutic range of intended use of anticoagulants ≤1.5 X ULN unless subject is receiving anticoagulant therapy as long as PT or PTT is within therapeutic range of intended use of anticoagulants
[a]Creatinine clearance should be calculated per institutional standard.	

11. Female subject of childbearing potential should have a negative urine or serum pregnancy within 72 hours prior to receiving the first dose of study medication. This applies even if the subject practices true abstinence* from heterosexual contact. If the urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required.

12. A female subject of childbearing potential is a sexually mature women who (1) has not undergone hysterectomy [the surgical removal of the uterus] or bilateral oophorectomy [the surgical removal of both ovaries] or (2) has not been naturally postmenopausal for at least 24 consecutive months [i.e., has had menses at any time during the preceding 24 consecutive months]. The female subject must: either commit to true abstinence* from heterosexual contact (which must be reviewed on a monthly basis), or agree to use, and be able to comply with, effective contraception without interruption (2 methods of birth control), 28 days prior to starting IP therapy (including dose interruptions), and while on study medication or for a longer period if required by local regulations following the last dose of IP.

13. Male subjects must practice true abstinence* or agree to use a condom during sexual contact with a pregnant female or female of childbearing potential starting with the first dose of study therapy, during dose interruptions, and for up to 6 months following last dose of study therapy, even if he has undergone a successful vasectomy.

** True abstinence is acceptable when this is in line with the preferred and usual lifestyle of the subject. [Periodic abstinence (eg, calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception].*

5.1.3 Subject Exclusion Criteria

The subject must be excluded from participating in the trial if the subject:

1. Is currently participating and receiving study therapy or has participated in a study of an investigational agent and received study therapy or used an investigational device within 4 weeks of the first dose of treatment.

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

3. Has a known history of active TB (Bacillus Tuberculosis)

4. Hypersensitivity to pembrolizumab or any of its excipients.

5. Has had a prior anti-cancer monoclonal antibody (mAb) within 4 weeks prior to study Day 1 or who has not recovered (i.e., ≤ Grade 1 or at baseline) from adverse events due to agents administered more than 4 weeks earlier.

6. Taxane therapy within the past 3 months (90 days) prior to study Day 1.

7. Has had prior chemotherapy, targeted small molecule therapy, or radiation therapy within 2 weeks prior to study Day 1 or who has not recovered (i.e., ≤ Grade 1 or at baseline) from adverse events due to a previously administered agent.

    - Note: Subjects with ≤ Grade 2 neuropathy are an exception to this criterion and may qualify for the study.

    - Note: If subject received major surgery, they must have recovered adequately from the toxicity and/or complications from the intervention prior to starting therapy.

8. Has a known additional malignancy that progressed or required treatment within the last five years. Exceptions include basal cell carcinoma of the skin or squamous cell carcinoma of the skin that has undergone potentially curative therapy or in situ cervical cancer.

9. Has known active central nervous system (CNS) metastases and/or carcinomatous meningitis. Subjects with previously treated brain metastases may participate provided they are stable (without evidence of progression by imaging for at least four weeks prior to the first dose of trial treatment and any neurologic symptoms have returned to baseline), have no evidence of new or enlarging brain metastases, and are not using steroids for at least 7 days prior to trial treatment. This exception does not include carcinomatous meningitis which is excluded regardless of clinical stability.

10. Has active autoimmune disease that has required systemic treatment in the past 2 years (i.e. with use of disease modifying agents, corticosteroids or immunosuppressive drugs). Replacement therapy (eg., thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency, etc.) is not considered a form of systemic treatment.

11. Has known history of or active (non-infectious) pneumonitis/interstitial lung disease requiring treatment with steroids Has an active infection requiring systemic therapy.

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

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

14. Is pregnant or breastfeeding, or expecting to conceive or father children within the projected duration of the trial, starting with the pre-screening or screening visit through 120 days after the last dose of trial treatment.

15. Has received prior therapy with an anti-PD-1, anti-PD-L1, or anti-PD-L2 agent.

16. Has a known history of Human Immunodeficiency Virus (HIV) (HIV 1/2 antibodies, testing not mandatory).

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

18. Has received a live vaccine or live-attenuated vaccine within 30 days of planned start of study therapy.

    Note: Administration of killed vaccines is allowed.

5.2 Trial Treatments

The treatment to be used in this trial is outlined below in Table 2.

Table 2 Trial Treatment

Drug	Dose/Potency	Dose frequency	Route of Administration	Use
Pembrolizumab	200 mg	Q3W	IV infusion	Experimental
Nab-paclitaxel	100 mg/m^2	Days 1 and 8 of 21-day cycle	IV infusion	Standard of care therapy

Pembrolizumab will be administered first, followed by nab-paclitaxel.

BEFORE 2/2019 amendment for TNBC, and BEFORE+AFTER 2/2019 for all HR+BC: In the first cycle pembrolizumab is omitted in all patients in order to conduct tissue analyses after treatment with nab-paclitaxel alone.

AFTER 2/2019 amendment (ONLY FOR TNBC): In the first cycle nab-paclitaxel is omitted in all patients – see rationale in section 4.3.5.

Nab-paclitaxel will be given for a minimum of 4 cycles and afterwards, the investigator will determine whether to continue the drug based on safety profile and clinical judgment. If the nab-paclitaxel is stopped (regardless of reason), pembrolizumab may be continued.

Pembrolizumab will be given for a maximum of 24 months of uninterrupted treatment or 35 administrations of study medication, whichever is later.

Risks associated with Pemrolizumab

Very common side effects seen in >20% of patients treated with pembrolizumab/KEYTRUDA include the following:

- Itching of the skin
- Feeling tired, lack of energy
- Feeling not hungry
- Short of breath
- Cough

Very common side effects seen in ≥10% to 20% of patients treated with pembrolizumab/ KEYTRUDA include the following:

- Joint pain
- Fever
- Swelling of legs &/or feet
- Weakness
- Back pain
- Rash
- Low level of salt in the blood that may cause you to feel tired, confused, headache, muscle cramps or upset stomach
- Stomach pain
- Sick to your stomach
- Loose or watery stools
- Infrequent or hard stools
- Vomiting
- Decrease in blood cells that carry oxygen which may cause you to feel tired orshort of breath
- Loss of skin color

Common serious side effects seen in 1% to 4% of patients treated with pembrolizumab/KEYTRUDA include the following:

- Short of breath
- Feeling tired, lack of energy
- Low level of salt in the blood that may cause you to feel tired, confused, headache, muscle cramps or upset stomach
- Stomach pain
- Decrease in blood cells that carry oxygen that may cause you to feel tired or short of breath
- Inflammation of the lungs so you may feel short of breath and cough. Rarely this might lead to death
- Joint pain
- Weakness
- Back pain
- Inflammation of the bowels/gut that can cause stomach pain with loose or watery stools, or stools that are black, tarry, sticky or have blood or mucus
- Feeling not hungry
- Loose or watery stools
- Sick to your stomach
- Fever
- Vomiting

Immune-mediated serious side effects seen in 1.0% or less of patients treated with pembrolizumab/KEYTRUDA include the following:

- Inflammation of the skin so you may have widespread peeling of the skin, itching, skin redness
- Inflammation of the bowels/gut so you may feel stomach pain with loose or watery stools, or stools that are black, tarry, sticky or have blood or mucus
- Inflammation of the lungs so you may feel short of breath and cough. Rarely this might lead to death
- Inflammation of the liver that may cause a poor appetite, feeling tired, mild fever, muscle or joint aches, upset stomach and vomiting, bleeding and bruising more easily than normal, stomach pain, yellow eyes and skin, and dark urine
- Inflammation of the pituitary gland (a gland in the head), which may cause headaches, upset stomach, changes in behavior, double vision, few to no menstrual cycles, weakness, vomiting and dizziness or fainting. This inflammation of the pituitary gland may cause the adrenal glands (on top of the kidneys) to not make enough hormone causing tiredness, weight loss, muscle weakness, feeling faint, joint, muscle and abdominal aches, nausea, vomiting, diarrhea, fever, salt craving, rapid heart rate, and sometimes darkening of the skin like a suntan.
- Too much thyroid hormone so you may feel anxious, angry, can't sleep, weak, tremble, increased sweating, weight loss, hair loss, tired, have diarrhea

- Too little thyroid hormone so you may feel tired, gain weight, feel cold, voice gets deeper, hair loss, have infrequent or hard bowel movements
- Inflammation of the kidney so you may pass less urine or have cloudy or bloody urine, swelling and low back pain
- Inflammation of the muscles so you may feel weak or pain in the muscles
- Inflammation of the pancreas (a gland in your abdomen that controls sugar levels) so you may have severe upper abdominal pain that may move to the back, sick to your stomach, and vomiting that gets worse when you eat
- Inflammation of the eye so you may have redness of the eye, blurred vision, sensitive to light, have eye pain, see floaters or have headaches
- Dizziness or fainting (low blood pressure), flushing, rash, fever, shortness of breath or upset stomach at the time of receiving your infusion (IV) or just after, or pain at the site of infusion
- Inflammation of the pancreas (diabetes) so you may have too much sugar in your blood, may need to urinate more often, lose weight, feel thirsty, and may 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

5.2.2 Dose Selection/Modification

5.2.2.1 Dose Selection

The rationale for selection of doses to be used in this trial is provided in Section 4.0 – Background and Rationale.

Details on preparation and administration of pembrolizumab and nab-paclitaxel are provided in the Pharmacy Manual.

5.2.2.2 Dose Modification

Pembrolizumab

AEs associated with pembrolizumab exposure, including coadministration with additional compounds, may represent an immunologic aetiology. These immune-related AEs (irAEs) may occur shortly after the first dose or several months after the last dose of pembrolizumab/combination treatment and may affect more than one body system simultaneously. Therefore, early recognition and initiation of treatment is critical to reduce complications. Based on

existing clinical study data, most irAEs were reversible and could be managed with interruptions of pembrolizumab/combination treatment, administration of corticosteroids and/or other supportive care. For suspected irAEs, ensure adequate evaluation to confirm etiology or exclude other causes. Additional procedures or tests such as bronchoscopy, endoscopy, skin biopsy may be included as part of the evaluation. Dose modification and toxicity management guidelines for irAEs associated with pembrolizumab/combination treatment are provided in Table 6.

Adverse events (both non-serious and serious) associated with pembrolizumab exposure, including coadministration with additional compounds, may represent an immunologic etiology. These adverse events may occur shortly after the first dose or several months after the last dose of pembrolizumab/combination treatment and may affect more than one body system simultaneously. Based on existing clinical study data, most irrAEs were reversible and could be managed with interruptions of Pembrolizumab must be withheld for drug-related toxicities and severe or life-threatening AEs as per Table 3 below. See Section 5.6.1 and Events of Clinical Interest Guidance Document for supportive care guidelines, including use of corticosteroids.

Attribution of Toxicity:

When study interventions are administered in combination, attribution of an adverse event to a single component is likely to be difficult. Therefore, while the investigator may attribute a toxicity event [to the combination, to [xxxxx alone] or to pembrolizumab alone], for adverse events listed in [Table 6], both interventions must be held according to the criteria in [Table 6 Dose Modification and Toxicity Management Guidelines for Immune-Related Adverse Events Associated with Pembrolizumab].

Holding Study Interventions:

When study interventions are administered in combination, if the AE is considered immune-related, both interventions should be held according to recommended dose modifications.

Restarting Study Interventions:

Participants may not have any dose modifications (no change in dose or schedule) of pembrolizumab in this study, as described in [Table 6].

- If the toxicity does not resolve or the criteria for resuming treatment are not met, the participant must be discontinued from all study interventions.

- If the toxicities do resolve and conditions are aligned with what is defined in [Table 6], the combination of [XXXX and pembrolizumab] may be restarted at the discretion of the investigator.[In these cases where the toxicity is attributed to [the combination or to XXXX alone], re-initiation of pembrolizumab as a monotherapy may be considered at the principal investigator's discretion .]

Table 3: Dose Modification and Toxicity Management Guidelines for Immune-related AEs Associated with Pembrolizumab

General instructions:

1. Severe and life-threatening irAEs should be treated with IV corticosteroids followed by oral steroids. Other immunosuppressive treatment should begin if the irAEs are not controlled by corticosteroids
2. Study intervention must be permanently discontinued if the irAE does not resolve or the corticosteroid dose is not ≤10 mg/day within 12 weeks of the last study intervention treatment.
3. The corticosteroid taper should begin when the irAE is ≤ Grade 1 and continue at least 4 weeks.
4. If study intervention has been withheld, study intervention may resume after the irAE decreased to ≤ Grade 1 after corticosteroid taper.

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 •
	Recurrent Grade 2, Grade 3 or 4	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 Grade 3 or Grade 4	Permanently discontinue		

AST / ALT elevation or Increased bilirubin	Grade 2 [a]	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 [b] or 4 [c]	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[d]		
Hyperthyroidism	Grade 2	Continue	• Treat with nonselective beta-blockers (eg, propranolol) or thionamides as appropriate	• Monitor for signs and symptoms of thyroid disorders.
	Grade 3 or 4	Withhold or permanently discontinue[d]		
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 increase 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
Myocarditis	Grade 1 or 2	Withhold	• Based on severity of AE administer corticosteroids	• Ensure adequate evaluation to confirm etiology and/or exclude other causes
Exfoliative Dermatologic Conditions	Suspected SJS, TEN, or DRESS	Withhold	• • Based on severity of AE administer corticosteroids	• • Ensure adequate evaluation to confirm etiology or exclude other causes
	Confirmed SJS, TEN, or DRESS	Permanently discontinue		
All other immune-related AEs	Intolerable/ persistent Grade 2	Withhold	• Based on type and severity of AE administer corticosteroids	• Ensure adequate evaluation to confirm etiology and/or exclude other causes
	Grade 3	Withhold or discontinue based on the type of event. Events that require discontinuation include and not limited to: Gullain-Barre Syndrome, encephalitis		

	Grade 4 or recurrent Grade 3	Permanently discontinue		

AE(s)=adverse event(s); ALT= alanine aminotransferase; AST=aspartate aminotransferase; CTCAE=Common Terminology Criteria for Adverse Events; DRESS=Drug Rash with Eosinophilia and Systemic Symptom; GI=gastrointestinal; IO=immuno-oncology; ir=immune related; IV=intravenous; SJS=Stevens-Johnson Syndrome; T1DM=type 1 diabetes mellitus; TEN=Toxic Epidermal Necrolysis; ULN=upper limit of normal.

Note: Non-irAE will be managed as appropriate, following clinical practice recommendations.

[a] AST/ALT: >3.0 to5.0 x ULN if baseline normal; >3.0 to 5.0 x baseline, if baseline abnormal; bilirubin:>1.5 to 3.0 x ULN if baseline normal; >1.5 to 3.0 x baseline if baseline abnormal

[b] AST/ALT: >5.0 to 20.0 x ULN, if baseline normal; >5.0 to 20.0 x baseline, if baseline abnormal; bilirubin:>3.0 to 10.0 x ULN if baseline normal; >3.0 to 10.0 x baseline if baseline abnormal

[c] AST/ALT: >20.0 x ULN, if baseline normal; >20.0 x baseline, if baseline abnormal; bilirubin: >10.0 x ULN if baseline normal; >10.0 x baseline if baseline abnormal

[d] The decision to withhold or permanently discontinue pembrolizumab is at the discretion of the investigator or treating physician. If control achieved or ≤ Grade 2, pembrolizumab may be resumed.

[e] Events that require discontinuation include, but are not limited to: encephalitis and other clinically important irAEs (eg, vasculitis and sclerosing cholangitis).

Dosing interruptions are permitted in the case of medical / surgical events or logistical reasons not related to study therapy (e.g., elective surgery, unrelated medical events, patient vacation, and/or holidays). Subjects should be placed back on study therapy within 3 weeks of the scheduled interruption, unless otherwise discussed with the Medical Monitor or PI. The reason for interruption should be documented in the patient's study record.

Nab-paclitaxel

As of Oct 6, 2014, approximately 11,867 subjects have been treated with nab-paclitaxel in clinical studies, with 3,905 in the Celgene development program worldwide and an estimated 7,962 in non-Celgene-sponsored studies globally. It is estimated that cumulative exposure to nab-paclitaxel during marketing experience is approximately 296,427 patients. Therefore, overall estimated cumulative exposure to nab-paclitaxel during clinical trials and commercial experience is approximately 308,294 patients. Clinically significant adverse drug reactions identified during clinical trials or post-marketing surveillance, considered by Celgene to be at least possibly associated with nab-paclitaxel, are provided below.

Very common (≥ 10%):
• anemia, red blood cell count decreased
• febrile neutropenia, leukopenia, lymphopenia, neutropenia, thrombocytopenia
• constipation
• diarrhea
• nausea
• vomiting
• abdominal pain, abdominal pain upper
• stomatitis, mucosal inflammation
• SMQ peripheral neuropathy

• dizziness
• headache
• asthenia, fatigue
• arthralgia, back pain, bone pain, chest pain, musculoskeletal pain, myalgia, pain in extremity
• edema, edema peripheral
• pyrexia
• chills
• decreased appetite
• dysgeusia
• weight decreased
• insomnia
• depression
• cough
• dyspnea
• alopecia
• rash, generalized rash, maculopapular rash
• pruritus
• nail disorder, nail discoloration, onycholysis
• alanine aminotransferase increased, aspartate aminotransferase increased
• dehydration
• epistaxis
• hypokalemia

Common (≥ 1% to < 10%):
• bone marrow depression (failure), pancytopenia
• candidiasis, cholangiitis,folliculitis, lower respiratory infection, nail infection, oral candidiasis, pneumonia, upper respiratory tract infection, urinary tract infection
• neutropenic sepsis, sepsis
• bronchitis
• pneumonitis
• colitis, intestinal obstruction, small intestinal obstruction
• dysphagia
• dyspepsia
• hyperbilirubinaemia, blood alkaline phosphatase increased, blood bilirubin increased, blood creatinine increased
• acute renal failure
• hematuria
• ataxia
• muscle weakness
• anxiety
• nasal congestion
• oropharyngeal pain

• dry mouth, dry throat, nasal dryness
• hemoptysis
• pulmonary embolism, deep vein thrombosis
• pleural effusion
• flushing, erythema
• dry skin
• palmar-plantar erythrodysaethesia syndrome
• hypertension
• hypotension
• tachycardia, cardiac failure congestive, palpitations
• increased lacrimation
• visual disturbance, visual Impairment vision blurred
• infusion site extravasation, infusion site inflammation, infusion site rash, infusion site reaction, injection site reactions, injection site infection, extravasation
• lymphedema

Uncommon (0.1% < 1.0%):
• left ventricular dysfunction
• arrhythmia, sinus bradycardia, atrioventricular block, supraventricular tachycardia
• cardiac arrest
• drug hypersensitivity, hypersensitivity, dermatitis allergic
• thrombotic thrombocytopenic purpura, hemolytic uremic syndrome
• cystoid macular edema, maculopathy
• conjunctivitis
• keratitis
• fluid retention
• malaise
• lethargy
• skin exfoliation
• urticaria
• erythema multiforme
• facial palsy, VIIth nerve paralysis

Elderly
In subjects ≥ 65 years old with metastatic breast cancer who received *nab*-paclitaxel monotherapy, a higher incidence of epistaxis, diarrhea, dehydration, fatigue and peripheral edema has been reported.

Table 4: Dose Modification for Drug-Related Adverse Events with Nab-paclitaxel

Hematologic Toxicity

The absolute neutrophil count (ANC) must be ≥1500/μL, and platelet count must be

≥100,000/µL on Day 1 of each cycle. Nab-paclitaxel should not be administered on Day 8 of the cycle until counts recover to ANC ≥500 cells/µL and platelets ≥50,000 cells/µL. If nab-paclitaxel cannot be administered on Day 8 of the cycle, the next dose of nab-paclitaxel should be administered on Day 1 of the following cycle when ANC and platelets counts have recovered to the acceptable levels. Nab-paclitaxel dose reductions for hematologic toxicity are as per below in the table.

Hematologic toxicity	**Occurrence**	**Nab-paclitaxel weekly dose (mg/m^2)**
• Neutropenic fever (ANC nadir <500/µL with fever >38 C), **or** • Delay of next cycle by greater than 7 days for ANC nadir <1500/µL (grade 1 to 4 neutropenia), **or** • ANC nadir <500/µL (grade 4 neutropenia) for greater than 7 days	First	75
	Second	50
	Third	Discontinue treatment
Platelet count nadir <50,000 µL	First	75
	Second	Discontinue treatment

Neurologic Toxicity

Nab-paclitaxel will be withheld for Grade 3 or 4 peripheral neuropathy and may be resumed at reduced doses when peripheral neuropathy recovers to Grade 1 or resolves.

Neurologic toxicity	**Occurrence**	**Nab-paclitaxel weekly dose modification**
Grade 3 or 4 peripheral neuropathy	First	Withhold treatment until improves to Grade =< 1, then resume at 75 mg/m^2
	Second	Withhold treatment until improves to Grade =< 1, then resume at 50 mg/m^2

	Third	Discontinue treatment

Hepatic Toxicity

Nab-paclitaxel should be withheld for Grade 3 or 4 hepatic toxicity.

Hepatic toxicity	**Nab-paclitaxel weekly dose modification**
AST level <10x ULN **or** Bilirubin level >ULN to 1.25x ULN	No dose modification, give 100 mg/m^2
AST level <10x ULN **and** Bilirubin level 1.26x to 2x ULN	Interrupt treatment until AST level <10x ULN and bilirubin level =< 1.25x ULN, then reduce to 75 mg/m^2. If toxicity does not resolve to above criteria by 3 weeks, discontinue treatment.
AST level <10x ULN **or** Bilirubin level 2.01x to 5x ULN	Interrupt treatment until AST level <10x ULN and bilirubin level =< 1.25x ULN, then reduce to 50 mg/m^2. If toxicity does not resolve to above criteria by 3 weeks, discontinue treatment.
AST level >10x ULN **or** Bilirubin level >5x ULN	Discontinue treatment

5.2.3 Timing of Dose Administration

Trial treatment should be administered on Day 1 of each cycle after all procedures/assessments have been completed as detailed in the Study Calendar (Section 4.3.8.3). Trial treatment may be administered up to 3 days before or after the scheduled Day 1 of each cycle due to administrative reasons. In the first cycle pembrolizumab is omitted in all patients in order to conduct tissue analyses after treatment with nab-paclitaxel alone. After 2/2019 amendment, all

TNBC patients will receive an immunotherapy run-in first, in the first cycle nab-paclitaxel is omitted and oly pembolizumab is fiven.

All trial treatments will be administered on an outpatient basis.

First, pembrolizumab 200 mg will be administered as a 30 minute IV infusion D1 every 3 weeks. Sites should make every effort to target infusion timing to be as close to 30 minutes as possible. However, given the variability of infusion pumps from site to site, a window of -5 minutes and +10 minutes is permitted (i.e., infusion time is 30 minutes: -5 min/+10 min).

Second, nab-paclitaxel 100 mg/m^2 will be injected into a vein [intravenous (I.V.) infusion] over 30 minutes D1,8 every 3 weeks. Sites should make every effort to target infusion timing to be as close to 30 minutes as possible. However, given the variability of infusion pumps from site to site, a window of -5 minutes and +10 minutes is permitted. It should not be infused at a faster rate (completing infusion in less than 25 minutes, see overdose in section 6.12.1). The use of an in-line filter is not recommended. Following administration, the intravenous line should be flushed with sodium chloride 9 mg/ml (0.9%) solution for injection to ensure complete administration of the complete dose, according to local practice.

The Pharmacy Manual contains specific instructions for the preparation of the pembrolizumab and nab-paclitaxel infusion fluid and administration of infusion solution.

5.2.4 Trial Blinding/Masking

This is an open-label trial; therefore, the Sponsor, investigator and subject will know the treatment administered.

5.3 Randomization or Treatment Allocation

N/A

5.4 Stratification

Please see cohorts as described above in Section 2.0.

5.5 Concomitant Medications/Vaccinations (allowed & prohibited)

Medications or vaccinations specifically prohibited in the exclusion criteria are not allowed during the ongoing trial. If there is a clinical indication for one of these or other medications or vaccinations specifically prohibited during the trial, discontinuation from trial therapy or vaccination may be required. The investigator should discuss any questions regarding this with Dr. Adams and the medical monitor. If necessary, Dr. Adams will discuss the situation with Merck, and/or Celgene Clinical Teams. The final decision on any supportive therapy or vaccination rests with the investigator and/or the subject's primary physician.

5.5.1 Acceptable Concomitant Medications

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

All concomitant medications received within 28 days before the first dose of trial treatment and 30 days after the last dose of trial treatment should be recorded. Concomitant medications administered after 30 days after the last dose of trial treatment should be recorded for SAEs and Events of Clinical Interest (ECIs).

5.5.2 Prohibited Concomitant Medications

Subjects are prohibited from receiving the following therapies during the Screening and Treatment Phase 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 or live-attenuated vaccines within 30 days prior to the first dose of trial treatment and while participating in the trial. Administration of killed vaccines is 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 Medical Monitor or PI.

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

The Exclusion Criteria describes other medications which are prohibited in this trial.

There are no prohibited therapies during the Post-Treatment Follow-up Phase.

5.6 Rescue Medications & Supportive Care

5.6.1 Supportive Care Guidelines

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

Note: if after the evaluation the event is determined not to be related, the investigator is instructed to follow the ECI reporting guidance but does not need to follow the treatment guidance (as outlined in the ECI guidance document). Refer to Section 5.2.1 for dose modification.

It may be necessary to perform conditional procedures such as bronchoscopy, endoscopy, or skin photography as part of evaluation of the event. Suggested conditional procedures, as appropriate, can be found in the ECI guidance document.

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

Table 5: 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	**Stop Infusion and monitor symptoms.** Additional appropriate medical therapy may	Subject may be premedicated 1.5h (± 30 minutes) prior to infusion of

NCI CTCAE Grade	Treatment	Premedication at subsequent dosing
responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDS, narcotics, IV fluids); prophylactic medications indicated for < =24 hrs	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.**	pembrolizumab (MK-3475) with: Diphenhydramine 50 mg po (or equivalent dose of antihistamine). Acetaminophen 500-1000 mg po (or equivalent dose of antipyretic).
<u>Grades 3 or 4</u> Grade 3: Prolonged (i.e., not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae (e.g., renal impairment, pulmonary infiltrates) Grade 4: Life-threatening; pressor or ventilatory support indicated	**Stop Infusion.** Additional appropriate medical therapy may include but is not limited to: IV fluids Antihistamines NSAIDS Acetaminophen Narcotics Oxygen Pressors Corticosteroids Epinephrine Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator. Hospitalization may be indicated. **Subject is permanently discontinued from further trial treatment administration.**	No subsequent dosing
Appropriate resuscitation equipment should be available in the room and a physician readily available during the period of drug administration.		

5.7 Diet/Activity/Other Considerations

5.7.1 Diet

Subjects should maintain a normal diet unless modifications are required to manage an AE such as diarrhea, nausea or vomiting.

5.7.2 Contraception

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

breast-feeding women may be enrolled if they are willing to use 2 methods of birth control or are considered highly unlikely to conceive. Highly unlikely to conceive is defined as 1) surgically sterilized, or 2) postmenopausal (a woman who is ≥45 years of age and has not had menses for greater than 1 year will be considered postmenopausal), or 3) not heterosexually active for the duration of the study. The two birth control methods can be either two barrier methods or a barrier method plus a hormonal method to prevent pregnancy. Subjects should start using birth control from study Visit 1 throughout the study period up to 120 days after the last dose of study therapy.

The following are considered adequate barrier methods of contraception: diaphragm, condom (by the partner), copper intrauterine device, sponge, or spermicide. Appropriate hormonal contraceptives will include any registered and marketed contraceptive agent that contains an estrogen and/or a progestational agent (including oral, subcutaneous, intrauterine, or intramuscular agents).

Subjects should be informed that taking the study medication may involve unknown risks to the fetus (unborn baby) if pregnancy were to occur during the study. In order to participate in the study they must adhere to the contraception requirement (described above) for the duration of the study and during the follow-up period defined in section 6.12.2-Reporting of Pregnancy and Lactation to the medical monitor, Merck, and Celgene. If there is any question that a subject will not reliably comply with the requirements for contraception, that subject should not be entered into the study.

5.7.3 Use in Pregnancy

Pembrolizumab

If a subject inadvertently becomes pregnant while on treatment with pembrolizumab or within at least 28 days of the subject's last dose of the drug, the subject will immediately be removed from the study. The site will contact the subject at least monthly and document the subject's status until the pregnancy has been completed or terminated. The outcome of the pregnancy will be reported to Dr. Adams, the NYU research coordinator, NYU regulatory specialist, NYUPCCsafetyreports@nyumc.org and Merck without delay and within 24 hours to Dr. Adams, the NYU research coordinator, NYU regulatory specialist, the medical monitor, Dr. Zujun Li, NYUPCCsafetyreports@nyumc.org and within 2 working days to Merck if the outcome is a serious adverse experience (e.g., death, abortion, congenital anomaly, or other disabling or life- threatening complication to the mother or newborn).

The study investigator will make every effort to obtain permission to follow the outcome of the pregnancy and report the condition of the fetus or newborn to the medical monitor and Merck. If a male subject impregnates his female partner the study personnel at the site must be informed immediately and the pregnancy reported to Dr. Adams, the NYU research

coordinator, NYU regulatory specialist, the medical monitor, Dr. Zujun Li, NYUPCCsafetyreports@nyumc.org and to Merck and followed as described above and in Section 6.12.2.

Nab-paclitaxel

Pregnancies and suspected pregnancies (including a positive pregnancy test regardless of age or disease state) of a female subject occurring while the subject is on IP, or within at least 28 days of the subject's last dose of IP), are considered immediately reportable events. IP is to be discontinued immediately. The pregnancy, suspected pregnancy, or positive pregnancy test must be reported to Dr. Adams, the NYU research coordinator, NYU regulatory specialist, NYUPCCsafetyreports@nyumc.org and Celgene Drug Safety immediately by facsimile, or other appropriate method, using the Pregnancy Initial Report Form, or approved equivalent form. The female subject may be referred to an obstetrician-gynecologist (not necessarily one with reproductive toxicity experience) or another appropriate healthcare professional for further evaluation.

The Investigator will follow the female subject until completion of the pregnancy, and must notify Dr. Adams, the NYU research coordinator, NYU regulatory specialist, the medical monitor, Dr. Zujun Li, NYUPCCsafetyreports@nyumc.org and Celgene Drug Safety immediately about the outcome of the pregnancy (either normal or abnormal outcome) using the Pregnancy Follow-up Report Form, or approved equivalent form.

IF THE OUTCOME OF THE PREGNANCY WAS ABNORMAL (E.G., SPONTANEOUS OR THERAPEUTIC ABORTION), THE INVESTIGATOR SHOULD REPORT THE ABNORMAL OUTCOME AS AN AE. IF THE ABNORMAL OUTCOME MEETS ANY OF THE SERIOUS CRITERIA, IT MUST BE REPORTED AS AN SAE TO CELGENE DRUG SAFETY IMMEDIATELY BY FACSIMILE, OR OTHERAPPROPRIATE METHOD, WITHIN 24 HOURS OF THE INVESTIGATOR'S KNOWLEDGE OF THE EVENT USING THE SAE REPORT FORM, OR APPROVED EQUIVALENT FORM.

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

Male Subjects

If a female partner of a male subject taking investigational product becomes pregnant, the male subject taking IP should notify the Investigator, and the pregnant female partner should be advised to call their healthcare provider immediately. Male patients treated with nab-paclitaxel are advised not to father a child during and up to 6 months after treatment.

5.7.4 Use in Nursing Women

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

5.8 Subject Withdrawal/Discontinuation Criteria

Subjects may withdraw consent at any time for any reason or be dropped from the trial at the discretion of the investigator should any untoward effect occur. In addition, a subject may be withdrawn by the investigator or the Sponsor if enrollment into the trial is inappropriate, the trial plan is violated, or for administrative and/or other safety reasons. Specific details regarding discontinuation or withdrawal are provided in Section 6.8.1 – Other Procedures.

A subject must be discontinued from the trial for any of the following reasons:

- The subject or legal representative (such as a parent or legal guardian) withdraws consent.
- Confirmed radiographic disease progression

  Note: A subject may be granted an exception to continue on treatment with confirmed radiographic progression if clinically stable or clinically improved, and continuation is in the best interest for the patient, per investigator.
- Unacceptable adverse experiences as described in Section 5.2.1.2
- Intercurrent illness that prevents further administration of treatment
- Investigator's decision to withdraw the subject
- The subject has a confirmed positive serum pregnancy test
- Noncompliance with trial treatment or procedure requirements
- The subject is lost to follow-up
- Completed 24 months of uninterrupted treatment with pembrolizumab or 35 administrations of study medication, whichever is later.

  Note: 24 months of study medication is calculated from the date of first dose.
- Administrative reasons

After the end of treatment, each subject will be followed for 30 days for adverse event monitoring (serious adverse events will be collected for 90 days after the end of treatment as described in Section 6.11.1). Subjects who discontinue for reasons other than progressive disease will have post-treatment follow-up for disease status until disease progression, initiating a non-study cancer treatment, withdrawing consent or becoming lost to follow-up. After documented disease progression each subject will be followed by telephone for overall survival until death, withdrawal of consent, or the end of the study, whichever occurs first.

5.9 Subject Replacement Strategy

N/A

5.10 Clinical Criteria for Early Trial Termination

Early trial termination will be the result of the criteria specified below:

1. Quality or quantity of data recording is inaccurate or incomplete
2. Poor adherence to protocol and regulatory requirements
3. Incidence or severity of adverse drug reaction in this or other studies indicates a potential health hazard to subjects
4. Plans to modify or discontinue the development of the study drug

In the event of Merck decision to no longer supply study drug, ample notification will be provided so that appropriate adjustments to subject treatment can be made.

6.0 TRIAL PROCEDURES

6.1 Trial Procedures

The Study Calendar in section 4.3.8.3 summarizes the trial procedures to be performed at each visit. Individual trial procedures are described in detail below. It may be necessary to perform these procedures at unscheduled time points if deemed clinically necessary by the investigator.

Furthermore, additional evaluations/testing may be deemed necessary by PI, Celgene and/or Merck for reasons related to subject safety. In some cases, such evaluation/testing may be potentially sensitive in nature (e.g., HIV, Hepatitis C, etc.), and thus local regulations may require that additional informed consent be obtained from the subject. In these cases, such evaluations/testing will be performed in accordance with those regulations.

6.2 Administrative Procedures

6.2.1 Methods of Subject Identification and Recruitment

The patients who are eligible for this research study come directly from the study investigators' clinical patient population. Thus, the investigators are very familiar with their patients' disease status and potential eligibility given the protocol's inclusion and exclusion criteria. The investigator will approach eligible potential subjects and explain the study in a private room, including the reasons why subjects will be eligible, risks, benefits, and the regimes to be evaluated. Consent will be obtained in a private room by the PI, Co-I, or research coordinator/research nurse at the time of the subject's visit prior to any study assessments/procedures. The subjects will be given a chance to ask questions to the person consenting him/her and will be able to take the consent home to discuss it with family/friends prior to signing. If the subject agrees s/he will sign the consent form either at the first contact (if the investigator/delegate is convinced that the subject understands) or at the time of a return visit after having had time to study the consent in more depth. Study procedures will not begin until after the consent form has been properly obtained. The subject is entitled to decide not to participate in the trial, without affecting their right to other medical care, and may discontinue participation in the trial at any time without penalty or loss of benefits to which they are entitled.

6.2.2 Process of Informed Consent

The informed consent will adhere to IRB/ERC requirements, applicable laws and regulations.

Consent will be obtained only by an IRB approved participating investigator who has completed requisite training for human subject research and has been instructed by the Principal Investigator about the research study and consent process. Investigators will review the informed consent form with patients and address any questions or concerns prior to obtaining written informed consent for participation and HIPAA authorization.

Patients who are evaluated and/or treated by physicians in the oncology program will be given a consent form (attached) describing participation in the study. Patients will be given adequate time to read the consent form. After patients have been evaluated by their physician, they will be given time to ask questions about the study in private exam rooms. Questions will be answered by a participating physician, nurse practitioner, or research nurse all of whom have completed requisite training for human subject research. Investigators will review the informed consent

form with patients and address any questions or concerns prior to obtaining written informed consent for participation. Investigators will stress that participation in the study is completely voluntary and will not affect the care patients receive or result in any loss of benefits to which patients are otherwise entitled.

For non-English speaking patients, institutional translation services will be utilized. For these patients the consent letter and all other information will be administered orally and a witness, not related to the research project, will be present while the oral presentation is given. A short form will be utilized for the subject to sign in his/her name and the translator and/or witness must sign the short form. The translator will also sign the main consent form.

For patients who cannot read a witness, not related to the research study will be present. The consent will be read to the patient. The patient will also be allowed to ask any questions s/he may have. The investigator will ask the patient questions to ensure s/he understands the study. If the investigator determines the subject understands the study, the patient will mark an X where his/her name would go and the witness will sign the consent form.

Any subsequent revised written informed consent form and any written information provided to the subject will receive the IRB's approval in advance of use. The subject will be informed in a timely manner if new information becomes available that may be relevant to the subject's willingness to continue participation in the trial. The communication of this information will be provided and documented via a revised consent form or addendum to the original consent form that captures the subject's dated signature.

6.2.3 Inclusion/Exclusion Criteria

All inclusion and exclusion criteria will be reviewed by the investigator or qualified designee to ensure that the subject qualifies for the trial.

6.2.4 Medical History

A medical history will be obtained by the investigator or qualified designee. Medical history will include all active conditions, and any condition diagnosed within the prior 10 years that are considered to be clinically significant by the Investigator. Details regarding the disease for which the subject has enrolled in this study will be recorded separately and not listed as medical history.

6.2.5 Inclusion/Exclusion Criteria

All inclusion and exclusion criteria will be reviewed by the investigator or qualified designee to ensure that the subject qualifies for the trial.

6.2.6 Medical History

A medical history will be obtained by the investigator or qualified designee. Medical history will include all active conditions, and any condition diagnosed within the prior 10 years that are considered to be clinically significant by the Investigator. Details regarding the disease for which the subject has enrolled in this study will be recorded separately and not listed as medical history.

6.3 Prior and Concomitant Medications Review

6.3.1 Prior Medications

The investigator or qualified designee will review prior medication use, including any protocol-specified washout requirement, and record prior medication taken by the subject within 28 days before starting the trial. Treatment for the disease for which the subject has enrolled in this study will be recorded separately and not listed as a prior medication.

6.3.2 Concomitant Medications

The investigator or qualified designee will record medication, if any, taken by the subject during the trial. All medications related to reportable SAEs and ECIs should be recorded as defined in Section 6.13.

6.4 Disease Details and Treatments

6.4.1 Disease Details

The investigator or qualified designee will obtain prior and current details regarding disease status.

6.4.2 Prior Treatment Details

The investigator or qualified designee will review all prior cancer treatments including systemic treatments, radiation and surgeries.

6.4.3 Subsequent Anti-Cancer Therapy Status

The investigator or qualified designee will review all new anti-neoplastic therapy initiated after the last dose of trial treatment. If a subject initiates a new anti-

cancer therapy within 30 days after the last dose of trial treatment, the 30 day Safety Follow-up visit must occur before the first dose of the new therapy. Once new anti-cancer therapy has been initiated the subject will move into survival follow-up.

6.4.4 Registration Procedures

Each patient must sign and date an informed consent form before undergoing any study specific procedure unless a procedure is being performed as part of the patient's standard of care. Once a patient has signed consent, the site must notify the designated NYU Research Coordinator and forward a copy of the signed consent to NYU Cancer Clinical Trials Office within 24 hours.

Enrollment in the study requires that all inclusion and exclusion criteria have been met. Enrollment occurs upon confirmation of registration from the NYU CI Clinical Trials Office. The following materials must be submitted to the Research Coordinator for registration:

1. Complete signed and dated informed consent form
2. Complete signed and dated informed consent checklist
3. Complete signed and dated eligibility checklist
4. All supporting documentation verifying each criterion has been met

Registration will occur within 24 hours of research coordinators receipt of all of the above documents. Once eligibility is verified, a unique patient study number will be issued. This number is unique to the participant and must be written on all data and correspondence for the participant. The NYU Clinical Trials Office research coordinator will return a signed eligibility confirmation worksheet with the subjects unique study number to the site study team upon registration. The patient will not be identified by name. This is the point, at which, the patient is considered on study. Subjects must not start any protocol procedures prior to registration.

6.4.5 Benefits to Subjects

It is possible that some study subjects who receive the study therapy may experience an improvement in their cancer. However, it is possible that subjects may not get any benefit from being in this research study. Other patients with breast cancer may benefit in the future from what we learn in this study.

6.4.6 Costs to Subjects and Payment for Participation

Subjects will not be paid for their participation in this research study. However, up to $50 dollars can be reimbursed for expenses related for each of the study treatment visits (parking, transportation, meals)

6.5 Clinical Procedures/Assessments

6.5.1 Adverse Event (AE) Monitoring

The investigator or qualified designee will assess each subject to evaluate for potential new or worsening AEs as specified in the Trial Flow Chart and more frequently if clinically indicated. Adverse experiences will be graded and recorded throughout the study and during the follow-up period according to NCI CTCAE Version 4.0 (see Section 10.2). Toxicities will be characterized in terms regarding seriousness, causality, toxicity grading, and action taken with regard to trial treatment.

For subjects receiving treatment with pembrolizumab all AEs of unknown etiology associated with pembrolizumab exposure should be evaluated to determine if it is possibly an event of clinical interest (ECI) of a potentially immunologic etiology (termed immune-related adverse events, or irAEs); see the separate ECI guidance document in Appendix 4 regarding the identification, evaluation and management of potential irAEs.

Please refer to section 6.12 for detailed information regarding the assessment and recording of AEs.

6.5.2 Physical Exam

The investigator or qualified designee will perform a complete physical exam during the screening period. Clinically significant abnormal findings should be recorded as medical history. A full physical exam should be performed during screening.

6.5.3

Not applicable.

6.5.4 Vital Signs

The investigator or qualified designee will take vital signs at screening and prior to the administration of each dose of trial treatment . Vital signs should include temperature, pulse, respiratory rate, oxygen saturation, weight and blood pressure. Height will be measured at screening only.

6.5.5 Eastern Cooperative Oncology Group (ECOG) Performance Scale

The investigator or qualified designee will assess ECOG status (see Section 10.1) at screening and prior to the administration of each dose of trial treatment.

6.5.6 Tumor Imaging and Assessment of Disease

CT of the chest and abdomen/ pelvis with IV contrast will be used, and per investigator discretion, PET/CT can be substituted. If IV contrast is contraindicated, a non-contrast CT of chest/abdomen/pelvis is acceptable. Bone scans may be used if clinically indicated. MRI brain or CT brain with IV contrast is required at baseline and as clinically indicated thereafter. The same imaging methods should be used throughout the trial. The gold standard for evaluating tumor response and BORR during the study will be RECIST 1.1 criteria (see Appendix, Section 10.3). Because of the distinct biologic mechanisms of anti-cancer activity of immunotherapeutic agents, cancer patients treated with immunotherapy need to be evaluated with special attention to the characteristics of immune-related tumor response. The immune related response criteria have been developed to adequately characterize additional patterns of response and progression specific to patients treated with immunotherapy, that cannot be captured by the conventional criteria such as such as RECIST. Immune-related RECIST criteria will therefore also be used in this study (see Appendix, Section 10.4). A 7-day window will be allowed around post-baseline imaging scans (i.e. should be obtained every 9 weeks from the date of allocation (+/- 7 days)). Frequency of imaging studies will be every 12 weeks (+/- 7 days) after 12 months on study treatment. Tumor assessment dates are fixed and should not be adjusted for dose interruptions, delays, or modifications.

6.6 Tumor Tissue Collection and Correlative Studies Blood Sampling

6.6.1 Tumor specimens

Formalin-fixed, paraffin-embedded (FFPE) tumor samples or newly obtained tumor samples will be obtained from all patients with biopsy accessible disease at baseline, then after monotherapy (cycle 1), and then after combination therapy with nab-paclitaxel and pembrolizumab (cycle 2), and at the time of disease progression (if patient consents and it is clinically feasible). Collection of these tumor samples is mandatory to conduct the correlative analysis as part of the objectives of the protocol is to establish predictive biomarkers. These samples will be analyzed and stored at the locations specified below. Only coded samples will be shared with the laboratories. Samples remaining after completion of the study will be destroyed once this study is completed at all participating sites. None of the samples collected in this study will be used to create a repository for future research studies.

- Immune Core lab and Department of Pathology , Tisch Cancer Institute, NYU Langone Medical Center

  The University of Texas at Austin, 107 W Dean Keeton Street, Austin, TX 78712
- Adaptive Biotechnologies, 1551 Eastlake Ave E, Ste 200, Seattle, WA 98102

- QualTek Molecular Laboratories, 300 Pheasant Run, Newtown, PA 18940

- Histogenetics, LLC. 300 Executive Blvd, Ossining, NY 10562

Whenever possible, the lesion biopsied should be taken amenable to serial biopsies and should not be the sole measurable lesion per RECIST 1.1 criteria. A minimum of 2 cores are required at each time point. Soft tissue and bone lesions are acceptable. Subsequent biopsies should be taken from the same lesion, if feasible. Newly-obtained is defined as a specimen obtained up to 6 weeks (42 days) prior to initiation of treatment on Day 1. Subjects for whom newly-obtained samples cannot be provided (e.g. inaccessible or subject safety concern) may submit an archived specimen only upon agreement from the medical monitor. Sections will be evaluated for stromal lymphocytes by hematoxylin and eosin (H&E) stain as per our group's previous work and our international guidance document on evaluation of TILs in breast cancer[20,70]. PD-1 expression in lymphocytes by IHC, PDL-1 expression (IHC in collaboration with Merck), and immune gene panels by Prosigna (NanoString Technologies Inc., Seattle, WA, http://www.nanostring.com) will also be performed. Changes in tumoral PDL-1 expression before and after nab-paclitaxel monotherapy will be investigated.

6.6.2 Diversity in antigen-specific T cell receptor (TCR) and TCR clonality

In collaboration with Adaptive Biotechnologies (Seattle, WA, http://adaptivebiotech.com), which have developed a novel method that amplifies rearranged TCR CDR3 sequences, the capacity of high-throughput sequencing technology will be used to sequence tens of thousands of TCR CDR 3 chains simultaneously. Because the technology utilizes genomic DNA, the frequency of sequenced CDR3 chains is representative of the relative frequency of each CDR sequence in the starting population of T cells. For each study sample, we will sequence 40,000 genomes at each time point.

6.6.3 Identification of Tumor Antigens

Collection and Processing of Tumor Specimens. Archived or newly obtained tumor specimen acquired from surgical resection, surgical/punch biopsy or core biopsy will be

processed per institutional guidelines, at NYULMC via the NYULMC Biorepository and Pathology Core Laboratory.

Tumor specimen acquired from surgical resection, surgical/punch biopsy or core biopsy will be preserved as formalin-fixed, paraffin-embedded (FFPE) slides. Archival tissue specimens—such as a flash-frozen or formalin-fixed, paraffin-embedded block—will be handled in a similar fashion. Participating sites will transport specimens under this clinical trial agreement to the laboratories performing the correlative analyses as specified in this protocol: NYU Langone Medical Center Core Laboratories and the Icahn School of Medicine (ISMMS) Biorepository and Pathology Core Laboratory.

Processing of Tumor Sample for Whole Exome and RNA Sequencing. The NYU or ISMMS Biorepository and Pathology Core Laboratory will then isolate genomic DNA, as well as total RNA from the specimens using standard tissue disruption, nucleic acid extraction and purification kits (Qiagen). The quantity and quality of isolated DNA and RNA are determined using a Qubit fluorometer (Life Technologies), as well as a Bioanalyzer 2100 (Agilent).

Whole Exome Sequencing and RNA Sequencing. Purified DNA and RNA will be transported from the pathology suite by a study coordinator to the NYU or ISMMS Genomics Core Facility (GCF) a Clinical Laboratory Improvement Amendments (CLIA) certified clinical genetics laboratory maintained by the NYU OSR or ISMMS Department of Genetics and Genomic Sciences. Sequencing of tumor specimens at ISMMS is done via a standardized urgent cancer sequencing pipeline which specifically prioritizes the preparation, sequencing and data analysis of subjects enrolled in clinical trials.

Whole Genome DNA Methylation Analysis: We will utilize the analysis of epigenetic changes for molecular classification and prediction of therapeutic response. Epigenetic changes of DNA are increasingly recognized as a potential driver in cancers where driver mutations were not identified. The Infinium MethylationEPIC BeadChip builds upon the Infinium HumanMethylation450 BeadChip with original CpGs plus an additional 350,000 CpGs in enhancer regions. The array provides quantitative methylation measurement at the single-CpG–site level with coverage of CpG islands, RefSeq genes, ENCODE open chromatin, enhancers and transcription factor binding sites, DNase hypersensitivity sites, miRNA promoter regions, and FANTOM5 enhancers. Technical components and performance of both arrays (450k and 850k) remain the same and data are compatible between both platforms. It has recently been shown that this assay can be equally well applied to DNA extracted from fresh frozen or formalin-fixed paraffin-embedded (FFPE) tissue with minimal amounts of input material. the RF is an ensemble method, which combines the outputs of many classification trees to produce a more powerful classifier. A classification tree separates samples into tumor subgroups by repeatedly applying binary splitting rules in a hierarchical manner. These splitting rules are 'learnt' by first providing the known classes of a reference sample set. Starting at the

'root' of a tree, a splitting rule is applied to separate the reference set into two subsets. To establish this rule the algorithm picks the feature that leads to 'purest' split, i.e. the samples assigned to a resulting subset are mostly tumor entities of the same classes. The quality of the split is measured by the Gini impurity measure. The process is then repeated iteratively for each of the resulting subsets until no further improvement can be made. Figure 1 shows an example of a classification tree that uses CpG probes to separate between several tumor entities. Methylation of the Tumor DNa is compared to the methylation of the Normal DNA to elucidate differentially methylated sites between neoplastic and non-neoplastic DNA.

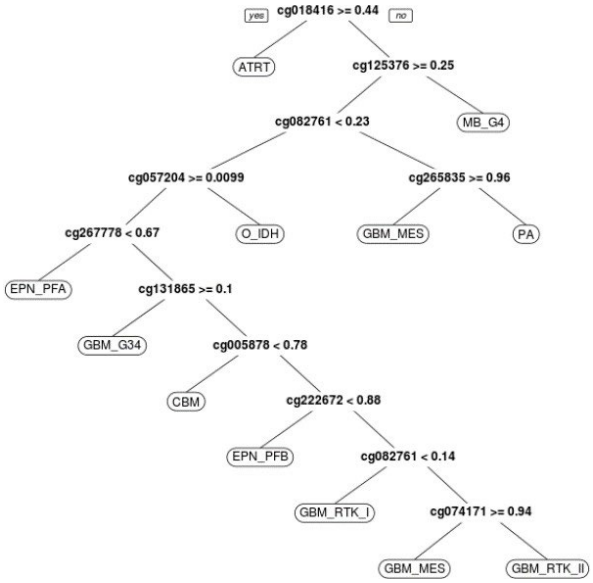


Figure 1. An example of a binary classification tree. From top, the 'root' of the tree, to the final 'leaves' the figure displays the hierarchical order of binary splitting rules. Each 'leaf' corresponds to a tumor entity. At each split, the identifier of the CpG probe and the actual splitting rule are shown.

To 'grow' a random forest, thousands of randomly generated trees are built. Each tree uses a random subset of the samples (drawn with replacement) and a random subset of CpG probes (drawn without replacement). In order to classify new samples, each tree assigns the sample into a particular class, and we say the tree 'votes' for the class. The random forest takes the majority vote of all trees to make a final prediction. In addition, the proportion of trees voting for a certain class can be interpreted as an empirical probability that the sample belongs to that class. The reference sample cohort can be regularly updated as new profiles are generated, as the tool has been optimized to take only a few hours for training and cross-validation with each update. Class prediction for each new sample takes a matter of seconds.

DNA methylation data will be correlated with mutational landscape identified by the NYU NGS580 analysis.

NGS 580 sequencing: The clinically approved panel provides extremely deep analysis (700x on average) of the 580 genes known to be associated with cancer. NYU NGS580 is a paired Tumor—Normal hybrid capture based massive parallel sequencing assay. NYU NGS580 is a custom targeted panel assay focused on a set of 580 genes implicated in both solid tumors and hematological malignancies. The panel aims to identify somatic aberrations- in a variety of specimen and cancer types- including single nucleotide variants (SNV), insertions and deletions (indel) and copy number variants (CNV) including focal amplifications and homozygous deletions. The bioinformatics pipelines can provide further information in terms of tumor mutation burden and mutational signatures.

The results of the NYU NGS 580 will be correlated with Liquid biopsy findings.

Whole Exome Sequencing. Whole exome sequencing (WES) will performed on sequencing libraries, which are prepared according to the manufacturer's protocol. The sequencing library is constructed as follows: The E210 focused acoustic energy system is used to shear genomic DNA which has been prepared according to the procedure outlined in § 5.6.2 into 250 base pair long fragments (Covaris). The fragments are extended in the presence of T4 DNA polymerase and polynucleotide kinase to create blunt-ends (New England Biolabs). Illumina PE genomic DNA adapters (Illumina) are then ligated to the DNA fragments in the presence of T4 DNA ligase (New England Biolabs). The adapter-ligated DNA fragments are amplified by ligation-mediated polymerase chain reaction (LM-PCR), and then purified using the SPRI AMPure XP magnetic bead purification system (Beckman Coulter). The concentration of DNA in the resulting sample is then assessed using a Bioanalyzer 2100 (Agilent) and Qubit fluorometer (Life Technologies). The gDNA adapter-ligated library is then dried in the presence of human Cot-1 DNA and blocking paired-end polymerase chain reaction oligomers (Integrated DNA Technologies). The dried sample is then reconstituted in hybridization buffer with Component A (Roche). The samples is denatured and then combined with the NimbleGen SeqCap EZ Exome oligonucleotide library (Roche), and the mixture is loaded onto a Tetrad Thermal Cycler (BIO-RAD) and allowed to hybridize for seventy-two (72) hours, at forty-seven (47) degrees Celsius. The sample is then combined with streptavidin Dynabeads (Invitrogen), and then washed. Washed bead-conjugated samples are then reconstituted, amplified by LM-PCR, and purified with the SPRI AMPure XP magnetic bead purification system. The concentration of DNA in the resulting sample is then assessed using a Bioanalyzer 2100 and Qubit fluorometer. The enriched sample is also analyzed by a quantitative PCR (qPCR) SYBR green reaction using control oligonucleotide primers (NimbleGen) on a LightCycler 480 II thermal cycler (Roche).

The enriched library is then added to one of eight flow cells at the DNA concentration indicated by the manufacturer (Illumina). The sample is then amplified using cBot (Illumina), and PhiX ver 3 DNA (Illumina) added for control purposes. The flow cell is then loaded into the HiSeq 2500 platform (Illumina), and sequenced according to manufacturers one hundred (100) base pair, paired-end protocol. Quality control

parameters such as the graphical focus quality of the captured images, the fluorescence intensity of individual bases, as well as per-base and per-cycle error rates are periodically monitored. If a deviation in quality control metrics is observed, corrective actions are taken with the help of a trained Illumina Service Engineer and Field Application Scientist. If the corrective actions are deemed to be inadequate the individual sequencing run is aborted. Base calling from captured images is performed by the HiSeq 2500 using software provided by the manufacturer. The results of an individual sequencing run are transferred via a secure connection to a dedicated server maintained by the ISMMS GCF. The primary sequencing data is used to generate an internal quality control report, before the data are made available to the Production Bioinformatics Group for downstream analysis.

RNA Sequencing. The RNA sequencing library is generated using the using the TruSeq mRNA Seq kit (Illumina). The primary sequencing data is used to generate an internal quality control report, before the data are made available to the Production Bioinformatics Group for downstream analysis.

Sequencing Data Transport and Handling. Data containing raw sequencing reads generated from each sequencing run are transferred via a secure connection from the ISMMS GCF primary storage server to two dedicated high-performance computer clusters maintained by the ISMMS Department of Genetics and Genomic Sciences.

Sequencing Data Analysis

Whole Exome Sequencing Data. Base quality score recalibration, insertion and deletion realignment, duplicate removal, genotyping variant calling is performed using the GATK toolkit. Somatic variant calling is performed using both Varscan2 and Mutect. Variants meeting quality control metrics are then manually reviewed by visual inspection of the read alignment and base calls using the Integrated Genome Viewer.

RNA Sequencing. RNASeq read mapping and expression analysis is conducted using TopHat and Cufflinks.

Validation of Sequence Variants Identified by High-throughput Sequencing. Variants are then cross-validated by the ISMMS GCF using an orthogonal high-throughput platform (Ion Proton™ or Ion PGM™, Life Technologies | Pacific Biosciences RS II, Pacific Biosciences) or by conventional Sanger sequencing. Upon completion of validation a variant calling file containing list of all somatic variants, as well as all associated pertinent information are then made available for use in antigen identification.

Reporting of Information Derived from Cancer Sequencing. Cancer sequencing is a major component of this particular research study, however, data derived from WES and/or RNASeq performed in the context of this study is considered to be for research purposes only. While clinical sequencing may be of additional benefit to the subject and

his/her physician this type of data reporting is outside of the scope of the present study and as such no genetic information will be reported back to the subject.

Human Leukocyte Antigen Genotyping. This HLA typing is done solely for the purpose of immune analyses as specified in this protocol, results will not be shared with the patient or physician. Genomic DNA isolated from peripheral blood mononuclear cells collected during study visit v1 will be used to determine the subject specific nine locus HLA haplotype type for use in epitope prediction. Subject HLA haplotype will be assess by sequence-based HLA typing, which relies on locus and group-specific amplification and sequencing of exons 2 and 3 of HLA-A, B, C; as well as exon 2 of HLA-DRB1, DRB3/4/5, DQB1, DQA1, DPA1, and DPB1 as per American Society for Histocompatibility and Immunogenetics/National Marrow Donor Program requirements for bone marrow transplant registration. This assessment will be performed by Histogenetics, LLC. (Ossining, NY), an American Society for Histocompatibility and Immunogenetics (ASHI) (Member #: 03-1-NY-2602) and CLIA-certified (Certificate: 33D0985173) laboratory.

Systematic identification of Mutation Derived Tumor Antigens (MTA)

MTA may be identified through the sequential use of WES followed by peptide-MHC binding affinity prediction[48,49]. We will use NETMHCCons v1.1 to identify patient specific neoantigens. RNA seq will be used to ensure expression of the variant antigen by the patient's tumor.

6.6.4 Peripheral blood

Key immune biomarkers will be evaluated on circulating leukocytes (PD-1, PD-L1, granzyme B, perforin, NKp44, HLA-DR, CD69) to evaluate changes during PD-1 blockade, as well as to evaluate them as predictive biomarkers. In addition, we will comprehensively evaluate the immune cell subset frequencies and expression of key receptors on peripheral blood mononuclear cells (PBMCs) and identify changes that occur after PD-1 blockade. Included in the analyses are CD4/CD8 and Th1/Th2 profiles, immunosuppressive Tregs (the development of which is promoted by PD-1 and PD-L1 ligation), dendritic cells [71] which are important antigen presenting cells (APCs), and inhibitory receptors PD-1, CTLA-4, TIM-3, and LAG-3, which can all contribute to T-cell exhaustion. Differential expression of these inhibitory receptors on subset of CD8 T cells is associated with differential cytokine production and degranulation, and there are also therapeutic immune checkpoint targets under development that may be altered on T cells after PD-1 blockade. Multi-parametric flow cytometry (12-color) will be used to quantify these biomarkers. Sequential samples of PBMC will be analyzed from patients before and during treatment with pembrolizumab.

Liquid Biopsy: Liquid biopsy enables analysis of tumor cells and tumor DNA directly from blood. We will perform a comprehensive liquid biopsy program in

which whole tumor cells as well as cell-free tumor DNA are captured from blood and profiled. Genetic heterogeneity is analyzed on a single cell level and compared with the levels of cell-free tumor DNA to determine response to therapy and predict disease recurrence. DNA from circulating leukocytes is used as a control for DNA NGS and methylation.

6.6.5 Gut Microbiome Analysis

Subjects will receive specific instructions about collection of stool. They will be given a stool collection kit to be returned at the required time points, along with instructions on how to use it. The stool will be aliquoted and stored at -80^{o}C until the time of analysis. Bacterial microbiome taxonomy, diversity, and abundance will be analyzed by pyrosequencing of 16S ribosomal RNA (rRNA) amplicons.

6.6.6 Laboratory Procedures/Assessments

Tumor tissues, stool and blood Samples will be analyzed at the two collaborating academic centers: NYU Langone Core Laboratories and The University of Texas at Austin
107 W Dean Keeton Street, Austin, TX 78712. Additionally, commercial laboratories will perform analyses as described in this protocol, no identifying information will be shared with these laboratories.

Laboratory Safety Evaluations (Hematology, Chemistry and Urinalysis) will be performed at the clinical laboratories of the participating sites.

Laboratory tests for hematology, chemistry, urinalysis, and others are specified in the study calendar.

Laboratory tests for cycle1 should be performed within 10 days prior to the first dose of treatment. After Cycle 1, pre-dose laboratory procedures can be conducted up to 72 hours prior to dosing. Results for clinically significant laboratory values (ANC, hemoglobin, platelet count, creatinine, bilirubin, AST and ALT) must be reviewed by the investigator or qualified designee and found to be acceptable prior to each dose of trial treatment.

6.7 Pharmacokinetic/Pharmacodynamic Evaluations n/a

6.8 Other Procedures

6.8.1 Withdrawal/Discontinuation

When a subject discontinues/withdraws prior to trial completion, all applicable activities scheduled for the final trial visit should be performed at the time of discontinuation. Any adverse events which are present at the time of discontinuation/withdrawal should be followed in accordance with the safety requirements outlined in Section 6.12 - Assessing and Recording Adverse Events.

6.9 Blinding/Unblinding

N/A

6.10 Screening

6.10.1 Screening Period

During the screening period, patient evaluation for trial entry will be performed based upon enrollment criteria (inclusion/exclusion criteria), history and physical exam, ECOG performance status (PS), EKG, and standard of care [69] labs.

6.10.2 Treatment Period

Patient evaluation will be performed at each visit that the patient receives the study drug and include history and physical exam, ECOG PS, measurement of SOC labs, and assessment of adverse events. Imaging will be performed every 9 weeks from the date of allocation (+/- 7 days) until after twelve months on study treatment during which imaging will be performed every 12 weeks (+/- 7 days). Tumor assessment dates are fixed and should not be adjusted for dose interruptions, delays, or modifications.

6.11 Post-Treatment Visits

6.11.1 Safety Follow-Up Visit

The mandatory Safety Follow-Up Visit should be conducted approximately 30 days after the last dose of trial treatment or before the initiation of a new anti-cancer treatment, whichever comes first. All AEs that occur prior to the Safety Follow-Up Visit should be recorded. SAEs

that occur within 90 days of the end of treatment or before initiation of a new anti-cancer treatment should also be followed and recorded.

6.11.2 Follow-up Visits

N/A

6.11.3 Survival Follow-up

Following study completion, patients will enter routine follow-up with their primary oncologist, who may be contacted to provide follow-up information on the patient's clinical and disease status until death or withdrawal of consent, whichever occurs first.

6.12 Assessing and Recording Adverse Events

An adverse event is defined as any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product or protocol-specified procedure, whether or not considered related to the medicinal product or protocol-specified procedure. Any worsening (i.e., any clinically significant adverse change in frequency and/or intensity) of a preexisting condition that is temporally associated with the use of the Merck and/or Celgene product, is also an adverse event.

Changes resulting from normal growth and development that do not vary significantly in frequency or severity from expected levels are not to be considered adverse events. Examples of this may include, but are not limited to, teething, typical crying in infants and children and onset of menses or menopause occurring at a physiologically appropriate time.

Merck product includes any pharmaceutical product, biological product, device, diagnostic agent or protocol-specified procedure, whether investigational (including placebo or active comparator medication) or marketed, manufactured by, licensed by, provided by or distributed by Merck for human use.

Adverse events may occur during the course of the use of the Merck and/or Celgene product in clinical trials or within the follow-up period specified by the protocol, or prescribed in clinical practice, from overdose (whether accidental or intentional), from abuse and from withdrawal.

Adverse events may also occur in screened subjects during any pre-allocation baseline period as a result of a protocol-specified intervention, including washout or discontinuation of usual therapy, diet, placebo treatment or a procedure.

Progression of the cancer under study is not considered an adverse event unless it is considered to be drug related by the investigator.

All adverse events will be recorded from the time the consent form is signed through 30 days following cessation of treatment and at each examination on the Adverse Event case report forms/worksheets. The reporting timeframe for adverse events meeting any serious criteria is described in section 6.13.

6.12.1 Definition of an Overdose for This Protocol and Reporting of Overdose to the NYU PI and to Merck and Celgene

Pembrolizumab

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

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

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

All reports of overdose with and without an adverse event must be reported within 24 hours to Dr. Adams, the NYU research coordinator, NYU regulatory specialist, the medical monitor, Dr. Zujun Li and to NYUPCCsafeteyreports@nyumc.org and within 2 working days hours to Merck Global Safety. (Attn: Worldwide Product Safety; FAX 215 993-1220)

Nab-paclitaxel

Overdose, as defined for this protocol, refers to pembrolizumab and nab-paclitaxel dosing only.

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

PO	any amount over the protocol-specified dose
IV	10% over the protocol-specified dose
SC	10% over the protocol-specified dose

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

On an infusion rate basis, an overdose is defined as any rate faster than the protocol-specified rate. For nab-paclitaxel, an infusion completed in less than 25 minutes may increase Cmax by approximately 20%, therefore a nab-paclitaxel infusion completed in less than 25 minutes will meet the infusion rate criterion for an overdose. Complete data about drug administration, including any overdose, regardless of whether the overdose was accidental or intentional, should be reported in the case report form.

Celgene Drug Safety Contact Information:

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

6.12.2 Reporting of Pregnancy and Lactation to Dr. Adams, Merck and Celgene

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), including the pregnancy of a male subject's female partner that occurs during the trial or within 120 days of completing the trial completing the trial, or 30 days following cessation of treatment if the subject initiates new anticancer therapy, whichever is earlier. All subjects and female partners of male subjects who become pregnant 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 PI, NYU research coordinator, regulatory specialist, the medical monitor Dr. Zujun Li, and to NYUPCCsafeteyreports@nyumc.organd within 2 working days to Merck Global Safety. (Attn: Worldwide Product Safety; FAX 215 993-1220)

6.13 Immediate Reporting of Adverse Events to the PI , Merck and Celgene

6.13.1 Serious Adverse Events

Expedited Reporting to Merck

A serious adverse event is any adverse event occurring at any dose or during any use of Merck's product that:

- Results in death;

- Is life threatening;
- Results in persistent or significant disability/incapacity;
- Results in or prolongs an existing inpatient hospitalization;
- Is a congenital anomaly/birth defect;
- Is a new cancer (that is not a condition of the study);
- Is associated with an overdose;
- Is an other important medical event

Refer to Table 6 for additional details regarding each of the above criteria.

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 Dr. Adams, the NYU research coordinator, the regulatory specialists, the medical monitor Dr. Zujun Li and to NYUPCCsafeteyreports@nyumc.org 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 IRB approved 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 Dr. Adams, the NYU research coordinator, the regulatory specialists, the medical monitor, Dr. Zujun Li and to NYUPCCsafeteyreports@nyumc.org 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.

Expedited Reporting to Celgene

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

Serious adverse events (SAE) are defined above. The investigator must inform Celgene in writing using a Celgene SAE form or MEDWATCH 3500A form of any SAE within 24 hours of being aware of the event. The written report must be completed and supplied to Celgene by facsimile within 24 hours. The initial report must be as complete as possible, including an assessment of the causal relationship between the event and the investigational product(s). Information not available at the time of the initial report (e.g., an end date for the adverse event or laboratory values received after the report) must be documented on a follow-up report. A final report to document resolution of the SAE is required. The Celgene tracking number (AX-CL-BRST-PI-006499) and the institutional protocol number should be included on SAE reports (or on the fax cover letter) sent to Celgene. A copy of the fax transmission confirmation of the SAE report to Celgene should be attached to the SAE and retained with the patient records. Participating study sites must report SAEs to Celgene as described and within 24 hours of awareness. Participating sites should also report SAEs to the primary study site.

6.13.2 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 Dr. Adams, the NYU research coordinator, the regulatory specialists, the medical monitor Dr. Zujun Li and to NYUPCCsafeteyreports@nyumc.org 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 Dr. Adams, the NYU research coordinator, the regulatory specialists, the medical monitor Dr. Zujun Li and to NYUPCCsafeteyreports@nyumc.org, 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).

1. Additional adverse events:

   A separate guidance document has been provided entitled “Event of Clinical Interest Guidance Document” (previously entitled, “Event of Clinical Interest and Immune-Related

Adverse Event Guidance Document"). This document can be found in Appendix 4 and provides guidance regarding identification, evaluation and management of ECIs and irAEs.

ECIs (both non-serious and serious adverse events) identified in this guidance document from the date of first dose through 90 days following cessation of treatment, or 30 days after the initiation of a new anticancer therapy, whichever is earlier, need to be reported within 24 hours to Dr. Adams, the NYU research coordinator, the regulatory specialists, the medical monitor, Dr. Zujun Li and to NYUPCCsafeteyreports@nyumc.org and within 2 working days to Merck Global Safety. (Attn: Worldwide Product Safety; FAX 215 993-1220), regardless of attribution to study treatment, consistent with standard SAE reporting guidelines.

Subjects should be assessed for possible ECIs prior to each dose. Lab results should be evaluated and subjects should be asked for signs and symptoms suggestive of an immune-related event. Subjects who develop an ECI thought to be immune-related should have additional testing to rule out other etiologic causes. If lab results or symptoms indicate a possible immune-related ECI, then additional testing should be performed to rule out other etiologic causes. If no other cause is found, then it is assumed to be immune-related.

6.13.3 Evaluating Adverse Events

An IRB approved investigator who is a qualified physician will evaluate all adverse events according to the NCI Common Terminology for Adverse Events (CTCAE), version 4.0. Any adverse event which changes CTCAE grade over the course of a given episode will have each change of grade recorded on the adverse event case report forms/worksheets.

All adverse events regardless of CTCAE grade must also be evaluated for seriousness.

Table 6 Evaluating Adverse Events

An investigator who is a qualified physician, will evaluate all adverse events as to:

V4.0 CTCAE Grading	**Grade 1**	**Mild; asymptomatic or mid symptoms; clinical or diagnostic observations only; intervention not indicated.**
	Grade 2	**Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL.**
	Grade 3	**Severe or medically significant but not immediately life-threatening; hospitalization or prolongation or hospitalization indicated; disabling; limiting self-care ADL.**
	Grade 4	**Life threatening consequences; urgent intervention indicated.**
	Grade 5	**Death related to AE**
Seriousness	A serious adverse event is any adverse event occurring at any dose or during any use of Merck product that:	
	†**Results in death**; or	
	†**Is life threatening; or** places the subject, in the view of the investigator, at immediate risk of death from the event as it occurred (Note: This does not include an adverse event that, had it occurred in a more severe form, might have caused death.); or	
	†**Results in a persistent or significant disability/incapacity** (substantial disruption of one's ability to conduct normal life functions); or	
	†**Results in or prolongs an existing inpatient hospitalization** (hospitalization is defined as an inpatient admission, regardless of length of stay, even if the hospitalization is a precautionary measure for continued observation. (Note: Hospitalization [including hospitalization for an elective procedure] for a preexisting condition which has not worsened does not constitute a serious adverse event.); or	
	†**Is a congenital anomaly/birth defect** (in offspring of subject taking the product regardless of time to diagnosis);or	
	Is a new **cancer;** (that is not a condition of the study) **or**	
	Is an overdose (whether accidental or intentional). Any adverse event associated with an overdose is considered a serious adverse event. An overdose that is not associated with an adverse event is considered a non-serious event of clinical interest and must be reported within 24 hours.	
	Other important medical events that may not result in death, not be life threatening, or not require hospitalization may be considered a serious adverse event when, based upon appropriate medical judgment, the event may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed previously (designated above by a †).	
Duration	Record the start and stop dates of the adverse event. If less than 1 day, indicate the appropriate length of time and units	
Action taken	Did the adverse event cause the Merck product to be discontinued?	
Relationship to test drug	Did the Merck product cause the adverse event? The determination of the likelihood that the Merck product caused the adverse event will be provided by an investigator who is a qualified physician. The investigator's signed/dated initials on the source document or worksheet that supports the causality noted on the AE form, ensures that a medically qualified assessment of causality was done. This initialed document must be retained for the required regulatory time frame. The criteria below are intended as reference guidelines to assist the investigator in assessing the likelihood of a relationship between the test drug and the adverse event based upon the available information. **The following components are to be used to assess the relationship between the Merck product and the AE**; the greater the correlation with the components and their respective elements (in number and/or intensity), the more likely the Merck product caused the adverse event (AE):	
	Exposure	Is there evidence that the subject was actually exposed to the Merck product such as: reliable history, acceptable compliance assessment (pill count, diary, etc.), expected pharmacologic effect, or measurement of drug/metabolite in bodily specimen?
	Time Course	Did the AE follow in a reasonable temporal sequence from administration of the Merck product? Is the time of onset of the AE compatible with a drug-induced effect (applies to trials with investigational medicinal product)?
	Likely Cause	Is the AE not reasonably explained by another etiology such as underlying disease, other drug(s)/vaccine(s), or other host or environmental factors

Relationship to Merck product (continued)	**The following components are to be used to assess the relationship between the test drug and the AE: (continued)**	
	Dechallenge	Was the Merck product discontinued or dose/exposure/frequency reduced? If yes, did the AE resolve or improve? If yes, this is a positive dechallenge. If no, this is a negative dechallenge. (Note: This criterion is not applicable if: (1) the AE resulted in death or permanent disability; (2) the AE resolved/improved despite continuation of the Merck product; or (3) the trial is a single-dose drug trial); or (4) Merck product(s) is/are only used one time.)
	Rechallenge	Was the subject re-exposed to the Merck product in this study? If yes, did the AE recur or worsen? If yes, this is a positive rechallenge. If no, this is a negative rechallenge. (Note: This criterion is not applicable if: (1) the initial AE resulted in death or permanent disability, or (2) the trial is a single-dose drug trial); or (3) Merck product(s) is/are used only one time). NOTE: IF A RECHALLENGE IS PLANNED FOR AN ADVERSE EVENT WHICH WAS SERIOUS AND WHICH MAY HAVE BEEN CAUSED BY THE MERCK PRODUCT, OR IF REEXPOSURE TO THE MERCK PRODUCT POSES ADDITIONAL POTENTIAL SIGNIFICANT RISK TO THE SUBJECT, THEN THE RECHALLENGE MUST BE APPROVED IN ADVANCE BY THE U.S. CLINICAL MONITOR AS PER DOSE MODIFICATION GUIDELINES IN THE PROTOCOL.
	Consistency with Trial Treatment Profile	Is the clinical/pathological presentation of the AE consistent with previous knowledge regarding the Merck product or drug class pharmacology or toxicology?
The assessment of relationship will be reported on the case report forms /worksheets by an investigator who is a qualified physician according to his/her best clinical judgment, including consideration of the above elements.		
Record one of the following	**Use the following scale of criteria as guidance (not all criteria must be present to be indicative of a Merck product relationship).**	
Yes, there is a reasonable possibility of Merck product relationship.	There is evidence of exposure to the Merck product. The temporal sequence of the AE onset relative to the administration of the Merck product is reasonable. The AE is more likely explained by the Merck product than by another cause.	
No, there is not a reasonable possibility Merck product relationship	Subject did not receive the Merck product OR temporal sequence of the AE onset relative to administration of the Merck product is not reasonable OR there is another obvious cause of the AE. (Also entered for a subject with overdose without an associated AE.)	

6.13.4 Responsibility for Reporting Adverse Events

All Adverse Events will be reported to regulatory authorities, IRB/IECs and investigators in accordance with all applicable global laws and regulations.

6.13.5 Investigator Reporting Responsibilities

The following describes events that must be reported to Dr. Adams in an expedited fashion.

Initial Report: Within 24 hours:
The following events must be reported to the study sponsor by telephone within 24 hours of awareness of the event:

- Unanticipated problems related to study participation,
- Serious adverse events, regardless of whether they are unexpected.

Additionally, an FDA Form 3500A (MEDWATCH Form; see http://www.fda.gov/downloads/Safety/MedWatch/HowToReport/DownloadForms/UCM082728.pdf) must be completed by the investigator and faxed to the study sponsor within 24 hours. The investigator shall maintain a copy of the MEDWATCH Form on file at the studysite.

Forward all medwatch to the Principal Investigator:

Dr. Sylvia Adams: 212-731-5795

Follow-up Report: Within 48 hours:
As a follow-up to the initial report, within the following 48 hours of awareness of the event, the investigator shall provide further information, as applicable, on the unanticipated device event or the unanticipated problem in the form of a written narrative. This should include a copy of the completed Unanticipated Problem form, and any other diagnostic information that will assist the understanding of the event. Significant new information on ongoing unanticipated adverse device effects shall be provided promptly to the study sponsor.

Other Reportable Events:

- **Deviations from the study protocol**
  Deviations from the protocol must receive both Sponsor and the investigator's IRB approval before they are initiated. Any protocol deviations initiated without Sponsor and the investigator's IRB approval that may affect the scientific soundness of the study, or affect the rights, safety, or welfare of study subjects, must be reported to the Sponsor and to the investigator's IRB as soon as a possible, but ***no later than 5 working days*** of the protocol deviation.

- **Withdrawal of IRB approval**
  An investigator shall report to the sponsor a withdrawal of approval by the

investigator's reviewing IRB as soon as a possible, but ***no later than 5 working days*** of the IRB notification of withdrawal of approval.

Investigator Reporting: Notifying the IRB

Federal regulations require timely reporting by investigators to their local IRB of unanticipated problems posing risks to subjects or others. The following describes the NYULMC IRB reporting requirements, though Investigators at participating sites are responsible for meeting the specific requirements of their IRB of record.

Report Promptly, But no Later than 5 Working Days:

Researchers are required to submit reports of the following problems promptly but no later than 5 working days from the time the investigator becomes aware of the event:

- **Unanticipated problems including adverse events that are unexpected and related**
  - *Unexpected:* An event is "unexpected" when its specificity and severity are not accurately reflected in the protocol-related documents, such as the IRB-approved research protocol, any applicable investigator brochure, and the current IRB-approved informed consent document and other relevant sources of information, such as product labeling and package inserts.
  - *Related to the research procedures:* An event is related to the research procedures if in the opinion of the principal investigator or sponsor, the event was more likely than not to be caused by the research procedures.
  - *Harmful:* either caused harm to subjects or others, or placed them at increased risk

6.13.6 Other Reportable Events:

The following events also require prompt reporting to the IRB, though ***no later than 5 working days***:

- **Complaint of a research subject** when the complaint indicates unexpected risks or the complaint cannot be resolved by the research team.
- **Protocol deviations or violations** (includes intentional and accidental/unintentional deviations from the IRB approved protocol) for any of the following situations:

  –one or more participants were placed at increased risk of harm

  –the event has the potential to occur again

  –the deviation was necessary to protect a subject from immediate harm
- **Breach of confidentiality**
- **Incarceration of a participant** when the research was not previously approved under Subpart C and the investigator believes it is in the best interest of the subject to remain on the study.

- **New Information indicating a change to the risks or potential benefits** of the research, in terms of severity or frequency. (e.g. analysis indicates lower-than-expected response rate or a more severe or frequent side effect; Other research finds arm of study has no therapeutic value; FDA labeling change or withdrawal from market)

6.13.7 Reporting Process

The reportable events noted above will be reported to the IRB using the form: "Reportable Event Form" or as a written report of the event (including a description of the event with information regarding its fulfillment of the above criteria, follow-up/resolution and need for revision to consent form and/or other study documentation).

Copies of each report and documentation of IRB notification and receipt will be kept in the Clinical Investigator's regulatory binder.

IND Annual Reports

If the FDA has granted an IND number, it is a requirement of 21 CFR 312.33, that an annual report is provided to the FDA within 60-days of the IND anniversary date. 21 CRF 312.33 provides the data elements that are to be submitted in the report. The Annual Report should be filed in the study's Regulatory Binder, and a copy provided to Merck and Celgene Corporation as a supporter of this study:

Merck & Co., Inc. (Attn: Worldwide Product Safety; FAX 215 993-1220)

Celgene Corporation
Attn: Medical Affairs Operations
Connell Corporate Park
400 Connell Drive Suite 700
Berkeley Heights, NJ 07922
Tel: (908) 673-9000

All adverse experience reports must include the patient number, age, sex, weight, severity of reaction (e.g. mild, moderate, severe), relationship to drug (e.g. probably related, unknown relationship, definitely not related), date and time of administration of test medications and all concomitant medications, and medical treatment provided. The investigator is responsible for evaluating all adverse events to determine whether criteria for "serious" and as defined above are present. The investigator is responsible for reporting adverse events to Celgene as described in the protocol. Participating study sites should NOT report SAEs to the FDA. Rather, participating sites should report SAEs to Celgene and the primary study site, and the primary site will be responsible for reporting to FDA.

Notifying participating investigators: It is the responsibility of the study sponsor to notify all participating investigators of any adverse event that meets the FDA 15-day reporting requirement criteria as note above in section 8.3.4. The same materials and timeline used to report to the FDA are used for notifying participating investigators.

7 STATISTICAL ANALYSIS PLAN

7.1 Statistical Analysis Plan Summary

For the TBNC cohort (primary cohort), a total sample size of 30 subjects (both male and female of all races) with metastatic TNBC treated with 0-2 prior lines of therapy for metastatic disease will be enrolled to evaluate the anti-tumor activity of the combination of nab-paclitaxel and pembrolizumab. The primary efficacy analysis in this TNBC cohort will be BORR based on RECIST 1.1. BOR is defined as the best response recorded from the start of the study treatment until disease progression. BORR is the number of subjects with a BOR of CR or PR, divided by the number of treated subjects. Assuming nab-paclitaxel would have a maximum BORR (defined as a best response with CR or PR) of approximately 30% for TNBC[31] in 1st to 3rd line monotherapy with a sample size of 30 subjects, the estimated exact 95% Clopper Pearson confidence interval would be 14.7% to 49.4% if the underlying rate is 30%. (Calculations from PASS 2014, NCSS J. Hintze, Kaysville, Utah). For the HR-positive (exploratory) cohort, an additional 20 subjects with metastatic HR-positive breast cancer will be enrolled to provide an initial understanding of the efficacy profiles of the combination of nab-paclitaxel and pembrolizumab in these patients. Descriptive statistics will be provided for efficacy endpoints. An estimated 65 patients will be screened for eligibility to reach a goal of about 50 participants.

The two analysis populations will be defined as:

- *safety run-in population*: all patients who receive any amount of study drug (pembrolizumab)
- *efficacy evaluable population*: all patients who receive any amount of study drug (pembrolizumab) and have at least one post-baseline disease assessment (similar to a modified intent to treat population). Analysis of efficacy endpoints will be performed on the efficacy evaluable population.

7.2 Statistical Analysis Plan

7.2.1 General Methods

Within each cohort, all baseline demographic, disease and treatment characteristics, will be summarized using frequency distributions for qualitative variables and summary statistics (mean, medians, standard deviations, etc.) and graphical displays (e.g., boxplots) for quantitative variables.

All endpoints will be summarized overall and by cohort (cTNBC, HR-positive, iTNBC groups). For the primary endpoint of BORR, 2 sided exact 95% Clopper Pearson confidence intervals will be provided for each cohort. Time to event analysis (PFS and OS for the TNBC group) will be performed using Kaplan-Meier methods. PFS is defined as the time elapsed between study enrollment date and date of tumor progression or death from any cause, with censoring of patients who are lost to follow-up. OS is defined as the time from date of study enrollment until death from any cause. Both, PFS and OS are measured in the intent-to-treat population (all patients who receive at least one dose of treatment). As the primary cohort of cTNBC is a single-arm cohort, any hypothesis testing to be performed among subgroups is for descriptive and future study purposes only.

7.2.2 Safety

Adverse events [72] as well as immune-related events will be closely monitored throughout the study. Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) for purposes of summarization. All AEs occurring during the study will be included in by-subject data listings and tabulated by MedDRA system organ class and preferred term. Safety endpoints for adverse events include the following: incidence of AEs, all treatment-emergent AEs (TEAEs) and all serious adverse events (SAEs). Severity of event, relationship to study drug, and discontinuation of patients from study therapy due to AEs and due to deaths will be recorded.

Counts and percentage of AE will be provided. Confidence intervals for rates of AEs will be estimated using exact binomial confidence intervals. A formal dose-limiting toxicity (DLT) evaluation (assessed on day 42) will be done after 12 patients during the safety run in have been treated with the combination of nab-paclitaxel and pembrolizumab (Phase Ib). If more than 4 of the first 12 patients have DLT (clinically significant, pre-specified AEs), then consideration would be given to modifying the nab-paclitaxel dose.

In the recently reported TNBC combination trial of nab-paclitaxel chemotherapy with immunotherapy (atezolizumab) (n=32 patients), grade 3/4 AEs had occurred in 56% of patients, including neutropenia (41%), thrombocytopenia (9%), and anemia (6%) (Adams, et al, SABCS 2015). At least one AE of any grade occurred in all patients in the trial. There were no treatment-related deaths observed in the study. Five patients discontinued nab-paclitaxel as a result of an AE (fatigue (n = 1; grade 2), asthenia (n = 1; grade 2), and peripheral neuropathy (n = 3; grade 1, 2, and 3)).

DLT specifically for this combination study (which is to avoid excess toxicity with the combination compared to known single agent toxicity) is defined as one of the following toxicities occurring during the DLT assessment window and considered by the investigator to be related to any of the study drugs.

Hematologic Toxicities:

- Grade 4 thrombocytopenia lasting greater than seven days

- Grade 4 neutropenia lasting greater than 14 days

Nonhematologic Toxicities:

- AST =/> 10x ULN
- ALT =/> 10x ULN

- Pneumonitis of Grade 3 or higher
- Colitis of Grade 3 or higher

7.2.3 Correlative Analyses

Analyses of immune cell subsets are exploratory in nature and will contribute to general understanding of the immunologic effects of PD-1 blockade. Importantly, we will assess baseline PD-L1 expression in tumors and immune cells and will examine the association with BORR within each cohort using graphical displays. Cell counts from flow cytometry and staining levels expressed as mean fluorescence intensity (MFI) or % positivity will be summarized using descriptive statistics. Staining levels expressed as scores will be tabulated categorically. Changes over time will be portrayed graphically by group, and marker expression will be quantified and plotted during course of therapy for individual patients. Changes in immune parameters on serial samples will be evaluated graphically and the association with changes in PD-1 checkpoint inhibition and changes in expression of functional indicators (CD107A, IFN-gamma, Ki-67, annexin, pAkt) during treatment will be explored.

LABELING, PACKAGING, STORAGE AND RETURN OF CLINICAL SUPPLIES

7.3 Investigational Product

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

Commercially packaged supplies of Pembrolizumab will be provided by Merck as summarized in Table 7.

Table 7 Product Descriptions

Product Name & Potency	Dosage Form

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

7.4 Packaging and Labeling Information

Clinical supplies will be affixed with a clinical label in accordance with regulatory requirements. Merck will provide Pembrolizumab (KEYTRUDA) in marketed package.

7.5 Clinical Supplies Disclosure

This trial is open-label; therefore, the subject, the trial site personnel, and pharmaceutical companies supplying the drugs are not blinded to treatment. Drug identity (name, strength) is included in the label text; random code/disclosure envelopes or lists are not provided.

7.6 Storage and Handling Requirements

Upon receipt of the of the study treatment supplies, an inventory will be performed and a drug receipt log filled out and signed by the person accepting the shipment. The designated study staff will count and verify that the shipment contains all the items noted in the shipment inventory. Any damaged or unusable study drug in a given shipment will be documented and the ~~sponsor~~ manufacturer will be notified.

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

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

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

7.7 Returns and Reconciliation

The investigator is responsible for keeping accurate records of the clinical supplies received from Merck and Celgene 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.

8 ADMINISTRATIVE AND REGULATORY DETAILS

8.1 Confidentiality

The study team will maintain clinical and laboratory data in a designed manner to ensure patient confidentiality. All study personnel have passed human subject protection courses. If applicable, tissue samples sent to collaborators outside of NYU will only be labeled with an assigned protocol-patient identification number without patient identifiers. Only IRB approved study personnel at NYU/Clinical trials office will have a link to the code. Systems used for electronic data capture are HIPPA compliant. All documents are kept in strictly confidential files and are only made accessible for review of sponsors, monitors and authorized representatives of regulatory agencies as described in the informed consent document.

Information about study subjects will be kept confidential and managed according to the requirements of the Health Insurance Portability and Accountability Act of 1996 (HIPAA). Those regulations require a signed subject authorization informing the subject of the following:

- What protected health information [23] will be collected from subjects in this study
- Who will have access to that information and why
- Who will use or disclose that information
- The rights of a research subject to revoke their authorization for use of their PHI.

In the event that a subject revokes authorization to collect or use PHI, the investigator, by regulation, retains the ability to use all information collected prior to the revocation of subject authorization. For subjects that have revoked authorization to collect or use PHI, the investigator cannot collect information regarding status until it is available from publically available website.

8.2 Compliance with Financial Disclosure Requirements

The study will comply with NYULMC applicable University conflict of interest policies for financial disclosure requirements. Any investigator who has a conflict of interest with this study (patent ownership, royalties, or financial gain greater than the minimum allowable by their institution, etc.) will have the conflict reviewed by a properly constituted Conflict of Interest Committee with a Committee-sanctioned conflict management plan.

8.3 Compliance with Law, Audit and Debarment

The investigator will permit study-related monitoring, audits, and inspections by the IRB/EC, the sponsor, government regulatory bodies, and University compliance and quality assurance groups of all study related documents (e.g. source documents, regulatory documents, data collection instruments, study data etc.). The investigator will ensure the capability for inspections of applicable study-related facilities (e.g. pharmacy, diagnostic laboratory, etc.).

Participation as an investigator in this study implies acceptance of potential inspection by government regulatory authorities and applicable University compliance and quality assurance offices.

8.4 Compliance with Trial Registration and Results Posting Requirements

Under the terms of the Food and Drug Administration Modernization Act (FDAMA) and the Food and Drug Administration Amendments Act (FDAAA), the Sponsor of the trial is solely responsible for determining whether the trial and its results are subject to the requirements for submission to the Clinical Trials Data Bank, http://www.clinicaltrials.gov. Information posted will allow subjects to identify potentially appropriate trials for their disease conditions and pursue participation by calling a central contact number for further information on appropriate trial locations and trial site contact information.

8.5 Quality Management System

The proposed trial entails moderate risks to subjects.

At the NYU Cancer Institute, all investigator-initiated protocols are subject to a standardized data and safety monitoring, which includes scientific peer review, Institutional Review Board (IRB) review, and Data and Safety Monitoring Committee (DSMC) review as well as internal auditing.

The review of AEs and trial conduct for this trial occurs at several levels:

(1) Principal Investigator: Adverse events are evaluated monthly by the principal investigator in conjunction with the research nurses, data manager and research team.

(2) DSMC: See section 10.6

(3) IRB: An annual report to the IRB is submitted by the trial PI for continuation of the protocol. It includes a summary of all AEs, total enrollment with demographics, protocol violations, and current status of subjects as well as available research data.

(4) In addition, the internal audit committee will inspect the source documents, including consent forms for randomly selected enrolled participants at regular intervals throughout the trial to verify adherence to the protocol; the completeness, accuracy and consistency of the data; and adherence to ICH Good Clinical Practice guidelines.

8.6 Data Management

The NYU Clinical Trials Office will oversee the data management of this trial.

Velos, an electronic database system will be used to house the data for this trial. Data is required to be input in the study database within 1 week of the patients visit. Each site will be responsible for entering the data into Velos.

Data Storage and Confidentiality:

We will take all necessary precautions to maintain confidentiality of data and prevent

unauthorized access to the data. All data will be maintained on a secure server and will be password protected with access limited to IRB-approved investigators/researchers. The matching clinical data may be collected from several sources including the medical record, lab facilities and from physician office charts.

The database will contain subject demographics, medical history, number of prior treatments, current therapy, all protocol required labs and radiology reports, adverse events, clinical response to the current intervention, and overall survival as well as information regarding the patient's preferences regarding re-contacting for future research.

All data that is subsequently utilized for research will be stripped of any personal identifiers and all subjects will be assigned a unique study ID number. No individual identifying information will be used in any reports or publications resulting from this database. Any unauthorized access to medical record information contained within the database will be reported to the IRB.

9 APPENDICES

10.1ECOG PERFORMANCE STATUS

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

10.2 Common Terminology Criteria for Adverse Events V4.0 (CTCAE)

The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized for adverse event reporting. (http://ctep.cancer.gov/reporting/ctc.html)

10.3 Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 Criteria for Evaluating Response in Solid Tumors

RECIST version 1.1* will be used in this study for assessment of tumor response. While either CT or MRI may be utilized, as per RECIST 1.1, CT is the preferred imaging technique in this study.

* As published in the European Journal of Cancer:

E.A. Eisenhauer, P. Therasse, J. Bogaerts, L.H. Schwartz, D. Sargent, R. Ford, J. Dancey, S. Arbuck, S. Gwyther, M. Mooney, L. Rubinstein, L. Shankar, L. Dodd, R. Kaplan, D. Lacombe, J. Verweij. New response evaluation criteria in solid tumors: Revised RECIST guideline (version 1.1). Eur J Cancer. 2009 Jan;45(2):228-47.

In addition, volumetric analysis will be explored by central review for response assessment.

10.4 Immune-Related RECIST Evaluation in Solid Tumors

Immune-Related RECIST (irRECIST)

irRECIST is RECIST 1.1 adapted as described below to account for the unique tumor response seen with immuno-therapeutics. irRECIST will be used by site investigators and local radiology review to assess tumor response and progression, and make treatment decisions. This data will be collected in the clinical database.

irRECIST takes into account the clinical condition/stability of subjects, as described in the Table below, in addition to response or progression via tumor imaging.

Clinically stable is defined by the following criteria:
- Absence of symptoms and signs indicating clinically significant progression of disease, including worsening of laboratory values
- No decline in ECOG performance status
- Absence of rapid progression of disease
- Absence of progressive tumor at critical anatomical sites (e.g., cord compression) requiring urgent alternative medical intervention

Table irRECIST: Tumor Imaging and Treatment after 1st Radiologic Evidence of PD **or** SD, CR or PR

	Clinically Stable		**Clinically Unstable**	
	Imaging	Treatment	Imaging	Treatment
1st radiologic	Repeat imaging at ≥4 weeks at site to	May continue study treatment at the	Repeat imaging at ≥ 4 weeks to confirm PD	Discontinue treatment

evidence of PD	confirm PD	Investigator's discretion while awaiting confirmatory scan by site	per physician discretion only	
Repeat scan confirms PD	No additional imaging required	Discontinue treatment (exception is possible upon consultation with PI or medical monitor).	No additional imaging required	N/A
Repeat scan shows SD, PR or CR	Continue regularly scheduled imaging assessments	Continue study treatment at the Investigator's discretion	Continue regularly scheduled imaging assessments	May restart study treatment if condition has improved and/or clinically stable per Investigator's discretion. Next scan should occur according to the every 9 week (63 ± 7 days) imaging schedule.

In determining whether or not the tumor burden has increased, decreased or stayed stable, site investigators should consider all target lesions as well as non-target lesions.

Any subject deemed **clinically unstable** should be discontinued from trial treatment at first evidence of progressive disease by tumor imaging and is not required to have repeat tumor imaging for confirmation.

For a **clinically stable** subject with first radiologic evidence of progressive disease (i.e., **unconfirmed progression of disease**), it is at the discretion of the site investigator to continue treating the subject with the assigned treatment per protocol until progression of disease is confirmed at least 28 days from the date of the tumor imaging first suggesting PD. If progression is not confirmed on the subsequent tumor imaging, the subject should continue to receive study therapy and have tumor imaging performed every 9 weeks from the date of allocation (± 7 days) in the first year or every 12 weeks after the first year, or sooner if clinically indicated, to monitor disease status. If radiologic progression is confirmed by subsequent tumor imaging, then the subject will be discontinued from trial treatment.

NOTE: If a subject with confirmed progression by tumor imaging (i.e. 2 scans at least 28 days apart demonstrating progressive disease) is clinically stable or clinically improved, and there is no further increase in the tumor burden at the confirmatory scan, an exception may be considered to continue treatment upon consultation with the PI or medical monitor.

10.5Events of Clinical Interest Guidance Document -attached

10.6NYU Multi-Center Data Safety and Monitoring Plan:

The data and safety monitoring of this trial is based on the 2011 NCI (National Cancer Institute) approved Data and Safety Monitoring Plan (DSMP).

Per the NYU Perlmutter Cancer Center (NYUPCC) Institutional DSMP, this phase II trial will be monitored by the NYUPCC Date and Safety Monitoring Committee (DSMC). The DSMC is a multidisciplinary committee (consisting of clinical investigators/oncologists, biostatisticians, nurses and research administration staff knowledgeable of research methodology and design and in proper conduct of clinical trials) that is responsible for monitoring safety, conduct and compliance in accordance with protocol data monitoring plans for clinical trials conducted in the NYUPCC. The DSMC reports to the Director of the NYUPCC (Benjamin Neel, MD, PhD).

This phase II trial will be monitored by the NYUPCC DSMC annually (from the date first patient is enrolled), at the completion of DLT evaluation for the run-in phase, and at the completion of the study prior to study closure. The annual review includes accrual data, subject demographics and adverse events. Additional interim reviews can be scheduled based on SAE reports, investigator identified issues, external information, etc. Besides the annual review, new SAEs are also reviewed by the DSMC monthly. Cancer Center's Phase I/II Committee also monitors the study monthly for AEs. The annual DSMC reports will be submitted to the IRB at the time of annual review.

Record Retention

Sponsor-Investigator will retain study essential documents for at least 2 years after the completion of the study with the IRB. After this time period, study documents will be archived at an outside location for a time period of 10 years.

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