

<b>Official Protocol Title:</b>	A Phase 1b Study to Evaluate safety and clinical activity of Pembrolizumab (MK-3475) in combination with Chemotherapy as Neoadjuvant Treatment for Triple Negative Breast Cancer (TNBC) -(KEYNOTE 173)
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### SUMMARY OF CHANGES

#### PRIMARY REASON(S) FOR THIS AMENDMENT:

Section Number (s)	Section Title(s)	Description of Change (s)	Rationale
3.2	Secondary Objective(s) & Hypothesis(es)	Updated objective regarding Event Free Survival (EFS) and Overall Survival (OS), changing the start point from surgery to first dose of trial treatment.	Revised for consistency with pembrolizumab trials in the neo-adjuvant setting.
8.1, 8.2, 8.7	Multiple sections	Updated/added text to reflect interim analyses.	To evaluate safety, EFS, and OS.
8.4.3	Derivations of Efficacy/Immunogenicity/Pharmacokinetics Endpoints	Updated the definitions of EFS and OS.	Revised to align with updates to secondary objectives.
8.6.1	Statistical Methods for Efficacy Analyses	Updated the condition for sensitivity analysis of pCR.	Clarified the original requirement.
8.6.2	Statistical Methods for Safety Analysis	Deleted the text regarding AE phasing.	Revised for consistency with pembrolizumab trials in the neo-adjuvant setting.

**ADDITIONAL CHANGE(S) FOR THIS AMENDMENT:**

<b>Section Number (s)</b>	<b>Section Title (s)</b>	<b>Description of Change (s)</b>	<b>Rationale</b>
Multiple sections	Multiple sections	Minor typographical corrections/insertions.	Correct minor typographical errors for clarity and consistency.
4.1	Background	Changed language regarding approved indications	The existing statement suggested that the drug gained an indication in the US for its mechanism and not its efficacy and safety. Wording to refer to Investigator brochure added to avoid additional revisions for new approval updates.
4.2.2.2	Rationale of selecting pembrolizumab 200mg Q3W dose	Minor revision to text regarding the selection of fixed-dose regimen	Updated for consistency with pembrolizumab documents.
5.2.1.5.1	Dose Modification and Toxicity Management Guidelines for Pembrolizumab	Modified to include required discontinuation for recurrence of Grade 2 pneumonitis	Updated for consistency with pembrolizumab documents.
5.6.1	Supportive Care Guidelines for Pembrolizumab	Removed reference to ECI/ECI guidance document; update includes Grade 2 infusion reaction	Updated for consistency with pembrolizumab documents.

## 1.0 TRIAL SUMMARY

Abbreviated Title	A Phase 1b Open-Label Study to Evaluate Pembrolizumab plus Chemotherapy as Neoadjuvant Treatment for Triple Negative Breast Cancer (TNBC)
Trial Phase	1b
Clinical Indication	Neoadjuvant treatment for locally-advanced TNBC
Trial Type	Interventional
Type of control	No Treatment Control
Route of administration	Intravenous
Trial Blinding	Unblinded Open-label
Treatment Groups	<p>Cohort A (KNp / KAC): Single dose pembrolizumab (K), followed by [pembrolizumab (K) Q3W + nab-paclitaxel (Np) weekly] x 4 cycles, followed by pembrolizumab + doxorubicin + cyclophosphamide (KAC) Q3W x 4 cycles</p> <p>Cohorts B &amp; C (KNpCb / KAC): Single dose pembrolizumab (K), followed by [pembrolizumab (K) Q3W + nab-paclitaxel (Np) weekly + carboplatin (Cb) Q3W] x 4 cycles, followed by pembrolizumab + doxorubicin + cyclophosphamide (KAC) Q3W x 4 cycles.</p> <p>Cohort D (KNpCb / KAC): Single dose pembrolizumab (K), followed by [pembrolizumab (K) Q3W + nab-paclitaxel (Np) weekly + carboplatin (Cb) weekly] x 4 cycles, followed by pembrolizumab + doxorubicin + cyclophosphamide (KAC) Q3W x 4 cycles.</p> <p>Cohorts E (KTCb / KAC): Single dose pembrolizumab (K), followed by [pembrolizumab (K) Q3W + paclitaxel (T) weekly + carboplatin (Cb) Q3W] x 4 cycles, followed by pembrolizumab + doxorubicin + cyclophosphamide (KAC) Q3W x 4 cycles.</p> <p>Cohort F (KTCb / KAC): Single dose pembrolizumab (K), followed by [pembrolizumab (K) Q3W + paclitaxel (T) weekly + carboplatin (Cb) weekly] x 4 cycles, followed by pembrolizumab + doxorubicin + cyclophosphamide (KAC) Q3W x 4 cycles.</p> <p>Note: each cycle = 21 days</p>
Number of trial subjects	Approximately 100 subjects will be enrolled.
Estimated duration of trial	The Sponsor estimates that the trial will require approximately 50 months from the time the first subject signs the informed consent until the last subject's last study-related phone call or visit.
Duration of Participation	Each subject will participate in the main part of the trial for approximately 42 weeks from the time the subject signs the Informed Consent Form through the 30-day follow up visit following definitive surgery. After a screening phase of ~28 days, each subject will be receiving study treatment based on the assigned cohort and dose level for approximately 27 weeks (9 cycles). An End of Treatment/Early Discontinuation Visit will be scheduled 3-6 weeks following discontinuation of treatment but prior to definitive surgery. Each subject will undergo definitive surgery 3-6 weeks after discontinuation of trial treatment. Approximately 30 days following definitive surgery, each subject will attend a safety Follow Up Visit. Subjects will be followed for 30 days following surgery for all adverse events and 90

	days for all serious adverse events (or 30 days following definitive surgery if the subject initiates new anticancer therapy, whichever is earlier). After surgery, subject's disease follow-up (e.g. imaging assessments and clinical evaluations) and anticancer treatment for recurrent or metastatic disease will be at the discretion of subject's treating physician per local standard of care. However, the investigator or site staff will contact the subject via telephone every 12 weeks for up to 24 months to obtain information regarding subject's disease and survival status.
Randomization Ratio	N/A

A list of abbreviations used in this document can be found in Section 12.7.

## 2.0 TRIAL DESIGN

### 2.1 Trial Design

This is a Phase 1b, multi-center, open-label study to evaluate safety, tolerability and clinical activity of pembrolizumab in combination with two chemotherapy regimens as neoadjuvant treatment for triple negative breast cancer (TNBC).

A commonly used standard neoadjuvant regimen for TNBC is a weekly taxane (e.g. paclitaxel) for 12 weeks followed by an anthracycline (e.g. doxorubicin 60mg/m<sup>2</sup>) plus cyclophosphamide at 600mg/m<sup>2</sup> (AC) every 3 weeks (Q3W) for 4 cycles. The chemotherapy regimens included in this study are built upon the aforementioned regimen and on emerging clinical trial data. Pembrolizumab in combination with these regimens will be studied in the following six cohorts:

- Cohort A (KNp/ KAC): Single dose pembrolizumab (K), followed by [pembrolizumab (K) Q3W + nab-paclitaxel (Np) weekly] x 4 cycles (1 cycle = 21 days), followed by KAC Q3W x 4 cycles
- Cohorts B & C (KNpCb / KAC): Single dose pembrolizumab (K), followed by [pembrolizumab (K) Q3W + nab-paclitaxel (Np) weekly + carboplatin (Cb) Q3W] x 4 cycles, followed by pembrolizumab + doxorubicin + cyclophosphamide (KAC) Q3W x 4 cycles.
- Cohort D (KNpCb / KAC): Single dose pembrolizumab (K), followed by [pembrolizumab (K) Q3W + nab-paclitaxel (Np) weekly + carboplatin (Cb) weekly] x 4 cycles, followed by pembrolizumab + doxorubicin + cyclophosphamide (KAC) Q3W x 4 cycles. Please refer to Table 1 for specific dose levels.
- Cohorts E (KTCb / KAC): Single dose pembrolizumab (K), followed by [pembrolizumab (K) Q3W + paclitaxel (T) weekly + carboplatin (Cb) Q3W] x 4 cycles, followed by pembrolizumab + doxorubicin + cyclophosphamide (KAC) Q3W x 4 cycles.
- Cohort F (KTCb / KAC): Single dose pembrolizumab (K), followed by [pembrolizumab (K) Q3W + paclitaxel (T) weekly + carboplatin (Cb) weekly] x 4 cycles, followed by pembrolizumab + doxorubicin + cyclophosphamide (KAC) Q3W x 4 cycles.

In all six cohorts, the dose and schedule of pembrolizumab will be fixed at 200mg Q3W; and a commonly used AC dose/schedule will be used, i.e. doxorubicin 60mg/m<sup>2</sup> Q3W plus cyclophosphamide 600mg/m<sup>2</sup> Q3W. The starting dose level of nab-paclitaxel is 125mg/m<sup>2</sup> weekly in Cohorts A, C, & D and 100mg/m<sup>2</sup> weekly in Cohort B. The starting dose level of paclitaxel is 80mg/m<sup>2</sup> weekly in Cohorts E and F. The starting dose level for carboplatin is AUC 6 Q3W in Cohort B, AUC 5 Q3W in Cohort C and E and AUC 2 QW in Cohorts D and F.

The study includes two parts. Part 1 is to determine a recommended Phase 2 dose (RP2D) of the combination regimen for Cohorts A, B, C, D, E and F respectively. Part 2 will consist of the expansion of the appropriate RP2D Cohort as defined in Section 5.2.1.2.



**Predefined Dose Levels for Cohorts A, B, C, D, E and F**

Predefined dose levels for Cohort A to F are shown in [Table 1](#).

Table 1 Dose levels in Cohorts A, B, C, D, E and F

Dose Level (DL)	Regimen Code	Dose levels for KNp or KNpCb	Dose levels for KAC	
<b>Cohort A</b>				
DL1*	KNp125 / KAC	K: 200 mg Q3W x 4 cycles Np: 125 mg/m <sup>2</sup> weekly x 12 wks	K: 200 mg Q3W x 4 cycles A: 60 mg/m <sup>2</sup> x 4 cycles C: 600 mg/m <sup>2</sup> x 4 cycles	
DL -1	KNp100 / KAC	K: 200 mg Q3W x 4 cycles Np: 100 mg/m <sup>2</sup> weekly x 12 wks		
<b>Cohort B</b>				
DL1	KNp100CbAUC6 / KAC	K: 200 mg Q3W x 4 cycles Np: 100 mg/m <sup>2</sup> weekly x 12 wks Cb: AUC6 Q3W x 4 cycles		
<b>Cohort C</b>				
DL1*	KNp125CbAUC5 / KAC	K: 200 mg Q3W x 4 cycles Np: 125 mg/m <sup>2</sup> weekly x 12 wks Cb: AUC5 Q3W x 4 cycles		
DL -1	KNp100CbAUC5 / KAC	K: 200 mg Q3W x 4 cycles Np: 100 mg/m <sup>2</sup> weekly x 12 wks Cb: AUC5 Q3W x 4 cycles		
<b>Cohort D</b>				
DL1*	KNp125CbAUC2 / KAC	K: 200 mg Q3W x 4 cycles Np: 125 mg/m <sup>2</sup> weekly x 12 wks Cb: AUC2 weekly x 12 wks		
DL -1	KNp125CbAUC1.5 / KAC	K: 200 mg Q3W x 4 cycles Np: 125 mg/m <sup>2</sup> weekly x 12 wks Cb: AUC1.5 weekly x 12 wks		
<b>Cohort E</b>				
DL1*	KP80CbAUC5 / KAC	K: 200 mg Q3W x 4 cycles T: 80 mg/m <sup>2</sup> weekly x 12 wks Cb: AUC5 Q3W x 4 cycles		
DL -1	KP70CbAUC5 / KAC	K: 200 mg Q3W x 4 cycles T: 70 mg/m <sup>2</sup> weekly x 12 wks Cb: AUC5 Q3W x 4 cycles		

Dose Level (DL)	Regimen Code	Dose levels for KNp or KNpCb	Dose levels for KAC
<b>Cohort F</b>			
DL1*	KP80CbAUC2 / KAC	K: 200 mg Q3W x 4 cycles T: 80 mg/m <sup>2</sup> weekly x 12 wks Cb: AUC2 weekly x 12 wks	
DL -1	KP80CbAUC1.5 / KAC	K: 200 mg Q3W x 4 cycles T: 70 mg/m <sup>2</sup> weekly x 12 wks Cb: AUC1.5 weekly x 12 wks	

\* Note that DL1 is the starting dose level.

K=pembrolizumab; Np=nab-paclitaxel; T= paclitaxel Cb=carboplatin; AC=doxorubicin+cyclophosphamide; Q3W=every 3 weeks.

### Regimen Dose Finding Decision

The tolerability of each regimen dose level will be evaluated based on the assessment of dose limiting toxicities (DLTs). The decisions to stay at or de-escalate a dose level will depend on the evaluation of DLTs during the DLT evaluation period of the first part of the combinations in all cohorts which is defined as from Day 1 of Cycle 1 through the end of Cycle 3. Tolerability of KAC will be evaluated based on the DLT rates of subjects treated during the DLT evaluation period for KAC, which is defined as from Day 1 of Cycle 6 through the end of Cycle 7. Detailed dose finding rules are provided in Section 5.2.1.2; DLT criteria are provided in Section 5.2.1.3.

The study is enrolling Cohorts C and D. Cohorts E and F will begin enrollment simultaneously upon approval of Amendment 04. Each group will enroll 10 subjects and eligible subjects will be randomly assigned to one of these groups. Decisions regarding de-escalation will be based on evaluating DLTs in accordance with the rules described in Section 5.2.1.2. Cohorts A and B have completed enrollment of 10 subjects. Cohorts C, D, E and F may be expanded depending on the demonstrated efficacy.

Regardless of which cohort or regimen dose level that a subject has been assigned, each subject will first receive a single dose of pembrolizumab 200mg as Cycle 1, followed by 4 cycles of KNp (Cohort A), KNpCb (Cohorts B, C, and D) or KTCb (Cohorts E and F) as Cycle 2 to Cycle 5, and then followed by 4 cycles of KAC as Cycle 6 to Cycle 9. Addition of one cycle of pembrolizumab alone allows for evaluation of potential early changes in the tumor after exposure to pembrolizumab.

**Confirmation of TNBC Status:** Subject’s TNBC status for eligibility at Screening will be based on the evaluation by the local pathologist in accordance with the criteria described in Section 5.1.2. However, a formalin-fixed paraffin-embedded (FFPE) tumor tissue sample or slides obtained at subject’s initial diagnosis must be submitted to a designated central laboratory for retrospective confirmation of subject’s TNBC status.

**Tumor biopsy for Translational Research:** All subjects are required to have 2 separate tumor core needle biopsies, utilizing multiple passes, at Screening after all other eligibility

criteria have been met and at end of Cycle 1 following the first dose of pembrolizumab. The biopsy at the end of Cycle 1 is required but only to be performed if there is adequate tumor volume left as determined by the investigator. For subjects with adequate tumor volume left at the end of Cycle 3 as assessed by the investigator, an additional core needle biopsy will be performed only on subjects who agree to participate. Tumor tissue samples will also be collected at definitive surgery for subjects who have not achieved pathological complete response (pCR) at that time. All tumor tissue samples collected at different time points during the study will be submitted to the designated central laboratories for translational research as described in more detail in Section 7.1.2.

**Breast MRI:** Breast MRI will be performed at Screening for more accurate clinical staging of the primary tumor and axilla lymphadenopathy. Breast MRI are also performed at the end of Cycle 5 following treatment with the first combination regimen (KNp, KNpCb or KTCb), and after completion of the second combination regimen (KAC; Cycle 9) but prior to surgery. Changes from the baseline will be assessed by the investigator per RECIST 1.1.

**Definitive surgery:** Definitive surgery will be performed as part of the local standard of care (SOC) approximately 3-6 weeks following the completion or early discontinuation of the study treatments. A thorough evaluation of breast cancer status, pathological staging per American Joint Committee of Cancer (AJCC) Breast Cancer Staging version 7 and assessment of surgical margins will be performed by local pathologist on all the tissues removed during the surgery.

Safety will be monitored as outlined in the Trial Flow Chart in Section 6 and described in more detail in Section 7.2. An End of Treatment/Early Discontinuation Visit will be scheduled 3-6 weeks following discontinuation of treatment and prior to definitive surgery. Adverse events (AEs) will be monitored throughout the trial and graded according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 (See Appendix 12.5). A Safety Follow-up Visit will be scheduled approximately 30 days following definitive surgery. Thereafter, subjects will be followed by telephone contact every 12 weeks ( $\pm 2$  weeks) to obtain information regarding subject's disease and survival status. Disease follow-up and anticancer treatment for recurrent or metastatic disease will be at the discretion of subject's treating physician per local SOC.

The study will be conducted in conformance with Good Clinical Practices.

Specific procedures to be performed during the trial, as well as their prescribed times and associated visit windows, are outlined in the Trial Flow Chart - Section 6.0. Details of each procedure are provided in Section 7.0 – Trial Procedures.

## **2.2 Trial Diagram**

The trial design is depicted in [Figure 1](#).

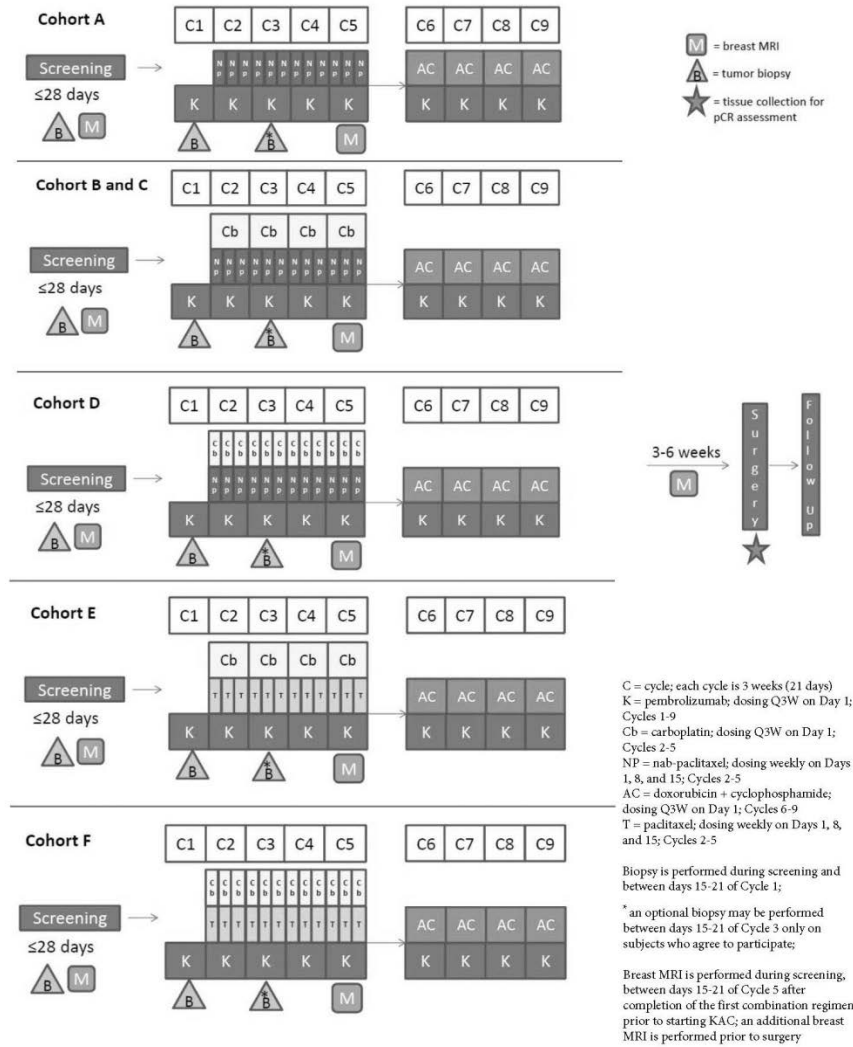


Figure 1 Trial Diagram

### 3.0 OBJECTIVE(S) & HYPOTHESIS(ES)

#### 3.1 Primary Objective(s) & Hypothesis(es)

- 1) **Objective (Cohort A):** To determine the safety and tolerability and to establish an RP2D for the combination regimen KNp/KAC as a neoadjuvant treatment for subjects with locally-advanced TNBC.
- 2) **Objective (Cohorts B, C, and D):** To determine the safety and tolerability and to establish an RP2D for the combination regimen KNpCb/KAC as a neoadjuvant treatment for subjects with locally-advanced TNBC.
- 3) **Objective (Cohorts E and F):** To determine the safety and tolerability and to establish an RP2D for the combination regimen KTCb/KAC as a neoadjuvant treatment for subjects with locally-advanced TNBC.

### **3.2 Secondary Objective(s) & Hypothesis(es)**

- 1) **Objective:** To evaluate the rate of pCR using the definition of ypT0 ypN0 (i.e. no invasive or noninvasive residual in breast or nodes) as assessed by the local pathologist at the time of definitive surgery in TNBC subjects treated with KNp/KAC (Cohort A), KNpCb/KAC (Cohorts B, C, and D) or KTCb/KAC (Cohorts E and F) as a neoadjuvant regimen at RP2D.
- 2) **Objective:** To evaluate the rate of pCR using an alternative definition, ypT0/Tis ypN0 (i.e. no invasive residual in breast or nodes; noninvasive breast residuals allowed) as assessed by local pathologist at the time of definitive surgery in TNBC subjects treated with KNp/KAC (Cohort A), KNpCb/KAC (Cohorts B, C, and D) or KTCb/KAC (Cohorts E and F) as a neoadjuvant regimen at RP2D.
- 3) **Objective:** To evaluate the objective response rate (ORR) using RECIST1.1 as assessed by site radiology review after completion of the first combination regimen (KNp,KNpCb or KTCb), and after completion of the second combination regimen (KAC) in Cohorts A, B, C, D, E and F in subjects who started with RP2D.
- 4) **Objective:** To evaluate the 6 month, 12 month and 24 month event free survival (EFS) rate from first dose of trial treatment as assessed by investigator per local SOC and 6 month, 12 month and 24 month overall survival (OS) rate from first dose of trial treatment in TNBC subjects treated with the RP2D KNp/KAC (Cohort A), KNpCb/KAC (Cohorts B, C, and D) or KTCb/KAC (Cohorts E and F).

### **3.3 Exploratory Objectives**

#### **1) Objectives for translational research:**

- To characterize the tumor microenvironments before treatment, changes after a single dose of pembrolizumab and after the combinations, this may include presence and changes of tumor infiltrating T lymphocytes (TILs), immune-related mRNA expression signatures, and PD-L1 expression.
- To perform tumor genetic profiling such as genetic testing for mutational burden based on tumor samples collected at Screening.

Additional translational research may include T cell clonality, neoantigen expression, presence and changes in circulating tumor markers such as ctDNA, and serum miRNA and protein changes at Screening and following treatment.

Correlation of clinical response (pCR and ORR) to tumor/ circulating markers at Screening and after treatments may be evaluated.

#### **2) Objective for pharmacogenetic research:**

- To explore the relationship between genetic variation and response to the treatment(s) administered. Variation across the human genome will be analyzed for association with clinical data collected in this study.

## **4.0 BACKGROUND & RATIONALE**

### **4.1 Background**

Pembrolizumab is a potent humanized immunoglobulin G4 (IgG4) monoclonal antibody (mAb) with high specificity of binding to the programmed cell death 1 (PD 1) receptor, thus inhibiting its interaction with programmed cell death ligand 1 (PD-L1) and programmed cell death ligand 2 (PD-L2). Based on preclinical in vitro data, pembrolizumab has high affinity and potent receptor blocking activity for PD 1. Pembrolizumab has an acceptable preclinical safety profile and is in clinical development as an intravenous (IV) immunotherapy for advanced malignancies. Keytruda™ (pembrolizumab) is indicated for the treatment of patients across a number of indications. For more details on specific indications refer to the Investigator's brochure.

#### **4.1.1 Pharmaceutical and Therapeutic Background**

##### **4.1.1.1 Disease Background**

Breast cancer is the most commonly diagnosed malignancy and the second leading cause of cancer death in women. In the United States, the estimated number of new cases and death from breast cancer in 2014 is approximately 232,670 and 40,000, respectively [1]. TNBC, which is phenotypically defined by lack of estrogen receptor (ER) and progesterone receptor (PR) expression, and the absence of human epidermal growth factor receptor-2 (HER2) overexpression and/or amplification, accounts for approximately 15%-20% of all breast cancers [2].

Compared to other breast cancer subtypes, TNBC is associated with younger age and more advanced tumor stage at diagnosis, African American race/ethnicity, higher tumor grade and poorer overall survival; TNBC is also associated with a higher risk of disease recurrence and higher recurrence in viscera within 5 years of diagnosis [3, 4].

TNBC is a heterogeneous disease with distinct pathological, genetic and clinical features among subtypes. Recent gene expression profiling has identified six distinct TNBC subtypes including two basal-like, an immunomodulatory, a mesenchymal, a mesenchymal stem-like, and a luminal androgen receptor subtype. They have different prognosis and sensitivity to treatments, for example, basal-like tumors are highly sensitive to platinum treatment [2]. Molecular characterization of basal vs. non-basal-like TNBC by Prat et al using two large datasets showed that 78.6% TNBC are basal-like while 68.5% basal-like tumors are TNBC, indicating a large overlap between the two [5]. Another finding from molecular characterization is that the majority of BRCA1 germline mutation carriers, when develop breast cancer, will develop basal-like subtype of TNBC; and the prevalence of BRCA1 in TNBC is around 10-20% [6, 7].

##### **4.1.1.2 Current and Emerging Neoadjuvant Treatments for TNBC**

Neoadjuvant chemotherapy with anthracycline/taxane-based regimen has been considered an important part of treatment strategy for patients with locally advanced TNBC [8, NCCN

guideline for invasive breast cancer version 1.2015]. Early prospective observational studies evaluating outcome of neoadjuvant chemotherapy in different breast cancer subtypes revealed that TNBC was more chemosensitive compared to non-TNBC, in particular, compared to the ER+/Her2- (luminal) subtype, with substantially increased pCR rate and clinical response rate. However, patients with TNBC had poorer prognosis as a group with significantly higher disease recurrence rate and low survival rate. The poor long term outcome in TNBC was found to be driven by those without achieving pCR after neoadjuvant chemotherapy. Patients who achieved pCR demonstrated sustained clinical benefit regardless of breast cancer subtypes [9, 10]. Recent reports of a large pooled analysis demonstrated strong association of pCR, when defined as no tumor in both breast and lymph nodes (ypT0 ypN0 or ypT0/is yp N0) following neoadjuvant therapy for breast cancer, with improved long-term benefit as measured by event-free survival and overall survival. Furthermore, this association was found to be strongest in patients with TNBC [11]. These findings have led to increased efforts in identifying new drugs and drug combinations that can deliver higher pCR in TNBC. Recent studies evaluating carboplatin and nab-paclitaxel in the neoadjuvant TNBC setting have shown some interesting results.

In a randomized Phase III study (GeparSepto) comparing weekly nab-paclitaxel 150mg/m<sup>2</sup>/125mg/m<sup>2</sup> with weekly paclitaxel 80mg/m<sup>2</sup> for 12 weeks with both arms followed by epirubicin 90mg/m<sup>2</sup> plus cyclophosphamide 600mg/m<sup>2</sup> Q3W for 4 cycles as neoadjuvant treatment for breast cancer, the pCR (ypT0 ypN0) in the TNBC subgroup was 48.2% in those who received nab-paclitaxel compared with 25.7% (p<0.001) in those who received paclitaxel [12]. The initial dose of nab-paclitaxel was 150mg/m<sup>2</sup> weekly. The dose was subsequently reduced to 125mg/m<sup>2</sup> weekly due to toxicity with 400/1200 enrolled subjects received 150mg/m<sup>2</sup> dose. The combined data showed that nab-paclitaxel was associated with a significantly higher rate of peripheral sensory neuropathy compared to paclitaxel 80mg/m<sup>2</sup> (62.3% vs. 42.1% for all grade, 39.6% vs. 31.6% for grade 1, 17% vs. 5.3% for grade 2, 5.7% vs. 5.3% for grade 3 (no grade 4 events).

Two randomized studies have shown significantly increased pCR by adding carboplatin to an anthracycline/taxane-based neoadjuvant regimen in TNBC. In the GeparSixto trial, a randomized Phase II study which enrolled a subset of patients with previously untreated stage II/III TNBC, addition of weekly carboplatin (1.5-2AUC) to the triple combination of weekly paclitaxel (80mg/m<sup>2</sup>) plus weekly non-pegylated liposomal doxorubicin (20mg/m<sup>2</sup>) plus Q3W bevacizumab (15mg/kg) for a total of 6 cycles, showed increased pCR (defined as ypT0 ypN0) from 36.9% to 53.2% (p = 0.005) [13]. Compared to patients without carboplatin, the following AEs were significantly higher in those who received carboplatin: grade 3/4 neutropenia (65% vs. 27%), grade 3/4 anemia (15% vs. < 1%), grade 3/4 thrombocytopenia (14% vs. <1%) and grade 3/4 diarrhea (17% vs. 11%). These hematological and non-hematological toxicities reduced when the dose of carboplatin was changed from AUC2 to AUC1.5.

In a randomized Phase III study (CALGB 40603) that evaluated the addition of carboplatin or/and bevacizumab to the standard neoadjuvant treatment for TNBC (paclitaxel 80mg/m<sup>2</sup> weekly for 12 weeks followed by doxorubicin plus cyclophosphamide Q2W for 4 cycles), addition of carboplatin Q3W at AUC6 to weekly paclitaxel vs. weekly paclitaxel alone significantly increased pCR rate for breast (defined as ypT0/is) from 42% to 53%, and pCR rate of breast/axilla (defined as ypT0/Tis ypN0) from 39% to 49% [14]. In this study,

addition of Q3W carboplatin at AUC6 showed significantly increased Grade 3/4 neutropenia (56% vs. 22%), and Grade 3/4 thrombocytopenia (20% vs. 4%). In a meta-analysis evaluating the value of platinum agents as neoadjuvant treatment for TNBC based on data pooled from 6 randomized studies and 22 retrospective studies, the pooled pCR rate in patients who received platinum treatments was 45%. Data from the 6 randomized trials showed a relative risk of 1.45 (95% CI, 1.25-1.68,  $p < 0.0001$ ) of not having a pCR in those who patients who received no platinum treatment [15].

#### **4.1.1.3 Targeting PD-1 immune checkpoints for cancer treatment**

It is widely accepted that cancer cells carry tumor-specific or tumor-associated antigens and therefore are immunogenic and subject to immune surveillance of the human body [16]. However, cancer cells can often escape immune system's surveillance and control via various mechanisms and progress into clinically evident disease, a process called cancer immunoediting [17, 18]. The ability of human cancer to evade the immune system's destruction has recently been recognized as an emerging hallmark of cancer [19].

In the adaptive immune system, cytotoxic T lymphocytes cells (CTLs, also called CD8+ or effector T cells) can recognize foreign antigens presented on the surface of antigen presenting cells (APC) via T cell receptor (TCR) and become activated executing the cell killing function. TCR-mediated T cell activations are tightly controlled by co-stimulatory and co-inhibitory signals or pathways that are triggered by the interactions between T cell surface receptors and their ligands. These inhibitory pathways, also called immune checkpoints, are crucial for maintaining self-tolerance and minimizing collateral tissue damage in the event of immune response to pathogens [20]. Cancer can exploit immune checkpoint pathways as one of the key mechanisms to avoid being detected and destroyed. Therefore, restoration of endogenous anti-cancer immunity by immune checkpoint blockade has become an attractive strategy of cancer immunotherapy [20, 21, 22].

Among many of the agents in clinical development that target immune checkpoint pathways, those that target pathways controlled by programmed cell death protein 1 (PD-1) and cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) are the most advanced and have shown unprecedented clinical anticancer activities and durable responses across multiple solid tumors [20, 23, 24, 25]. Two immune checkpoint inhibiting agents have been approved by the US Food and Drug Administration (FDA) for treating advanced melanoma: ipilimumab, a full human anti-CTLA-4 monoclonal antibody (mAb), and pembrolizumab (MK-3475), a humanized mAb targeting PD-1 [see details in Yervoy® US label, Keytruda® US Label]. In addition, nivolumab, a full human mAb targeting PD-1, has recently been approved for treating melanoma and advanced non-small cell lung cancer (NSCLC) [see details in Opdivo® US label].

PD-1 is a member of the extended CD28/CTLA-4 family of T cell regulators. It is a transmembrane receptor including an extracellular domain that resembles the immunoglobulin variable region, a transmembrane region, and an intracellular tail that contains separate potential phosphorylation sites for signaling. Binding of PD-1 to its ligands PD-L1 (also named B7-H1) and/or PD-L2 (also named B7-DC) will trigger downstream signaling inside T cells leading to decreased cytokine production such as IL-2, inhibition of cell proliferation, reduced T cell effector function and survival [20, 24, 26]. Unlike CTLA-4 which modulates the early phase of activation of naïve or memory T cells, PD-1 is expressed



on antigen-experienced T cells in the peripheral tissues and therefore regulates the effector phase of the T-cell activity [20, 23].

#### **4.1.1.4 Targeting PD-1 immune checkpoints for TNBC**

Several studies have demonstrated that the presence of TILs correlated with better prognosis in TNBC, independent of systemic therapy [27, 28]. In addition, unsupervised gene expression profiling of TNBCs has identified a gene signature enriched for cytotoxic CD8+ T cell genes and natural killer cell (NKC) activity, which is predictive of good clinical outcome [29]. These findings suggest an active role of acquired immunity in concurring TNBC [30].

PD-L1, which is not detected in normal breast tissue, has been reported to be expressed in about half of all breast cancers, particularly in HR-negative, high grade and proliferative tumors [31]. The presence of Treg cells, tumor PD-L1 expression, and PD-1–positive TILs has been associated with high histologic grade, ER negativity, and prominent tumor lymphocytic infiltration [31]. A recent publication reported that PD-L1 messenger ribonucleic acid (mRNA) is expressed in nearly 60% of breast tumors, independently of HR status, and is positively correlated with PD-L1 protein expression and increased TILs [32]. Another study mining the Cancer Genome Atlas (TCGA) RNA sequencing data showed that PD-L1 gene expression is significantly higher in TNBCs compared to non-TNBCs, and is associated with Phosphatase and TEnsin Homolog (PTEN) loss; in the same study, PD-L1 was found expressed in 20% of TNBCs [33]. This evidence demonstrates that TNBCs are characterized by PD-L1 positivity and presence of TILs, and thus suggest that PD-1 immune checkpoint inhibition is a therapeutic strategy worthy of further investigation for the treatment of this aggressive breast cancer subtype.

#### **4.1.2 Summary of Pembrolizumab Clinical Activities**

Pembrolizumab is a potent and highly selective humanized mAb of the IgG4/kappa isotype designed to directly block the interaction between PD-1 and its ligands, PD-L1 and PD-L2. Details regarding preclinical and clinical pharmacology studies can be found in pembrolizumab clinical investigator brochure and the US label.

##### **4.1.2.1 Summary of Pembrolizumab Clinical Activities in solid tumors**

As of 06-Jan-2015, approximately 8,000 patients have been treated with pembrolizumab in Merck-sponsored clinical trials and the melanoma Expanded Access Program. In addition, the worldwide post-marketing distribution of pembrolizumab through 31-Dec-2014 was 29,312 vials, which equates to approximately 2,840 patients. Pembrolizumab has been generally well tolerated, as expected based on preclinical findings and data from other anti-PD-1 monoclonal antibodies. Pharmacokinetics were as expected, based on pembrolizumab being an IgG mAb and based on preclinical data, which support dosing once every 2 or 3 weeks. Detailed study results are outlined in the Investigator Brochure, version 9 (May 2015).

Study KN001 is the first time in human Phase I study evaluating safety, pharmacokinetics and clinical activity of pembrolizumab, which is still on-going. The trial has been conducted in subjects with advanced melanoma and NSCLC. The cumulative evidence of high anti-cancer activities and acceptable safety profile has led to the accelerated approval of

pembrolizumab by the FDA for the treatment of patients with unresectable or metastatic melanoma and disease progression following ipilimumab and, if BRAF V600 mutation positive, a BRAF inhibitor [Keytruda US label]. A dose of 2mg/kg Q3W is the recommended dose in the pembrolizumab label.

In KN001 pembrolizumab monotherapy induced an ORR of 21% in patients with previously-treated NSCLC based on RECIST 1.1 as assessed by independent radiology review. Similar to melanoma, the responses in NSCLC were remarkably durable. Higher levels of PD-L1 expression in tumors of NSCLC were associated with increased activity (ORR 57% based on RECIST v.1.1 as assessed by independent radiology review); however, additional data are required to define the optimal PD-L1 cut point.

In addition, in KN001, in naïve and previously-treated patients with advanced NSCLC, pembrolizumab monotherapy, in an analysis of 313 patients from a validation data set for tumor PD-L1 expression, showed an ORR of 45.2 percent (95% CI, 33.5-57.3) in patients with  $\geq 50\%$  of tumor cells positive for PD-L1 expression (n = 73). In the other PD-L1 subgroups, ORR was 16.5% (95% CI, 9.9-25.1) in patients with 1-49% tumor cells positive (n = 103) and an ORR of 10.7% (95% CI, 2.3-28.2) in patients with  $< 1\%$  tumor cells positive (n = 28) for PD-L1 expression. In the total study population, ORR was 19.4 percent (95% CI, 16.0-23.2) (N = 495), which was consistent with data previously presented from this study.

#### **4.1.2.2 Summary of pembrolizumab clinical activity in metastatic TNBC**

In Study KN012, a cohort of 32 female patients with metastatic TNBC, PD-L1 positivity (defined as PD-L1 expression in  $\geq 1\%$  tumor cells or in stroma, using a prototype assay and the 22C3 antibody) was enrolled and received pembrolizumab 10mg/kg Q2W dose. Subjects with a median age of 51.9 years (range 29-72 years) and PD-L1 (+) metastatic TNBC (mTNBC) were enrolled in the study. The currently available prevalence of PD-L1 positivity in mTNBC is 58%, as determined by this study KN012. Most of these patients had received and progressed on multiple lines of therapy for advanced disease (median number of prior treatments for metastatic disease was 3). Based on a data cutoff of 06-Nov-2014, five patients (15.6%) experienced at least one drug-related serious adverse event (SAE); each of four patients experienced one of the following: Grade 3 anemia, headache, aseptic meningitis or pyrexia, and a fifth patient experienced Grade 5 disseminated intravascular coagulation with thrombocytopenia and decreased blood fibrinogen. Of the 27 patients with centrally confirmed measurable disease, one patient (3.7%) had a complete response (CR), 4 patients (14.8%) had a confirmed partial response (PR), 25.9% had stable disease (SD), and 44.4% had progressive disease (PD), as assessed by the central imaging vendor. At this cutoff, the median duration of response had not been reached (range 15 to 40+ weeks), and three patients (1 CR; 2 PR) were still on treatment after at least 11 months. Given that the current systemic treatments had little effect in this setting, this result looks very promising.

## **4.2 Rationale**

### **4.2.1 Rationale for the Trial and Selected Subject Population**

It is well known that TNBC has the worst prognosis and is the most difficult to treat among the breast cancer subtypes. Due to lack of specific molecular targets, treatment of TNBC has

been relying on chemotherapy, in particular, regimens based on the combination of anthracycline and taxanes. The effect of chemotherapy in the metastatic setting has been poor. Even though TNBC is considered chemosensitive compared to other breast cancer subtypes in the early setting, disease recurrence rate with the current regimen is still high and those with recurrent disease have a very poor outcome. Therefore TNBC is a disease with high unmet medical need.

Neoadjuvant treatment is an important part of the treatment strategy for locally advanced TNBC due to having established a positive and significant correlation of pCR with long-term clinical benefit such as event-free survival and overall survival as shown via large meta-analysis [11]. Much effort has been made to identify novel agents and new drug combinations that can improve pCR rates in this setting, which is the rationale to evaluate pembrolizumab, a novel immunotherapeutic agent, in combination with new chemotherapeutic regimens.

## **4.2.2 Rationale for Dose Selection/Regimen**

### **4.2.2.1 Rationale for Testing Pembrolizumab in combination with the selected TNBC neoadjuvant regimens**

The rationale for testing pembrolizumab in combination with the selected chemotherapy regimens are as follows:

1. Pembrolizumab functions as an immune checkpoint blockade by targeting PD-1, which helps to restore the endogenous anti-cancer immunity. Pembrolizumab has shown significant clinical anti-cancer activity across multiple tumor types including melanoma, NSCLC, Head and Neck cancer, bladder cancer and has gained FDA approval for treating advanced melanoma. Preliminary data has also shown promising clinical activity of pembrolizumab in metastatic TNBC patients who have failed multiple prior treatments. Therefore further testing of pembrolizumab in both the metastatic and early stage such as a neoadjuvant setting is warranted.
2. Weekly nab-paclitaxel followed by epirubicin and cyclophosphamide as neoadjuvant treatment has shown a significantly improved pCR rate compared with the standard weekly paclitaxel followed by epirubicin and cyclophosphamide in the TNBC subgroup of the Phase III randomized study, GeparSepto. In this study, 2/3 of the TNBC subjects received 125mg/m<sup>2</sup> weekly nab-paclitaxel and 1/3 of the TNBC subjects received 150mg/m<sup>2</sup> weekly nab-paclitaxel [12]. The pCR rate was 48.2% in the TNBC subgroup who received nab-paclitaxel compared with 25.7% (p<0.001) in those who received paclitaxel (pCR in this trial was defined as ypT0 ypN0). Therefore nab-paclitaxel can be a more interesting combination partner. The safety profile of weekly nab-paclitaxel at 125mg/m<sup>2</sup> is expected to be better than what was shown in the GeparSepto study, which has a combined safety profile of all treated subjects. Overlapping toxicities of pembrolizumab and nab-paclitaxel are not expected. It is worth noting that nab-paclitaxel has not been approved by regulatory authorities as a treatment for neoadjuvant TNBC nor has it been recommended as a treatment option by the NCCN or ESMO guidelines for the neoadjuvant TNBC indication.

3. Carboplatin in combination with weekly paclitaxel at 80mg/m<sup>2</sup> versus paclitaxel alone followed by the standard anthracycline/cyclophosphamide combination has shown increased pCR rates as neoadjuvant treatment for TNBC via 2 randomized trials using either weekly carboplatin at AUC 1.5 – 2 [the Phase II GeparSixto trial, 13] or carboplatin at AUC6 Q3W [the Phase III CALGB 40603 trial, 14]. A meta-analysis by Petrelli et al to compare TNBC patients who received carboplatin vs. those who did not receive carboplatin in the neoadjuvant setting, showed the risk of not having a pCR for those without carboplatin was 1.45 (95% CI, 1.25-1.68, p<0.0001) [15] compared to those who have received carboplatin. These data provide a good rationale for carboplatin to be included as part of the neoadjuvant combination regimen. In this study, nab-paclitaxel and carboplatin have been selected as a novel combination regimen to be combined with pembrolizumab. This new combination is expected to produce a higher pCR rate, if tolerated. It is worth noting that the combination of nab-paclitaxel and carboplatin has neither been evaluated clinically in the neoadjuvant nor metastatic setting for TNBC.
4. Pembrolizumab relies on a functional immune system to exert its anti-tumor effect. Theoretically, an even greater tumor cell reduction might be achieved by enhancing the antigen presentation via administration of pembrolizumab in combination with standard cytotoxic chemotherapy, provided that the immune suppression by some of these agents (e.g. carboplatin and cyclophosphamide) do not significantly compromise the anti-tumor effect of pembrolizumab. Optimal supportive care may alleviate some of these potential negative impacts.

#### **4.2.2.2 Rationale of selecting pembrolizumab 200mg Q3W dose**

The dose of pembrolizumab planned to be studied in this trial is 200mg Q3W. A 2mg/kg Q3W dose is approved for metastatic melanoma in some countries. Information on the rationale for selecting 200mg Q3W is summarized below.

An open-label Phase I trial (KN001) is being conducted to evaluate the safety and clinical activity of single agent pembrolizumab. The dose escalation portion of this trial evaluated three dose levels, 1mg/kg, 3mg/kg, and 10mg/kg, administered every 2 weeks (Q2W) and dose expansion cohort evaluated 2mg/kg Q3W and 10mg/kg Q3W in subjects with advanced solid tumors. All dose levels were well tolerated and no dose-limiting toxicities were observed. This first in human study of pembrolizumab showed evidence of target engagement and objective evidence of tumor size reduction at all dose levels. No Maximum Tolerated Dose (MTD) has been identified.

In KN001, two randomized cohort evaluations (Cohorts B2 and D) of melanoma subjects receiving pembrolizumab at a dose of 2mg/kg Q3W versus 10mg/kg Q3W have been completed, and one randomized Cohort (Cohort B3) evaluating 10mg/kg Q3W versus 10mg/kg Q2W has also been completed. The clinical efficacy and safety data demonstrate a lack of clinically important differences in efficacy or safety profile at these doses. For example, in Cohort B2, advanced melanoma subjects who had received prior ipilimumab therapy were randomized to receive pembrolizumab at 2mg/kg Q3W versus 10mg/kg Q3W, and the ORR was 28% (22/79) in the 2mg/kg Q3W group and 28% (21/76) in the 10mg/kg Q3W group (per RECIST 1.1 by independent central review). The proportion of subjects

with drug-related AEs, grade 3-5 drug-related AEs, serious drug-related AEs, death or discontinuation due to an AE was comparable between groups. Cohort D, which compared 2mg/kg Q3W versus 10mg/kg Q3W in advanced melanoma subjects naïve to ipilimumab, also demonstrated overall similarity in efficacy and safety profiles between two doses. In Cohort B3, advanced melanoma subjects (irrespective of prior ipilimumab therapy) were randomized to receive pembrolizumab at 10mg/kg Q2W versus 10 mg/kg Q3W. The results demonstrate that the ORR was 35.0% (41/117) in the 10mg/kg Q2W group and 30.8% (33/107) in the 10mg/kg Q3W group (per RECIST 1.1 by independent central review) (cut-off date of 18-April-2014). The proportion of subjects with drug-related AEs, Grade 3-5 drug-related AEs, serious drug related AEs, death or discontinuation due to an AE was comparable between groups.

An integrated body of evidence suggests that 200mg Q3W is expected to provide similar response to 2mg/kg Q3W, 10mg/kg Q3W and 10mg/kg Q2W. Previously, a flat pembrolizumab exposure-response relationship for efficacy and safety has been found in subjects with melanoma in the range of doses between 2mg/kg and 10mg/kg. Exposures for 200mg Q3W are expected to lie within this range and will be close to those obtained with 2mg/kg Q3W dose.

A population PK model, which characterized the influence of body weight and other patient covariates on exposure, has been developed using available data from 1139 subjects from PN001, of which the majority (94.6% [N=1077]) were patients with advanced melanoma. The distribution of exposures from the 200 mg fixed dose are predicted to considerably overlap those obtained with the 2mg/kg dose and importantly will maintain individual patient exposures within the exposure range established in melanoma as associated with maximal clinical response. Additionally, this comparison also demonstrates that the 200mg Q3W regimen provides no substantive differences in pharmacokinetic variability (range of the distribution of individual exposures) as seen with weight-based dosing.

In translating to other solid tumor indications, similarly flat exposure-response relationships for efficacy and safety as observed in subjects with melanoma can be expected, as the anti-tumor effect of pembrolizumab is driven through immune system activation rather than through a direct interaction with tumor cells, rendering it independent of the specific tumor type. In addition, available pharmacokinetic results in subjects with melanoma, NSCLC, and other solid tumor types support a lack of meaningful difference in pharmacokinetic exposures obtained at tested doses among tumor types. Thus, the 200 mg Q3W fixed dose regimen is considered an appropriate fixed dose for other solid tumor indications as well.

Taken together, the choice of 200mg Q3W as an appropriate dose is based on simulations performed using the population PK model of pembrolizumab showing that the fixed dose of 200mg Q3W will provide exposures that 1) are optimally consistent with those obtained with 2mg/kg dose Q3W; 2) body weight based dosing does not provide an advantage over fixed dosing and that both dosing strategies should provide adequate and similar control of PK variability; 3) will maintain individual patient exposures in the exposure range established in melanoma as associated with maximal efficacy response; 4) will maintain individual patients exposure in the exposure range established in melanoma that are well tolerated and safe; and

5) the dynamics of pembrolizumab target engagement would not vary meaningfully with tumor type.

A fixed-dose regimen is expected to simplify the dosing regimen (potentially reducing dosing errors), as well as be more convenient for physicians. A fixed dosing scheme will also reduce complexity in the logistical chain at treatment facilities, as well as reducing waste.

#### **4.2.2.3 Starting Dose for This Trial**

KNp125 followed by KAC (Cohort A Dose Level 1) and KNp100CbAUC6 followed by KAC (Cohort B Dose Level 1) have completed enrollment. KNp125CbAUC5 followed by KAC (Cohorts C Dose Level 1) and KNp125CbAUC2 followed by KAC (Cohort D Dose Level 1) are enrolling. KT80CbAUC5 followed by KAC (Cohorts E Dose Level 1) and KNT80CbAUC2 followed by KAC (Cohort F Dose Level 1) will begin enrollment simultaneously upon approval of the Amendment 04.

#### **Rationale for Cohort A starting dose**

The GeparSepto trial that evaluated weekly nab-paclitaxel versus weekly standard paclitaxel dosing for 12 weeks followed by 4 cycles of epirubicin and cyclophosphamide standard combination demonstrated significant improvement in the primary endpoint pCR in the nab-paclitaxel arm, especially in the subgroup of subjects with TNBC (see Section 4.1 for details). The initial nab-paclitaxel dose was 150mg/m<sup>2</sup> weekly, which was subsequently reduced to 125mg/m<sup>2</sup> weekly due to toxicity with 400/1200 enrolled subjects received nab-paclitaxel at 150mg/m<sup>2</sup>. In all nab-paclitaxel-treated subjects, the discontinuation rate was 21% for nab-paclitaxel vs. 14% for paclitaxel. The discontinuation for nab-paclitaxel due to AE, progression, patient and investigator's decision were 17%, 1.7%, 1.2% and 1%, respectively; the discontinuation for paclitaxel due to AE, progression, patient and investigator's decision were 6.2%, 5%, 1%, 1.2% and 1 death (0.2%). There was no statistically significant difference in Grade 3/4 anemia, neutropenia, febrile neutropenia. The most significant Grade 3/4 toxicity of nab-paclitaxel in the combined data versus paclitaxel was peripheral sensory neuropathy (10.2% vs. 2.7%). In an analysis that only included the patients enrolled after nab-paclitaxel was reduced to 125mg/m<sup>2</sup> and have received all scheduled cycles of taxane, the Grade 3/4 peripheral sensory neuropathy was reduced (62.3% vs. 42.1% for all grade, 39.6% vs. 31.6% for Grade 1, 17% vs. 5.3% for Grade 2, 5.7% vs. 5.3% for Grade 3 (no Grade 4 events). Unfortunately, the data did not include those who were prematurely discontinued from treatment.

Given that nab-paclitaxel 125mg/m<sup>2</sup> (albeit mixed with 33% who received 150mg/m<sup>2</sup> dose) has been tested in a large Phase III study with significantly improved pCR, in particular in the TNBC subgroup, it is reasonable to first target the dose level of nab-paclitaxel that has demonstrated improved efficacy. The doses for AC combination are standard for neoadjuvant TNBC. Overlapping toxicities between pembrolizumab and these chemotherapy agents are not expected based on the pembrolizumab toxicity profile in a Phase I/II study (KN021) that evaluated pembrolizumab in combination with various chemotherapy regimens in NSCLC including carboplatin and paclitaxel.

### **Rationale for Cohort B starting dose**

Cohort B DL1 (KNp100CbAUC6 / KAC) will be the initial dose level tested for Cohort B. This initial dose level is selected as the combination regimen nab-paclitaxel 100mg/m<sup>2</sup> weekly plus carboplatin AUC6 Q3W, has been tested via Phase III study and is an approved chemotherapy regimen for treating advanced NSCLC [Abraxane Label, 34]. It is therefore safer to start Cohort B with dose level of nab-paclitaxel plus carboplatin having been tested in a large trial.

### **Rationale for Cohorts C & D starting dose**

DL1 for Cohort C is nab-paclitaxel 125 mg/m<sup>2</sup> weekly plus carboplatin AUC5 Q3W. The rationale for the dose of nab-paclitaxel is based on data from GeptoSepto in which the tolerability and higher rate of pCR were demonstrated (see Rationale for Cohort A starting dose). The rationale for the dose of carboplatin is based on data from the Phase III CALGB 40603 study [14]. However, only about 60% of subjects were able to complete the required 12 paclitaxel doses. Furthermore, the grade 3-4 neutropenia rate was 56%. Based on the toxicity data, the carboplatin dose for this study will be AUC of 5.

DL1 for Cohort D is nab-paclitaxel 125 mg/m<sup>2</sup> weekly plus weekly carboplatin AUC2. Weekly carboplatin (1.5-2AUC) was tested in the GeparSixto trial, a randomized Phase II study with the addition of weekly paclitaxel (80mg/m<sup>2</sup>), weekly non-pegylated liposomal doxorubicin (20mg/m<sup>2</sup>) and Q3W bevacizumab (15mg/kg). The response rate was 53% within the range of Q3W carboplatin, suggesting the equivalency between weekly and every 3 week dosing of carboplatin. Moreover, some data suggested that weekly dosing may be more tolerable. As such, it has become the preferred carboplatin dosing for some clinicians [34].

### **Rationale for Cohorts E & F starting dose**

DL1 for Cohort E is paclitaxel 80 mg/m<sup>2</sup> weekly plus carboplatin AUC5 Q3W and DL1 for Cohort F is paclitaxel 80 mg/m<sup>2</sup> weekly plus carboplatin AUC2 weekly. The rationale for the dose of carboplatin with paclitaxel is based on data from the Phase III CALGB 40603 and GeparSixto studies as described previously [13, 14]. While the results of the GeparSepto showed higher pCR with Nab-paclitaxel when compared to paclitaxel, the ETNA study, which compared Nab-paclitaxel 125 mg/m<sup>2</sup> day 1, 8, 15 of 4 weeks cycle for 4 cycles to paclitaxel 90 mg/m<sup>2</sup> with similar scheduled followed by anthracycline-based chemotherapy combination Q3W for 4 cycles as neoadjuvant treatment for breast cancer, showed no statistically significant difference in pCR between the two TNBC arms (41.3% vs. 37.3%). [35] Furthermore, the nab-paclitaxel-containing has slightly higher rate of grade  $\geq$  3 neutropenia (30.6% vs. 19.7%) and peripheral neuropathy (4.5% vs. 1.8%). Thus, currently, there is no clear data supporting higher efficacy with nab-paclitaxel versus solvent-based paclitaxel.

#### **4.2.2.4 Maximum Dose/Exposure for This Trial**

The maximum and the target dose regimen for Cohort A will be KNp125 / KAC. The rationale can be found in Section 4.2.2.3. The maximum and the target dose regimens for

each cohort is as follows: Cohort B will be KNp100CbAUC6 / KAC, Cohort C will be KNp125CbAUC5 / KAC, Cohort D will be KNp125CbAUC2 / KAC, Cohort E will be KT80CbAUC5 / KAC and Cohort F will be KT80CbAUC2.

Two randomized trials have tested carboplatin in combination with weekly paclitaxel 80mg/m<sup>2</sup> followed by standard AC dosing in the neoadjuvant TNBC setting. In both studies, addition of carboplatin has demonstrated improved pCR for TNBC. The Phase III CALGB 40603 study combined carboplatin AUC6 Q3W with weekly paclitaxel [14]; the Phase II GeparSixto study combined weekly carboplatin at AUC1.5 or 2 with weekly paclitaxel [13]. The weekly carboplatin seems to have greater toxicity than carboplatin AUC6 Q3W, hence, carboplatin AUC6 Q3W was selected as the combination regimen in Cohort B. It is worth noting that in the CALGB 40603 study the carboplatin AUC6 Q3W plus weekly paclitaxel 80mg/m<sup>2</sup> arm showed statistically significant increase in Grade 3/4 neutropenia (56% vs. 22%) and Grade 3/4 thrombocytopenia (20% vs. 4%) compared to paclitaxel alone arm.

Nab-paclitaxel 100mg/m<sup>2</sup> weekly in combination with carboplatin AUC6 Q3W versus paclitaxel 80mg/m<sup>2</sup> weekly in combination with carboplatin AUC6 Q3W has been tested in a phase III study in patients with advanced NSCLC [36]. The nab-paclitaxel/carboplatin combination showed statistically significantly higher Grade 3/4 thrombocytopenia and anemia but statistically significantly lower neutropenia and sensory neuropathy compared to the paclitaxel and carboplatin combination. The target dose level with carboplatin AUC6 is selected as the target dose level to retain efficacy but in consideration of the available safety data.

#### **4.2.2.5 Rationale for Dose Interval and Trial Design**

The standard neoadjuvant treatment is typically 4 cycles of taxane (12 x weekly dosing) followed by 4 cycles of anthracycline / cyclophosphamide combination (e.g. doxorubicin 60mg/m<sup>2</sup> Q3W + cyclophosphamide 600mg/m<sup>2</sup> Q3W). This trial will test the new combination using the same dosing interval and schedule. Prior to starting the combination regimen, all subjects will receive one cycle of pembrolizumab alone and will undergo tumor core biopsy during the last week of cycle 1 (see Section 2). This allows for assessing early changes in tumor microenvironment following exposure to pembrolizumab treatment.

#### **4.2.3 Rationale for Endpoints**

##### **4.2.3.1 Safety Endpoints**

The primary goal for the study is to determine the recommended Phase 2 dose level for each of the pembrolizumab chemotherapy combinations therefore the safety primary endpoint will be DLT rates as observed during the DLT evaluation periods. Other safety parameters such as incidence of AE/SAEs (including fatal SAEs), immune-related AEs (irAEs) and laboratory abnormalities, rates of dose interruption and discontinuation due to AEs, and events of clinical interest (ECI) are important endpoints for safety and tolerability evaluations.



### **4.2.3.2 Efficacy Endpoints**

pCR is a key efficacy endpoint for evaluation of neoadjuvant treatment in TNBC and has been used as a surrogate efficacy endpoint by regulatory agencies for the approval of new TNBC neoadjuvant treatments (<http://www.fda.gov/downloads/drugs/guidancecompliance/regulatoryinformation/guidances/ucm305501.pdf>). Clinical response (CR/PR) per RECIST1.1, EFS and OS rates are useful endpoints to evaluate drug efficacy in this setting but with limitations in a Phase 1b trial.

### **4.2.3.3 Planned Exploratory Biomarker Research**

#### **Planned Genetic Analysis**

Understanding genetic determinants of drug response is an important endeavor during medical research. This research will evaluate whether genetic variation within a clinical trial population correlates with response to the treatment(s) under evaluation. If genetic variation is found to predict efficacy or adverse events, the data might inform optimal use of therapies in the patient population. This research contributes to understanding genetic determinants of efficacy and safety associated with the treatments in this study.

One of the exploratory translational research objectives is to characterize the tumor microenvironments before treatment, after a single dose of pembrolizumab and after the combination regimens, including presence and changes of TILs, immune-related mRNA expression signatures, and PD-L1 expression.

Pembrolizumab functions to enhance T-cell mediated adaptive immunity of the host by releasing PD-1/PD-L1 mediated immune checkpoint blockade, therefore PD-L1 expression in tumor cells and possibly stroma may be highly relevant. However, in order for tumor cells to be eliminated, tumor cell immunogenicity, presence of cytotoxic TILs (e.g. CD8+ TILs) and ratio of the cytotoxic and regulatory TILs (CD8+/FoxP3+ TILs) are critical so as immune enhancing and immune inhibitory cytokines. This translational research objective will be carried out using immunohistochemistry (IHC) such as IHC to evaluate PD-L1 expression, proportion of TILs based on markers of T cell phenotype. Baseline and post-treatment status of immune-related gene expression signatures in tumor microenvironment will also be evaluated using mRNA profiling technology in tumor tissues obtained during the study.

T cell clonality, neoantigen expression, presence and changes in circulating tumor markers such as ctDNA, plasma proteomic change may also be evaluated using plasma samples. This may shed light on whether a combination with chemotherapy will enhance immune-mediated anti-tumor activity by pembrolizumab.

TNBC is a heterogeneous disease with distinct subtypes. Therefore tumor genetic profiling using technology such as targeted next generation sequencing, whole exome sequencing (genome-wide), genetic testing of tumor mutational burden and identify subpopulations that are more responsive to pembrolizumab or pembrolizumab chemotherapy combination is critical.

In addition, understanding the somatic and germline genetic determinants of drug response is an important endeavor during medical research. Particular emphasis will be placed on the following biological determinants/pathways such as BRCA1/2, PI3K, PTEN, EGFR, MEK,

FGFR, MET, and Notch signaling etc. This translational research will be prioritized based on tumor tissue availability.

#### **4.2.3.4 Future Biomedical Research**

The Sponsor will conduct Future Biomedical Research on specimens collected for future biomedical research during this clinical trial. This research may include genetic analyses (DNA), gene expression profiling (RNA), proteomics, metabolomics (serum, plasma) and/or the measurement of other analytes.

Such research is for biomarker testing to address emergent questions not described elsewhere in the protocol (as part of the main trial) and will only be conducted on specimens from appropriately consented subjects. The objective of collecting specimens for Future Biomedical Research is to explore and identify biomarkers that inform the scientific understanding of diseases and/or their therapeutic treatments. The overarching goal is to use such information to develop safer, more effective drugs/vaccines, and/or to ensure that subjects receive the correct dose of the correct drug/vaccine at the correct time. The details of this Future Biomedical Research sub-trial are presented in Section 12.2 - Collection and Management of Specimens for Future Biomedical Research. Additional informational material for institutional review boards/ethics committees (IRBs/ERCs) and investigational site staff is provided in Section 12.3.

#### **4.3 Benefit/Risk**

Subjects in clinical trials generally cannot expect to receive direct benefit from treatment/vaccination during participation, as clinical trials are designed to provide information about the safety and effectiveness of an investigational medicine.

Additional details regarding specific benefits and risks for subjects participating in this clinical trial may be found in the accompanying Investigators Brochure and Informed Consent documents.

### **5.0 METHODOLOGY**

#### **5.1 Entry Criteria**

##### **5.1.1 Diagnosis/Condition for Entry into the Trial**

Female subjects at least 18 years of age with newly diagnosed, locally advanced non-metastatic TNBC will be enrolled in this trial.

### 5.1.2 Subject Inclusion Criteria

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

1. Be a female subject  $\geq 18$  years of age on day of signing informed consent
2. Have TNBC histologically defined as follows:
  - ER negative: with  $<1\%$  of tumor cells positive for ER by IHC irrespective of staining intensity; AND
  - PR negative: with  $<1\%$  tumor cells positive for PR by IHC irrespective of staining intensity; AND
  - HER2 negative:
    - IHC 1+, as defined by incomplete membrane staining that is faint/barely perceptible and within  $>10\%$  of invasive tumor cells; OR
    - IHC 0, as defined by no staining observed or membrane staining that is incomplete and is faint/barely perceptible and within  $\leq 10\%$  of the invasive tumor cells; OR
    - FISH negative based on:
      - Single-probe average *HER2* copy number  $<4.0$  signals/cell, **OR**
      - Dual-probe *HER2/CEP17* ratio  $<2.0$  with an average *HER2* copy number  $<4.0$  signals/cell
3. Have previously untreated locally advanced non-metastatic (M0) TNBC fulfilling the following combined primary tumor (T) and regional lymph node (N) staging per AJCC for breast cancer staging criteria version 7 as assessed by the investigator based on baseline breast MRI and clinical assessment:
  - T1c, N1-N2
  - T2, N0-N2
  - T3, N0-N2
  - T4a-c, N0-N2

*Note: ipsilateral multifocal primary tumor is allowed and the tumor with the most advanced T stage should be used to assess the eligibility.*

4. Provide 2 separate core needle biopsies from the primary tumor at screening to the central laboratory and agree to have a core needle biopsy after single dose pembrolizumab treatment if tumor biopsy is feasible as judged by the investigator.
5. Have Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1.
6. Demonstrate adequate organ function as defined in [Table 2](#). All screening labs should be performed within 10 days of treatment initiation.

Table 2 Adequate Organ Function Laboratory Values

<b>Organ System</b>	<b>Laboratory Value</b>
<b>Hematological</b>	
Absolute neutrophil count (ANC)	$\geq 1,500$ cells / $\mu\text{L}$ without granulocyte colony-stimulating factor (G-CSF) support within 2 weeks prior to the first dose of study treatment
Platelet count	$\geq 100,000$ / $\mu\text{L}$ without transfusion within 2 weeks prior to the first dose of study treatment
Hemoglobin	$\geq 9$ g/dL or $\geq 5.6$ mmol/L without transfusion or EPO dependency
<b>Renal</b>	
Serum creatinine <b>OR</b> Calculated creatinine clearance (CrCl) (calculated per institutional standard)	$\leq 1.5$ X upper limit of normal (ULN) <b>OR</b> $\geq 50$ mL/min
<b>Hepatic</b>	
Total bilirubin	$\leq 1.5$ X ULN <b>OR</b> Direct bilirubin $\leq$ ULN for subjects with total bilirubin levels $> 1.5$ X ULN
Aspartate aminotransferase [AST (SGOT)] and alanine aminotransferase [ALT (SGPT)]	$\leq 2.5$ X ULN
Albumin	$\geq 3.0$ g/dL
Lactate Dehydrogenase (LDH)	$< 2.5$ X ULN
<b>Coagulation</b>	
International Normalized Ratio (INR) or Prothrombin Time (PT)	$\leq 1.5$ X ULN unless subject is receiving anticoagulant therapy as long as PT or aPTT/PTT is within therapeutic range of intended use of anticoagulants
Activated Partial Thromboplastin Time (aPTT) or Partial Thromboplastin Time (PTT)	$\leq 1.5$ X ULN unless subject is receiving anticoagulant therapy as long as PT or aPTT/PTT is within therapeutic range of intended use of anticoagulants

7. Have left ventricular ejection fraction (LVEF) of  $\geq 50\%$  or  $\geq$  institution lower limit of normal (LLN) as assessed by echocardiogram (ECHO) or multigated acquisition (MUGA) scan performed at screening.
8. Female subjects of childbearing potential (Section 5.7.2) must be willing to use an adequate method of contraception as outlined in Section 5.7.2 – Contraception, for the course of the study through 12 months after the last dose of study medication for subjects who have received cyclophosphamide, and for six months after the last dose of study medication for subjects who did not.

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

9. Must have a negative urine or serum pregnancy test within 72 hours prior to receiving the first dose of study treatment for female subjects of childbearing potential. If the urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required.

### **5.1.3 Subject Exclusion Criteria**

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

1. Has evidence of metastatic breast cancer, concurrent bilateral invasive breast cancer, or inflammatory breast cancer.
2. Has another malignancy within the last 5 years. Exceptions include basal cell carcinoma of the skin, squamous cell carcinoma of the skin that has undergone potentially curative surgery, or in situ cervical cancer.
3. Has received prior chemotherapy, targeted therapy, radiation therapy, immunotherapy that target immune checkpoints, co-stimulatory or co-inhibitory pathways for T cell receptors within the past 12 months.

*Note:* subjects entering the trial after undergoing a sentinel lymph node biopsy will be eligible if they meet all other criteria.

4. 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 study treatment.

*Note:* subject should be excluded he/she received an investigational agent with anti-cancer or anti-proliferative intent within the last 12 months.

5. Has received a live vaccine within 30 days of the first dose of study treatment.
  - a. *Note:* Seasonal influenza vaccines for injection are generally inactivated flu vaccines and are allowed; however intranasal influenza vaccines (e.g., FluMist®) are live attenuated vaccines, and are not allowed.
6. Has an active autoimmune disease that has required systemic treatment in past 2 years (i.e. with use of disease modifying agents, corticosteroids or immunosuppressive drugs). Replacement therapy (e.g., thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency, etc.) is not considered a form of systemic treatment.
7. 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.
8. Has a known history of Human Immunodeficiency Virus (HIV) (HIV 1/2 antibodies).
9. Has known active Hepatitis B (e.g., HBsAg reactive) or Hepatitis C (e.g., HCV RNA [qualitative] is detected).
10. Has evidence of current pneumonitis.
11. Has a history of non-infectious pneumonitis requiring treatment with steroids or a history of interstitial lung disease.

12. Has an active infection requiring systemic therapy.
13. Has significant cardiovascular disease, such as :
  - History of myocardial infarction, acute coronary syndrome or coronary angioplasty/stenting/bypass grafting within the last 6 months
  - Congestive heart failure (CHF) New York Heart Association (NYHA) Class II-IV or history of CHF NYHA class III or IV
14. 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.
15. Has known psychiatric or substance abuse disorders that would interfere with cooperation with the requirements of the trial.
16. Is pregnant or breastfeeding, or expecting to conceive children within the projected duration of the trial, starting with the screening visit through 12 months after the last dose of trial treatment for subjects who have received cyclophosphamide, and for six months after the last dose of study medication for subjects who have not.
17. Has a known hypersensitivity to the components of the study therapy or its analogs.

## 5.2 Trial Treatment(s)

The trial treatments to be used in this trial are outlined below in [Table 3](#).

Table 3 Trial Treatments

Drug	Dose/Potency	Dose Frequency	Route of Administration	Dosing Time of each 3-week cycle	Use
Pembrolizumab	200 mg	Q3W	IV Infusion	Day 1 of Cycles 1-9	Experimental
Nab-paclitaxel	125 mg/m <sup>2</sup> , or 100mg/m <sup>2</sup>	Weekly	IV Infusion	Day 1, 8, 15 of Cycles 2-5	Experimental
Paclitaxel	80 mg/m <sup>2</sup> , or 70mg/m <sup>2</sup>	Weekly	IV Infusion	Day 1, 8, 15 of Cycles 2-5	Experimental
Carboplatin	AUC6 or AUC5	Q3W	IV Infusion	Day 1 of Cycles 2-5	Experimental
	AUC2 or AUC1.5	Weekly	IV Infusion	Day 1, 8, 15 of Cycles 2-5	Experimental
Doxorubicin	60 mg/m <sup>2</sup>	Q3W	IV Injection	Day 1 of Cycle 6-9	Standard of care
Cyclophosphamide	600 mg/m <sup>2</sup>	Q3W	IV Infusion	Day 1 of Cycle 6-9	Standard of care

Trial treatment should begin on the day of treatment allocation or within 3 days after the treatment allocation date.

All supplies indicated in [Table 3](#) above will be provided centrally by the Sponsor or locally by the trial site, subsidiary or designee, depending on local country operational or regulatory requirements.

For any commercially available product that is provided by the trial site, subsidiary or designee every attempt will be made to source these supplies from a single lot/batch number. The trial site will be responsible for recording the lot number, manufacturer and expiry date of any locally purchased 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 trial treatments in accordance with the protocol and any applicable laws and regulations.

## **5.2.1 Dose Selection/Modification**

### **5.2.1.1 Dose Selection (Preparation)**

The rationale for selection of the combination regimens and doses to be used in this trial is provided in Section 4.2.2, Rationale for Dose Selection /Regimen.

Pembrolizumab will be used at a fixed dose of 200mg Q3W.

The dose amount required for nab-paclitaxel, paclitaxel, doxorubicin and cyclophosphamide will be calculated based on milligrams per square meter of body surface area ( $\text{mg}/\text{m}^2$ ).

The dose amount required for carboplatin will be calculated as AUC.

### **5.2.1.2 Rules for Dose Finding**

#### **Part 1**

##### **Dose Finding Based on DLT Evaluation Period**

DLTs observed during the DLT evaluation period will be used to determine whether a dose level is tolerable or not tolerable, and to determine dose level de-escalation. The DLT evaluation period is defined from Day 1 Cycle 1 through end of Cycle 3 (i.e. through 2 cycles of the first combination regimen) as well as Day 1 Cycle 6 through end of Cycle 7 (i.e. through 2 cycles of the second combination regimen). Based on the criteria below for each of the combination regimens, a RP2D combining two regimens will be established for Cohort A through F, separately.

The study will start with DL1 for all cohorts as described in Section 2.1 and in [Table 1](#).

In Part 1 at any dose level tested, a maximum of 10 subjects are planned to be enrolled and can be enrolling continuously. Decisions regarding regimen dose level de-escalation can be made on an on-going basis and when 6 and 10 subjects are evaluable for DLT at a given dose level for each combination regimen based on the following rules. During the first combination regimen, if DLTs are observed in  $\geq 3$  out of the first 6 subjects, or  $\geq 4$  out of 10 subjects, the dose level will be deemed unacceptably toxic and an additional 10 subjects will be enrolled into the next lower dose level for DLT assessment, or the cohort may be stopped. Subjects who are enrolled but not fully evaluable for DLT at the current dose level that is determined to be intolerable will receive subsequent doses in accordance with the doses in the next lower dose level. For example, if the dose DL1 is determined to be intolerable, the

remaining subjects enrolled but not yet evaluable for DLT will receive remaining treatment at the dose level DL -1 for Cohorts A, C, D, E and F or will be treated at whatever DL-1 had been for Cohort B (KNp100CbAUC5 / KAC) because we have no dose level -1 in Cohort B. If the current dose is DL -1, the study or the cohort may be stopped.

#### Tolerability evaluation for KAC

No formal dose finding will occur during the KAC portion of the treatment as the regimen includes a fixed dose for pembrolizumab and the standard AC dose combination as specified in Section 2. However, DLTs will be monitored through the first 2 cycles of KAC treatment for the first 10 subjects enrolled in Part 1 who received a given KNp or KNpCb dose. If  $\geq 4$  subjects experience a DLT during the KAC treatment, then the toxicity profile will be thoroughly evaluated by the sponsor medical and statistical team in consultation with the investigators to determine which component is the major contributor to the toxicity. If addition of pembrolizumab is determined to be the major contributor to the DLTs, then pembrolizumab will be dropped from the KAC combination and subsequent subjects will be dosed with AC only following KNp, KNpCb or KTCb treatment. If the DLTs are determined to be related to AC, a dose reduction may be considered after consultation between the sponsor medical monitor and investigator. If the DLTs that occurred during the KAC treatment period are primarily due to cumulative toxicities of chemotherapies and the dose levels assessed for KNp,KNpCb or KTCb are already at DL -1 as listed in [Table 1](#), then the regimen may be considered as unacceptable. If the dose levels assessed for KNp, KNpCb or KTCb are at DL1 for Cohorts A, C, D, E and F when KAC reaches DLT, then the regimen at the next lower dose level will be evaluated.

#### Part 2

Once a target RP2D has been identified for Cohorts C, D, E and F the cohort(s) may be expanded by enrolling an additional 10 subjects at the recommended dose level. Should no RP2D be identified for Cohorts C, D, E or F then the study will end.

##### **5.2.1.3 Definition of Dose-Limiting Toxicities**

All toxicities will be graded using National Cancer Institute Common Toxicity Criteria for Adverse Events version 4.0 (NCI-CTCAE v4.0).

An AE is considered to be a DLT if it is considered by the investigator to be clinically relevant and attributed (definitely, probably, or possibly) to a component of the regimen evaluated during the DLT evaluation period for that particular regimen and meet the criteria in [Table 4](#). Subjects who experience a DLT in Part 1 which cannot be managed by a dose decrease should be discontinued from the trial unless the investigator considers it in the best interest of the subject to continue on the trial. The investigator should discuss with the Sponsor medical monitor before resuming study treatment for the subject.



Table 4 Dose-Limiting Toxicity Criteria

Toxicity	DLT Definition
Hematologic	<ul style="list-style-type: none"> <li>• Grade 4 neutropenia lasting <math>\geq</math> 8 days</li> <li>• Febrile neutropenia Grade 3 or Grade 4</li> <li>• Grade 4 thrombocytopenia that requires platelet transfusion, or Grade 3 thrombocytopenia with bleeding</li> </ul>
Non-hematologic	<ul style="list-style-type: none"> <li>• Grade 4 toxicity</li> <li>• Grade <math>\geq</math>3 symptomatic hepatic toxicities lasting for &gt;48 hours, or Grade <math>\geq</math>3 asymptomatic hepatic toxicities lasting for <math>\geq</math> 7 days</li> <li>• Grade <math>\geq</math>3 non-hematologic, non-hepatic organ toxicity, excluding the following               <ul style="list-style-type: none"> <li>○ Grade 3 nausea, vomiting or diarrhea that resolves to Grade <math>\leq</math>1 within 7 days of appropriate supportive therapy</li> <li>○ Grade 3 asymptomatic or mildly symptomatic rash that can be adequately managed with supportive care, or resolves to asymptomatic and/or Grade <math>\leq</math>2 within 7 days with appropriate supportive therapy</li> <li>○ Grade 3 fatigue that resolves to Grade <math>\leq</math>2 within 7 days</li> <li>○ Grade 3 fever (in the absence of any clinically significant source of fever) that resolves to Grade <math>\leq</math>2 within 7 days with supportive care</li> <li>○ Grade 3 laboratory abnormality that is asymptomatic and deemed by the investigator not to be clinically significant</li> <li>○ Grade 3 autoimmune thyroiditis or other endocrine abnormality that can be managed by endocrine therapy that would not necessitate initiation of systemic corticosteroids</li> <li>○ Grade 3 tumor flare, defined as local pain, irritation, or rash localized at sites of known or suspected tumor</li> <li>○ hypersensitivity/infusion reactions lasting <math>\leq</math>2 days</li> </ul> </li> </ul>
Other	<ul style="list-style-type: none"> <li>• Any treatment delays for <math>\geq</math>14 days due to unresolved toxicity</li> <li>• Grade 5 treatment-related AE</li> <li>• A dose reduction of the study treatment during the DLT evaluation period</li> </ul>

#### 5.2.1.4 Replacement of Subjects in Part 1

In order to be included for safety evaluation in Part 1, a subject must be evaluable. Subjects are considered non-evaluable and will be replaced if:

- they are enrolled but not treated;
- they discontinue from the trial prior to completing all safety evaluations due to reasons other than drug-related adverse events;
- they received <90% of the total infusion in Cycle 1 or Cycle 2 (e.g., because the infusion had to be discontinued due to an infusion reaction) and did not experience a drug-related event.

Non-evaluable subjects will not be counted toward the cohort total for DLT evaluation.

### 5.2.1.5 Dose Modification

#### 5.2.1.5.1 Dose Modification and Toxicity Management Guidelines for Pembrolizumab

##### **Dose modification and toxicity management for immune-related AEs associated with pembrolizumab**

AEs associated with pembrolizumab exposure may represent an immunologic etiology. These immune-related AEs (irAEs) may occur shortly after the first dose or several months after the last dose of pembrolizumab 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 trial data, most irAEs were reversible and could be managed with interruptions of pembrolizumab, 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. Based on the severity of irAEs, withhold or permanently discontinue pembrolizumab and administer corticosteroids. Dose modification and toxicity management guidelines for irAEs associated with pembrolizumab are provided in [Table 5](#).

**Table 5 Dose Modification and Toxicity Management Guidelines for Immune-related AEs Associated with Pembrolizumab**

<b>General instructions:</b>				
<ol style="list-style-type: none"> <li>1. Corticosteroid taper should be initiated upon AE improving to Grade 1 or less and continue to taper over at least 4 weeks.</li> <li>2. For situations where pembrolizumab has been withheld, pembrolizumab can be resumed after AE has been reduced to Grade 1 or 0 and corticosteroid has been tapered. Pembrolizumab must be permanently discontinued if AE does not resolve within 12 weeks of last dose or corticosteroids cannot be reduced to <math>\leq 10</math> mg prednisone or equivalent per day within 12 weeks.</li> <li>3. For severe and life-threatening irAEs, IV corticosteroid should be initiated first followed by oral steroid. Other immunosuppressive treatment should be initiated if irAEs cannot be controlled by corticosteroids.</li> </ol>				
<b>Immune-related AEs</b>	<b>Toxicity grade or conditions (CTCAEv4.0)</b>	<b>Action taken to pembrolizumab</b>	<b>irAE management with corticosteroid and/or other therapies</b>	<b>Monitor and follow-up</b>
Pneumonitis	Grade 2	Withhold	<ul style="list-style-type: none"> <li>• Administer corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper</li> </ul>	<ul style="list-style-type: none"> <li>• Monitor participants for signs and symptoms of pneumonitis</li> <li>• Evaluate participants with suspected pneumonitis with radiographic imaging and initiate corticosteroid treatment</li> <li>• Add prophylactic antibiotics for opportunistic infections</li> </ul>
	Grade 3 or 4, or recurrent Grade 2	Permanently discontinue		
Diarrhea / Colitis	Grade 2 or 3	Withhold	<ul style="list-style-type: none"> <li>• Administer corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper</li> </ul>	<ul style="list-style-type: none"> <li>• 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).</li> <li>• Participants with <math>\geq</math> Grade 2 diarrhea suspecting colitis should consider GI consultation and performing endoscopy to rule out colitis.</li> <li>• 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.</li> </ul>
	Grade 4	Permanently discontinue		

<b>Immune-related AEs</b>	<b>Toxicity grade or conditions (CTCAEv4.0)</b>	<b>Action taken to pembrolizumab</b>	<b>irAE management with corticosteroid and/or other therapies</b>	<b>Monitor and follow-up</b>
AST / ALT elevation or Increased bilirubin	Grade 2	Withhold	<ul style="list-style-type: none"> <li>Administer corticosteroids (initial dose of 0.5- 1 mg/kg prednisone or equivalent) followed by taper</li> </ul>	<ul style="list-style-type: none"> <li>Monitor with liver function tests (consider weekly or more frequently until liver enzyme value returned to baseline or is stable)</li> </ul>
	Grade 3 or 4	Permanently discontinue	<ul style="list-style-type: none"> <li>Administer corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper</li> </ul>	
Type 1 diabetes mellitus (T1DM) or Hyperglycemia	Newly onset T1DM or Grade 3 or 4 hyperglycemia associated with evidence of $\beta$ -cell failure	Withhold	<ul style="list-style-type: none"> <li>Initiate insulin replacement therapy for participants with T1DM</li> <li>Administer anti-hyperglycemic in participants with hyperglycemia</li> </ul>	<ul style="list-style-type: none"> <li>Monitor participants for hyperglycemia or other signs and symptoms of diabetes.</li> </ul>
Hypophysitis	Grade 2	Withhold	<ul style="list-style-type: none"> <li>Administer corticosteroids and initiate hormonal replacements as clinically indicated.</li> </ul>	<ul style="list-style-type: none"> <li>Monitor for signs and symptoms of hypophysitis (including hypopituitarism and adrenal insufficiency)</li> </ul>
	Grade 3 or 4	Withhold or permanently discontinue <sup>1</sup>		
Hyperthyroidism	Grade 2	Continue	<ul style="list-style-type: none"> <li>Treat with non-selective beta-blockers (eg, propranolol) or thionamides as appropriate</li> </ul>	<ul style="list-style-type: none"> <li>Monitor for signs and symptoms of thyroid disorders.</li> </ul>
	Grade 3 or 4	Withhold or permanently discontinue <sup>1</sup>		
Hypothyroidism	Grade 2-4	Continue	<ul style="list-style-type: none"> <li>Initiate thyroid replacement hormones (eg, levothyroxine or liothyronine) per standard of care</li> </ul>	<ul style="list-style-type: none"> <li>Monitor for signs and symptoms of thyroid disorders.</li> </ul>
Nephritis and Renal dysfunction	Grade 2	Withhold	<ul style="list-style-type: none"> <li>Administer corticosteroids (prednisone 1-2 mg/kg or equivalent) followed by taper.</li> </ul>	<ul style="list-style-type: none"> <li>Monitor changes of renal function</li> </ul>
	Grade 3 or 4	Permanently discontinue		

<b>Immune-related AEs</b>	<b>Toxicity grade or conditions (CTCAEv4.0)</b>	<b>Action taken to pembrolizumab</b>	<b>irAE management with corticosteroid and/or other therapies</b>	<b>Monitor and follow-up</b>
Myocarditis	Grade 1 or 2	Withhold	<ul style="list-style-type: none"> <li>Based on severity of AE administer corticosteroids</li> </ul>	<ul style="list-style-type: none"> <li>Ensure adequate evaluation to confirm etiology and/or exclude other causes</li> </ul>
	Grade 3 or 4	Permanently discontinue		
All other immune-related AEs	Intolerable/persistent Grade 2	Withhold	<ul style="list-style-type: none"> <li>Based on type and severity of AE administer corticosteroids</li> </ul>	<ul style="list-style-type: none"> <li>Ensure adequate evaluation to confirm etiology and/or exclude other causes</li> </ul>
	Grade 3	Withhold or discontinue based on the type of event. Events that require discontinuation include and not limited to: Guillain-Barre Syndrome, encephalitis		
	Grade 4 or recurrent Grade 3	Permanently discontinue		
<p>1. Withhold or permanently discontinue pembrolizumab is at the discretion of the investigator or treating physician.</p> <p><b>NOTE:</b>            For participants with Grade 3 or 4 immune-related endocrinopathy where withhold of pembrolizumab is required, pembrolizumab may be resumed when AE resolves to ≤ Grade 2 and is controlled with hormonal replacement therapy or achieved metabolic control (in case of T1DM).</p>				

**Dose modification and toxicity management of infusion-reactions related to pembrolizumab**

Pembrolizumab may cause severe or life threatening infusion-reactions including severe hypersensitivity or anaphylaxis. Signs and symptoms usually develop during or shortly after drug infusion and generally resolve completely within 24 hours of completion of infusion. Dose modification and toxicity management guidelines on pembrolizumab associated infusion reaction are provided in [Table 6](#).

Table 6 Pembrolizumab Infusion Reaction Dose Modification and Treatment Guidelines

NCI CTCAE Grade	Treatment	Premedication at Subsequent Dosing
<b>Grade 1</b> 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
<b>Grade 2</b> Requires therapy or infusion interruption but responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDs, narcotics, IV fluids); prophylactic medications indicated for $\leq 24$ hrs	<b>Stop Infusion.</b> Additional appropriate medical therapy may include but is not limited to: IV fluids Antihistamines NSAIDs Acetaminophen Narcotics Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator. If symptoms resolve within 1 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 study drug treatment	Subject may be premedicated 1.5h ( $\pm$ 30 minutes) prior to infusion of _____ with: Diphenhydramine 50 mg po (or equivalent dose of antihistamine). Acetaminophen 500-1000 mg po (or equivalent dose of analgesic).

NCI CTCAE Grade	Treatment	Premedication at Subsequent Dosing
<p><b>Grades 3 or 4</b>            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</p>	<p><b>Stop Infusion.</b>            Additional appropriate medical therapy may include but is not limited to:            Epinephrine**            IV fluids            Antihistamines            NSAIDs            Acetaminophen            Narcotics            Oxygen            Pressors            Corticosteroids            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.            **In cases of anaphylaxis, epinephrine should be used immediately.  <b>Subject is permanently discontinued from further study drug treatment.</b></p>	<p>No subsequent dosing</p>
<p>Appropriate resuscitation equipment should be available at the bedside and a physician readily available during the period of drug administration.            For further information, please refer to the Common Terminology Criteria for Adverse Events v4.0 (CTCAE) at <a href="http://ctep.cancer.gov">http://ctep.cancer.gov</a></p>		

**Other allowed dose interruption for pembrolizumab**

Pembrolizumab may be interrupted for situations other than treatment-related AEs such as medical / surgical events or logistical reasons not related to study therapy. Subjects should be placed back on study therapy within 3 weeks of the scheduled interruption, unless otherwise discussed with the Sponsor. The reason for interruption should be documented in the patient's study record.

**5.2.1.5.2 Dose modification / Discontinuation Guidelines for Nab-paclitaxel, Paclitaxel, Carboplatin, Doxorubicin and Cyclophosphamide**

This section provides dose modification/discontinuation guidelines for the 4 chemotherapeutic agents administered as the study treatments. During the combination treatment period, the investigator should use their clinical judgment to determine which compound(s) contributed to the toxicity in order to apply dose modifications.

In [Table 7](#), levels of dose reduction are provided for each chemotherapy agent based on the starting dose level. Detailed dose modifications/reductions guidelines are provided in [Table 8](#) and [Table 9](#). Specific guidance for options following discontinuation of one or more chemotherapeutic agents and handling of missing doses are also provided.

Table 7 Levels of dose reduction

<b>Chemotherapy and starting dose</b>	<b>Dose reduction to:</b>	<b>Reference</b>
Nab-paclitaxel 125mg/m <sup>2</sup>	100 mg/m <sup>2</sup>	Abraxane label for pancreatic cancer and NSCLC
Nab-paclitaxel 100mg/m <sup>2</sup>	75 mg/m <sup>2</sup>	
Paclitaxel 80mg/m <sup>2</sup>	70 mg/m <sup>2</sup>	
Carboplatin AUC6	AUC5	
Carboplatin AUC5	AUC4	
Doxorubicin 60mg/m <sup>2</sup>	Reduced by 20%, i.e. 48mg/m <sup>2</sup> for doxorubicin	NCCN guideline
cyclophosphamide 600mg/m <sup>2</sup>	Reduced by 20%, i.e. 480mg/m <sup>2</sup> for cyclophosphamide	NCCN guideline

**Instruction on discontinuation of a component or entire regimen**

During the first part of the combination therapy (KNp for Cohort A or KNpCb for Cohorts B, C and D or KTCb for Cohorts E and F), if one or more than one component must be discontinued due to toxicity, the investigator can select one of the following options at his/her own discretion for the subject:

- If nab-paclitaxel or paclitaxel is discontinued,
  - Start and complete the KAC regimen as planned per protocol, then followed by surgery
- If only carboplatin is discontinued (applies to Cohorts B, C,D, E and F),
  - Continue with KNp or KT followed by KAC as planned per protocol, then followed by surgery
- If only pembrolizumab is discontinued,
  - Continue with chemotherapy regimen alone (Np / NpCb / TCb followed by AC) as planned per protocol, then followed by surgery

During the second part of the combination therapy (KAC), if one or more than one component should be discontinued, the investigator can select one of the following options at his/her own discretion for the subject:

- If doxorubicin and/or cyclophosphamide are discontinued,
  - Discontinue all study treatment including pembrolizumab and proceed with surgery
- If only pembrolizumab is discontinued
  - Continue doxorubicin and cyclophosphamide for the remaining cycles as planned per protocol and followed by surgery

Subjects who are discontinued from the study treatment and continue with other neoadjuvant treatment prior to the definitive surgery will be inevaluable for pCR and/or imaging assessments.



***Instruction on making up missed doses:***

If a dose delay does not require discontinuation of chemotherapy, subjects may resume treatment with the next scheduled dose in the regimen and continue on treatment to complete the full number of cycles per protocol.

Table 8 Dose modification guideline for nab-paclitaxel, paclitaxel and carboplatin

Toxicities	Grade or actual value	Nab-paclitaxel or paclitaxel alone or with carboplatin
<b>Hematological</b>		
<b>Neutropenia</b>	$\geq 1000/\text{mm}^3$ G2/G1	No change to Nab-paclitaxel or paclitaxel and carboplatin <ul style="list-style-type: none"> <li>For <math>\text{ANC} \leq 1500/\text{mm}^3</math>, prophylactic myeloid growth factors (filgrastim) use at the discretion of the investigator,               <ul style="list-style-type: none"> <li>Should not be given on the same day as chemotherapy.</li> <li>Pegfilgrastim may not be used with nab-paclitaxel due to its weekly dosing schedule</li> </ul> </li> </ul>
	$< 1000/\text{mm}^3$ G3/G4	Hold Nab-paclitaxel or paclitaxel and/or carboplatin until $\text{ANC} \geq 1000/\text{mm}^3$ . G-CSF may be used between days 2–6 at discretion of the investigator. Pegfilgrastim may not be used with nab-paclitaxel due to its weekly dosing schedule. Resume Nab-paclitaxel and/or carboplatin based on timing of recovery: <ul style="list-style-type: none"> <li><math>\leq 1</math> week: No change to Nab-paclitaxel, or paclitaxel and carboplatin</li> <li><math>&gt; 1</math> but <math>&lt; 3</math> weeks: Dose-reduce nab-paclitaxel to <math>100\text{mg}/\text{m}^2</math> or <math>75\text{mg}/\text{m}^2</math>, and paclitaxel to <math>70\text{ mg}/\text{m}^2</math> and/ or carboplatin to AUC 5 or AUC 4 for all subsequent cycles.</li> <li><math>\geq 3</math> weeks: Stop nab-paclitaxel, paclitaxel and /or carboplatin (see general instruction at the beginning of the section)</li> </ul>
<b>Febrile neutropenia</b>	$\text{ANC} \leq 1000/\text{mm}^3$ , fever $\geq 38.5^\circ$ CG3 and G4	Hold nab-paclitaxel or paclitaxel and / or carboplatin until resolved ( $\text{ANC} > 1000/\text{mm}^3$ , fever $< 38.5^\circ\text{C}$ , and resolution of any signs of infection). G-CSF may be used between days 2–6 at discretion of the investigator. Pegfilgrastim may not be used with nab-paclitaxel or paclitaxel due to its weekly dosing schedule. Resume Nab-paclitaxel or paclitaxel and or carboplatin according to number of episodes: <ul style="list-style-type: none"> <li>First episode: no change to nab-paclitaxel or paclitaxel and carboplatin. Consider adding prophylactic GCSF for subsequent cycles.</li> <li>Second episode: Reduce Nab-paclitaxel to <math>100\text{mg}/\text{m}^2</math> or <math>75\text{mg}/\text{m}^2</math>, and paclitaxel to <math>70\text{ mg}/\text{m}^2</math> and/ or carboplatin to AUC 5 or AUC 4 for all subsequent doses.</li> <li>Third episode: Discontinue nab-paclitaxel or paclitaxel, and /or carboplatin (see general instruction at the beginning of the section)</li> </ul>

Toxicities	Grade or actual value	Nab-paclitaxel or paclitaxel alone or with carboplatin
<b>Thrombocytopenia</b>	75–<100,000/mm <sup>3</sup> G1	Hold nab-paclitaxel or paclitaxel and / or carboplatin until $\geq 100,000/\text{mm}^3$ , resume treatment based on timing of recovery: <ul style="list-style-type: none"> <li>• <math>\leq 1</math> week—no change to nab-paclitaxel, paclitaxel and carboplatin.</li> <li>• <math>&gt; 1</math> but <math>&lt; 3</math> weeks— Reduce Nab-paclitaxel to <math>100\text{mg}/\text{m}^2</math> or <math>75\text{mg}/\text{m}^2</math>, and paclitaxel to <math>70\text{ mg}/\text{m}^2</math> and/ or carboplatin to AUC 5 or AUC 4 for all subsequent doses.</li> <li>• <math>\geq 3</math> weeks: Discontinue nab-paclitaxel or paclitaxel and /or carboplatin (see general instruction at the beginning of the section)</li> </ul>
	$< 75,000/\text{mm}^3$ $\geq \text{G}2$	Hold nab-paclitaxel, paclitaxel and/or carboplatin until $\geq 100,000/\text{mm}^3$ . <ul style="list-style-type: none"> <li>• Reduce Nab-paclitaxel to <math>100\text{mg}/\text{m}^2</math> or <math>75\text{mg}/\text{m}^2</math>, and paclitaxel to <math>70\text{ mg}/\text{m}^2</math> and/ or carboplatin to AUC 5 or AUC 4 for all subsequent doses.</li> <li>• Stop nab-paclitaxel or paclitaxel and/or carboplatin if held for <math>\geq 3</math> weeks in a row, (see general instruction at the beginning of the section)</li> </ul>
<b>Anemia</b>	All grades	No change to nab-paclitaxel or paclitaxel and carboplatin <ul style="list-style-type: none"> <li>• Iron studies should be done and iron should be replaced as indicated.</li> <li>• Red blood cell transfusions can be given at the investigators discretion.</li> </ul>
<b>Nausea/Vomiting</b>	Grade 1 or 2	No change to Nab-paclitaxel or paclitaxel and carboplatin
	$\geq$ Grade 3	Hold Nab-paclitaxel or paclitaxel and/or carboplatin until resolved to $\leq$ grade 1. <ul style="list-style-type: none"> <li>• Resume nab-paclitaxel or paclitaxel and/or carboplatin at previous dose with modification of premedication</li> <li>• Second episode <math>\geq</math> Grade 3 despite with maximum supportive care, reduce Nab-paclitaxel to <math>100\text{mg}/\text{m}^2</math> or <math>75\text{mg}/\text{m}^2</math>, and paclitaxel to <math>70\text{ mg}/\text{m}^2</math> and/ or carboplatin to AUC 5 or AUC 4 for all subsequent cycles</li> </ul>
<b>Mucositis/Stomatitis</b>	Grade 1 or 2	No change to Nab-paclitaxel or paclitaxel and carboplatin
	$\geq$ Grade 3	Hold Nab-paclitaxel or paclitaxel until resolved to $\leq$ grade 1. <ul style="list-style-type: none"> <li>• Resume nab-paclitaxel or paclitaxel and /or carboplatin at previous dose with modification of premedication</li> <li>• Second episode <math>\geq</math> Grade 3 despite with maximum supportive care, reduce Nab-paclitaxel to <math>100\text{mg}/\text{m}^2</math> or <math>75\text{mg}/\text{m}^2</math>, and paclitaxel to <math>70\text{ mg}/\text{m}^2</math> and/ or carboplatin to AUC 5 or AUC 4 for all subsequent cycles</li> </ul>

Toxicities	Grade or actual value	Nab-paclitaxel or paclitaxel alone or with carboplatin
Neurotoxicity	Grade 1–2	No change to nab-paclitaxel or paclitaxel and carboplatin
	Grade 3	Hold nab-paclitaxel or paclitaxel and /or carboplatin until neuropathy improves to $\leq$ grade 2. <ul style="list-style-type: none"> <li>Resume nab-paclitaxel dose reduced to 100mg/m<sup>2</sup> or 75mg/m<sup>2</sup>, and paclitaxel to 70 mg/m<sup>2</sup> and/ or carboplatin to AUC 5 or AUC 4 for all subsequent doses.</li> <li>Discontinue nab-paclitaxel or paclitaxel and/ or carboplatin if held for <math>\geq</math> 3 weeks in a row, (see general instruction at the beginning of the section)</li> </ul>
	Grade 4	<ul style="list-style-type: none"> <li>Discontinue nab-paclitaxel or paclitaxel and/or carboplatin if held for <math>\geq</math> 3 weeks in a row, (see general instruction at the beginning of the section)</li> </ul>
Hepatic	Grade 1	<ul style="list-style-type: none"> <li>No change to nab-paclitaxel or paclitaxel and/or carboplatin</li> </ul>
	$\geq$ Grade 2 or 3	<ul style="list-style-type: none"> <li>Bilirubin fractionation should be performed if total bilirubin <math>&gt;</math> 1.5xULN. Dose may continue if isolated bilirubinemia is mostly indirect such as in subject with Gilbert</li> <li>Hold nab-paclitaxel or paclitaxel and/or carboplatin until resolve to Grade 1 and resume the dose at previous level</li> <li>Discontinue nab-paclitaxel or paclitaxel and/or carboplatin if held for <math>\geq</math> 3 weeks in a row, (see general instruction at the beginning of the section)</li> </ul>
	Grade 4	<ul style="list-style-type: none"> <li>Discontinue nab-paclitaxel or paclitaxel and/or carboplatin (see general instruction at the beginning of the section)</li> </ul> Note all concurrent ALT/AST $>$ 3xULN and Total bilirubin $>$ 2xULN should be discontinued and evaluated for potential Hy's law
Anaphylaxis /hypersensitivity	severe	<ul style="list-style-type: none"> <li>Stop infusion immediately and discontinue treatment (see general instruction at the beginning of the section)</li> </ul>
Other significant toxicities excluding fatigue, alopecia and leukopenia at discretion of the investigators	Grade 2	<ul style="list-style-type: none"> <li>Hold nab-paclitaxel or paclitaxel and/or carboplatin until resolve to <math>\leq</math> Grade 1</li> <li>Resume at the previous dose and increase supportive care measure, if available</li> </ul>
	$\geq$ Grade 3	<ul style="list-style-type: none"> <li>Hold nab-paclitaxel or paclitaxel and/or carboplatin, and discuss with sponsor medical monitor for further instructions</li> <li>If <math>\geq</math> Grade 3 toxicity recurs upon rechallenge, discontinue treatment permanently</li> </ul>

Table 9 Dose Modification Guidelines for Doxorubicin and Cyclophosphamide (AC)

Toxicities	Grade or actual value	Doxorubicin and cyclophosphamide
<b>Hematological</b>		
<b>Neutropenia</b>	$\geq 1000/\text{mm}^3$ (G2/G1)	No change to AC
	$< 1000/\text{mm}^3$ G3/G4	Hold AC until $\text{ANC} \geq 1000/\text{mm}^3$ . Resume AC based on timing of recovery: <ul style="list-style-type: none"> <li>• <math>\leq 1</math> week: No change to AC</li> <li>• <math>\geq 1</math> but <math>&lt; 3</math> weeks: Reduce AC by 20% for all subsequent cycles.</li> <li>• <math>\geq 3</math> weeks: discontinue AC (see general instruction at the beginning of the section)</li> </ul>
<b>Febrile neutropenia</b>	$\text{ANC} \leq 1000/\text{mm}^3$ , fever $\geq 38.5^\circ\text{C}$ G3 and G4	Hold AC until resolved ( $\text{ANC} > 1000/\text{mm}^3$ , fever $< 38.5^\circ\text{C}$ , and resolution of any signs of infection) Resume AC according to number of episodes: <ul style="list-style-type: none"> <li>• First episode: no change to AC.</li> <li>• Second episode: Reduce AC by 20% for all subsequent cycles</li> <li>• Third episode: Discontinue AC (see general instruction at the beginning of the section)</li> </ul>
<b>Thrombocytopenia</b>	$75 - < 100,000/\text{mm}^3$ Grade 1	Hold AC until $\geq 100,000/\text{mm}^3$ , resume paclitaxel based on timing of recovery: <ul style="list-style-type: none"> <li>• <math>\leq 1</math> week—no change to AC.</li> <li>• <math>&gt; 1</math> but <math>&lt; 3</math> weeks— Reduce AC by 20% for all subsequent cycles</li> <li>• <math>\geq 3</math> weeks: Discontinue AC (see general instruction at the beginning of the section)</li> </ul>
	$< 75,000/\text{mm}^3$ $\geq$ Grade 2	Hold AC until $\geq 100,000/\text{mm}^3$ . <ul style="list-style-type: none"> <li>• Reduce AC by 20% for all subsequent cycles</li> <li>• Discontinue AC if held for <math>\geq 3</math> weeks in a row, (see general instruction at the beginning of the section)</li> </ul>
<b>Anemia</b>	All grades	No change to AC <ul style="list-style-type: none"> <li>• Iron studies should be done and iron should be replaced as indicated.</li> <li>• Red blood cell transfusions can be given at the investigators discretion.</li> </ul>
<b>Nausea/Vomiting</b>	Grade 1 or 2	No change to AC
	$\geq$ Grade 3	Hold AC until resolved to $\leq$ grade 1. <ul style="list-style-type: none"> <li>• Resume AC at previous dose with modification of premedication</li> <li>• Second episode <math>\geq</math> Grade 3 despite with maximum supportive care, reduce AC by 20% for all subsequent cycles</li> </ul>
<b>Mucositis/Stomatitis</b>	Grade 1 or 2	No change to AC
	$\geq$ Grade 3	Hold AC until resolved to $\leq$ grade 1. <ul style="list-style-type: none"> <li>• Resume AC at previous dose with modification of premedication</li> <li>• Second episode <math>\geq</math> Grade 3 despite with maximum supportive care, reduce AC by 20% for all subsequent cycles</li> </ul>

Toxicities	Grade or actual value	Doxorubicin and cyclophosphamide
Hepatic	Grade 1	<ul style="list-style-type: none"> <li>No change to AC</li> </ul>
	≥ Grade 2 or 3	<ul style="list-style-type: none"> <li>Hold AC until resolve to Grade 1 and resume the dose at previous level</li> <li>Discontinue AC if held for ≥ 3 weeks in a row, (see general instruction at the beginning of the section)</li> </ul>
	Grade 4	<ul style="list-style-type: none"> <li>Discontinue AC (see general instruction at the beginning of the section)</li> </ul> Note all concurrent ALT/AST >3xULN and Total bilirubin >2xULN should be discontinued and evaluated for potential Hy's law
Cardiac toxicity	Grade 1 or 2	<ul style="list-style-type: none"> <li>No change to AC</li> </ul>
	≥ Grade 3	<ul style="list-style-type: none"> <li>Discontinue doxorubicin (see general instruction at the beginning of the section)</li> </ul>
Anaphylaxis/ hypersensitivity	Mild	<ul style="list-style-type: none"> <li>Complete AC infusion, observe until symptom resolved</li> </ul>
	moderate	<ul style="list-style-type: none"> <li>Stop infusion and treat per standard practice</li> <li>Resume infusion at half of the infusion speed if symptom resolve</li> <li>Stop if symptom recurs</li> </ul>
	severe	<ul style="list-style-type: none"> <li>Stop infusion immediately and discontinue treatment (see general instruction at the beginning of the section)</li> </ul>
Other significant toxicities excluding fatigue, alopecia and leukopenia at discretion of the investigators	Grade 2	<ul style="list-style-type: none"> <li>Hold AC until resolve to ≤ Grade 1</li> <li>Resume at the previous dose and increase supportive care measure, if available</li> </ul>
	≥ Grade 3	<ul style="list-style-type: none"> <li>Hold AC and discuss with sponsor medical monitor for further instructions</li> <li>If ≥ Grade 3 toxicity recurs upon rechallenge, discontinue treatment permanently</li> </ul>

## 5.2.2 Timing of Dose Administration

On each trial treatment dosing day, trial treatments should be administered after all procedures/ assessments have been completed as listed in the Trial Flow Chart (Section 6).

Refer to the product label for detailed instructions on preparation and administration precautions on combination chemotherapy agents included in the trial: nab-paclitaxel, carboplatin, doxorubicin and cyclophosphamide.

### 5.2.2.1 Pembrolizumab

Pembrolizumab will be administered on Cycle 1 Day 1 (with a window of +3 days) as the first trial treatment. For Cycle 2-9, trial treatments should be administered in accordance with the schedules provided in Table 3 (Section 5.2) with a window of +/- 2 days for Cycle 2-5 and a window of +/- 3 days for Cycle 6-9.

At each treatment, a fixed dose of 200 mg pembrolizumab will be administered as a 30 minute IV infusion. Sites should make every effort to target infusion timing to be as close to 30 minutes as possible. However, given the variability of infusion pumps from site to site,

a window of -5 minutes and +10 minutes is permitted (i.e., infusion time is 30 minutes: -5 min/+10 min).

The Pharmacy Manual contains specific instructions for pembrolizumab reconstitution, preparation of the infusion fluid, and administration.

When pembrolizumab is administered on the same day with chemotherapy agents, pembrolizumab should be administered prior to chemotherapy agents.

#### **5.2.2.2 Nab-paclitaxel**

Nab-paclitaxel, at a dose level of 125mg/m<sup>2</sup> or 100mg/m<sup>2</sup>, will be administered on Days 1, 8, and 15 during Cycle 2-5 as IV infusion administered per institutional guidelines. .

For Cohort A, when nab-paclitaxel is administered on the same day with pembrolizumab during Cycle 2-5, nab-paclitaxel should be administered after pembrolizumab.

For Cohorts B, C, and D, when nab-paclitaxel is administered on the same day together with pembrolizumab and carboplatin, nab-paclitaxel should be administered after pembrolizumab but prior to the administration of carboplatin.

Premedication to prevent hypersensitivity reactions is generally not required for nab-paclitaxel per product label.

#### **5.2.2.3 Paclitaxel**

Paclitaxel, at a dose level of 80mg/m<sup>2</sup> will be administered on Days 1, 8, and 15 during Cycle 2-5 as IV infusion administered per institutional guidelines.

For Cohorts E, and F, when paclitaxel is administered on the same day together with pembrolizumab and carboplatin, paclitaxel should be administered after pembrolizumab but prior to the administration of carboplatin.

Additional premedication should be administered as per standard practice.

#### **5.2.2.4 Carboplatin**

Carboplatin at AUC 6 or 5, will be administered on Day 1 of Cycles 2-5 and carboplatin at AUC 2 or 1.5 will be administered on Day 1, 8, 15 of Cycles 2-5 as an IV infusion administered per institutional guidelines immediately following the administration of nab-paclitaxel. Additional premedication should be administered as per standard practice.

#### **5.2.2.5 Cyclophosphamide**

Cyclophosphamide should be administered intravenously per institutional guidelines on Day 1 of Cycle 6-9 following the administration of pembrolizumab. Additional premedication should be administered as per standard practice.

#### **5.2.2.6 Doxorubicin**

Doxorubicin should be administered IV push on Day 1 of Cycle 6-9 following the administration of pembrolizumab. Additional premedication should be administered as per standard practice.

### **5.2.3 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**

At any time during Part 1 or Part 2 of the study, if more than one cohort is open for enrollment, eligible subjects will be randomly assigned to a cohort; otherwise, subjects will be enrolled to the cohort that is open for enrollment.

Treatment allocation will occur centrally using an interactive voice response/integrated web response system (IVRS/IWRS).

### **5.4 Stratification**

No stratification based on age, sex or other characteristics will be used in this trial.

### **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 any medication or vaccination specifically prohibited during the trial, discontinuation from trial therapy or vaccination may be required. The investigator should discuss any questions regarding this with the Sponsor Clinical Director. The final decision on any supportive therapy or vaccination rests with the investigator and/or the subject's primary physician. However, the decision to continue the subject on trial therapy or vaccination schedule requires the mutual agreement of the investigator, the Sponsor and the subject.

#### **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.

Supportive care is permitted for managing drug-related toxicities. See guidelines in Section 5.6 for more details.

All concomitant medications received within 28 days before the first dose of trial treatment through the safety follow-up visit should be recorded. After the safety follow-up visit, record all medications administered for the treatment of SAEs and ECIs as defined in Section 7.2.

#### **5.5.2 Prohibited Concomitant Medications**

Subjects are prohibited from receiving the following therapies from the time of screening until after definitive surgery:

- Immunotherapy not specified in this protocol
- Chemotherapy not specified in this protocol

- Investigational agents not specified in this protocol
- Radiation therapy
- Live vaccines within 30 days prior to the first dose of trial treatment and while participating in the trial. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, varicella, zoster, yellow fever, intranasal influenza, rabies, BCG, and typhoid vaccine.

*Note: Seasonal influenza vaccines for injection are generally inactivated flu vaccines and are allowed; however intranasal influenza vaccines (e.g., Flu-Mist®) are live attenuated vaccines, and are not allowed.*

- Glucocorticoids for any purpose other than to modulate symptoms from an irAE of suspected immunologic etiology or for use as a pre-medication for chemotherapeutic agents specified in the protocol.
  - *Note: Inhaled steroids are allowed for management of asthma.*
  - *Note: Use of prophylactic corticosteroids to avoid allergic reactions (e.g., to IV contrast dye) is permitted.*

Subjects who are discontinued from the study treatment and continue with other neoadjuvant treatment prior to the definitive surgery will be inevaluable for pCR and/or imaging evaluations. Details are described in Section 8.4. The anti-cancer treatment received will be recorded in the CRF. Subjects may receive other medications that the investigator deems to be medically necessary. If there is a clinical indication for any medication or vaccination specifically prohibited during the trial, discontinuation from trial therapy may be required.

Following the definitive surgery, subjects can receive adjuvant treatment or metastatic treatments based on subject's disease status, with the regimen at the discretion of the subject's physician.

The Exclusion Criteria describes other prior medications prohibited for trial enrollment.

Site staff should refer to the local product label for permitted and prohibited medications, as well as, drug interactions for each chemotherapy agent used as trial treatment.

## **5.6 Rescue Medications & Supportive Care**

### **5.6.1 Supportive Care Guidelines for Pembrolizumab**

Subjects should receive appropriate supportive care measures as deemed necessary by the treating investigator. Suggested supportive care measures for the management of AEs with potential immunologic etiology are outlined along with the dose modification guidelines in Section 5.2.1.5.1, [Table 5]. Where appropriate, these guidelines include the use of oral or IV 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 of the event, it is determined not to be related to pembrolizumab, the Investigator does not need to follow the treatment guidance. Refer to [Table 6] in Section 5.2.1.5.1 for guidelines regarding dose modification and supportive care.

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

## **5.6.2 Supportive Care Guidelines for Chemotherapy Agents**

Instructions regarding supportive care for the chemotherapeutic agents administered in this study can be found in the local product label for each agent. Infusion reactions and injection site reactions will be managed by the investigators according to the local product labels.

## **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.

Female subjects will be considered of non-reproductive potential if they are either:

1. postmenopausal (defined as at least 12 months with no menses without an alternative medical cause; in women < 45 years of age a high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a post-menopausal state in women not using hormonal contraception or hormonal replacement therapy. In the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.);

OR

2. have had a hysterectomy and/or bilateral oophorectomy, bilateral salpingectomy or bilateral tubal ligation/occlusion, at least 6 weeks prior to screening;

OR

3. has a congenital or acquired condition that prevents childbearing.

Female subjects of reproductive potential must agree to avoid becoming pregnant while receiving study drug and for 12 months after the last dose of study drug for subjects who have received cyclophosphamide, and for six months after the last dose of study medication for subjects who have not, by complying with one of the following:

1. practice abstinence<sup>†</sup> from heterosexual activity;

OR

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

Acceptable methods of contraception are<sup>†</sup>:

1. Single method (one of the following is acceptable):

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

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

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

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

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

Subjects should be informed that taking the study medication may involve unknown risks to the fetus (unborn baby) if pregnancy were to occur during the study. In order to participate in the study subjects of childbearing potential must adhere to the contraception requirement (described above) from the day of study medication initiation (or 14 days prior to the initiation of study medication for oral contraception) throughout the study period up to 12 months after the last dose of trial therapy for subjects who have received cyclophosphamide, and for six months after the last dose of study medication for subjects who have not. If there is any question that a subject of childbearing potential will not reliably comply with the requirements for contraception, that subject should not be entered into the study.

### **5.7.3 Pregnancy**

If a subject inadvertently becomes pregnant while on treatment with pembrolizumab, the subject will immediately be removed from study treatment. The site will contact the subject at least monthly and document the subject's status until the pregnancy has been completed or terminated. The outcome of the pregnancy will be reported to the Sponsor without delay and within 24 hours if the outcome is a serious adverse experience (e.g., death, abortion, congenital anomaly, or other disabling or life-threatening complication to the mother or

newborn). The study investigator will make every effort to obtain permission to follow the outcome of the pregnancy and report the condition of the fetus or newborn to the Sponsor.

#### **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 procedures; including specific details regarding withdrawal from Future Biomedical Research, are provided in Section 7.1.4 – Other Procedures.

In this trial, a subject may discontinue from treatment but continue to participate in the regularly scheduled activities, as long as the subject does not withdraw consent. Once a subject has discontinued treatment, even though he/she continues to be monitored in the trial, he/she may be allowed to begin treatment again if deemed medically appropriate.

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.
- The subject is lost to follow-up

A subject must be discontinued from treatment (but should continue to be monitored in the trial) for any of the following reasons:

- The subject or legal representative (such as a parent or legal guardian) withdraws consent for treatment
- Unacceptable adverse experiences as described in Section 5.2.1.5.2
- Intercurrent illness that prevents further administration of treatment
- Investigator's decision to withdraw the subject from study treatment due to disease progression or other reasons. See Section 7.1.2.10 for details on disease progression evaluation.
- The subject has a confirmed positive serum pregnancy test
- Noncompliance with trial treatment or procedure requirements
- Administrative reasons

The End of Treatment/Early Discontinuation and Follow-up visit procedures are listed in Section 6 (Protocol Flow Chart) and Section 7.1.5 (Visit Requirements). Following definitive surgery, each subject will be followed for 30 days for any adverse events (serious adverse events will be collected for 90 days after definitive surgery or 30 days

following definitive surgery if the subject initiates new anticancer therapy, whichever is earlier, as described in Section 7.2.3.1).

### **5.9 Subject Replacement Strategy**

Refer to Section 5.2.1.4 for replacement of subjects in Part 1 of the trial. A subject who discontinues from Part 2 of the trial will not be replaced.

### **5.10 Beginning and End of the Trial**

The overall trial begins when the first subject signs the informed consent form. The overall trial ends when the last subject completes the last study-related phone-call or visit, discontinues from the trial or is lost to follow-up (i.e. the subject is unable to be contacted by the investigator).

### **5.11 Clinical Criteria for Early Trial Termination**

The clinical trial may be terminated early if the extent (incidence and/or severity) of emerging effects/clinical endpoints is such that the risk/benefit ratio to the trial population as a whole is unacceptable. In addition, further recruitment in the trial or at (a) particular trial site(s) may be stopped due to insufficient compliance with the protocol, GCP and/or other applicable regulatory requirements, procedure-related problems or the number of discontinuations for administrative reasons is too high.

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

1. Quality or quantity of data recording is inaccurate or incomplete as assessed by the Sponsor
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 Sponsor 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 FLOW CHART

Trial Period:	Screening Phase	Treatment Phase <sup>a</sup>																	End of Treatment or early discon <sup>b</sup> .	Surgery	Post-Surgery		
Treatment Cycle:	Screening	C1 D1	C2 D1	C2 D8	C2 D15	C3 D1	C3 D8	C3 D15	C4 D1	C4 D8	C4 D15	C5 D1	C5 D8	C5 D15	C6 D1	C7 D1	C8 D1	C9 D1			Safety Follow-up Visit	Survival Follow Up <sup>c</sup>	
Scheduling Window (Days) <sup>d</sup> :	-28 to -1	+3	±2	±2	±2	±2	±2	±2	±2	±2	±2	±2	±2	±2	±2	±3	±3	±3	±3	3-6 weeks post treatment but prior to surgery	3-6 wks. post trmt.	30 days post surgery (± 3 days)	Every 12 weeks (±2 weeks)
<b>Administrative Procedures</b>																							
Informed Consent <sup>e</sup>	X																						
Informed Consent for Future Biomedical Research	X <sup>f</sup>																						
Inclusion/Exclusion Criteria	X																						
Subject Identification Card	X																						
Demographics and Medical History	X																						
Prior and Concomitant Medication Review <sup>g</sup>	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Treatment allocation via IVRS/IWRS		X																					
End of Treatment/Post-study Anticancer Therapy Status																				X		X	
Survival Status																						X	
<b>Administration of Trial Treatment</b>																							
Pembrolizumab		X	X			X			X			X			X	X	X	X					
Nab-paclitaxel			X	X	X	X	X	X	X	X	X	X	X	X									
Paclitaxel			X	X	X	X	X	X	X	X	X	X	X	X									

Trial Period:	Screening Phase	Treatment Phase <sup>a</sup>																	End of Treatment or early discon <sup>b</sup> .	Surgery	Post-Surgery						
		C1 D1	C2 D1	C2 D8	C2 D15	C3 D1	C3 D8	C3 D15	C4 D1	C4 D8	C4 D15	C5 D1	C5 D8	C5 D15	C6 D1	C7 D1	C8 D1	C9 D1			Safety Follow-up Visit	Survival Follow Up <sup>c</sup>					
Scheduling Window (Days) <sup>d</sup> :	-28 to -1	+3	±2	±2	±2	±2	±2	±2	±2	±2	±2	±2	±2	±2	±2	±2	±2	±2	±3	±3	±3	±3	3-6 weeks post treatment but prior to surgery	3-6 wks. post trmt.	30 days post surgery (± 3 days)	Every 12 weeks (±2 weeks)	
Carboplatin (Cohorts B C & E)			X			X			X			X															
Carboplatin (Cohorts D & F)			X	X	X	X	X	X	X	X	X	X	X	X													
Doxorubicin																			X	X	X	X					
Cyclophosphamide																			X	X	X	X					
<b>Clinical Safety Assessments</b>																											
Review Adverse Events <sup>h</sup>	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X <sup>i</sup>		X <sup>i</sup>		
12-Lead ECG (Locally performed)	X																		X				X				
MUGA or ECHO for LVEF Assessment	X																										
Full Physical Examination	X																										
Directed Physical Examination		X	X			X			X			X							X	X	X	X	X				
Vital Signs, Height and Weight <sup>j</sup>	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X	
ECOG Performance Status <sup>k</sup>	X	X	X			X			X			X							X	X	X	X	X		X		
<b>Laboratory tests/ analysis by a LOCAL laboratory</b>																											
Pregnancy Test – Urine or Serum β-HCG <sup>l</sup>	X																										
Blood for menopausal status (if applicable) <sup>m</sup>	X																										

Trial Period:	Screening Phase	Treatment Phase <sup>a</sup>																	End of Treatment or early discon <sup>b</sup> .	Surgery	Post-Surgery		
		C1 D1	C2 D1	C2 D8	C2 D15	C3 D1	C3 D8	C3 D15	C4 D1	C4 D8	C4 D15	C5 D1	C5 D8	C5 D15	C6 D1	C7 D1	C8 D1	C9 D1			Safety Follow-up Visit	Survival Follow Up <sup>c</sup>	
Treatment Cycle:	Screening																						
Scheduling Window (Days) <sup>d</sup> :	-28 to -1	+3	±2	±2	±2	±2	±2	±2	±2	±2	±2	±2	±2	±2	±2	±2	±2	±2	±2	3-6 weeks post treatment but prior to surgery	3-6 wks. post trmt.	30 days post surgery (± 3 days)	Every 12 weeks (±2 weeks)
PT/INR and aPTT/PTT <sup>n</sup>	X																						
CBC with Differential <sup>p</sup>	X <sup>o</sup>		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X <sup>q</sup>	
Chemistry Panel <sup>p</sup>	X <sup>o</sup>		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X <sup>q</sup>	
Urinalysis <sup>p</sup>	X <sup>o</sup>		X			X						X			X	X	X	X	X	X		X <sup>q</sup>	
T3, FT4 and TSH <sup>p</sup>	X <sup>o</sup>											X						X	X	X			
<b>Laboratory tests/ analysis by a CENTRAL laboratory</b>																							
Blood for Exploratory Biomarkers (Plasma, Serum) <sup>f</sup>	X		X			X												X	X				
Correlative Blood Samples (DNA, RNA) <sup>g</sup>		X	X			X												X	X				
Blood for Genetics <sup>l</sup>		X																					
<b>Efficacy Measurements</b>																							
Breast MRI and clinical tumor staging	X																		X <sup>u</sup>	X <sup>u</sup>			
pCR assessment																					X		
<b>Tumor Tissue sample collection</b>																							
Core tumor tissue biopsy for translational research	X	X <sup>u</sup>						X <sup>v</sup>															
Definitive surgery																					X <sup>w</sup>		
FFPE tissue or slides for TNBC status <sup>x</sup>	X																						

- a. In general, assessments/procedures are performed on Day 1 of each cycle prior to dosing of any study treatment (or prior to weekly dosing of nab-paclitaxel) unless otherwise specified. Each treatment cycle is 3 weeks (21 days); If treatment is delayed, all procedures should be performed based on the new dosing schedule.
- b. The End of Treatment/Discontinuation Visit should be conducted 3-6 weeks post treatment discontinuation and before definitive surgery.
- c. After the completion of definitive surgery, the subject should be contacted by telephone every 12 weeks ( $\pm$  2weeks) to assess for survival or disease recurrence status.
- d. Site personnel will access the IVRS prior to dosing on Cycle 1, Day 1 to obtain the subject's allocation number. Cycle 1 treatment must be given within 3 days following allocation (+ 3 days). The window for each visit during Cycle 2 through Cycle 5 is  $\pm$ 2 days and the window for each visit during Cycle 6 through Cycle 9 is  $\pm$  3 days.
- e. Written consent must be obtained prior to performing any protocol specified procedure. Results of a test performed prior to the subject signing consent as part of routine clinical management are acceptable in lieu of a screening test if performed within the specified time frame (e.g., within 28 days prior to the first dose of trial treatment). Screening number will be assigned when the trial informed consent is signed.
- f. Signing the informed consent for future biomedical research (FBR) sample is optional. Detailed instructions for the collection and management of specimens for FBR are provided in the Procedures Manual and Section 12.2.
- g. Prior medications – Record all medications taken within 30 days prior to the screening visit. Concomitant medications – Enter new medications started during the screening period through the Safety Follow-up visit. Record all medications taken for AEs as defined in Section 7.2.
- h. AEs and laboratory safety measurements will be graded per NCI CTCAE version 4.0. All AEs, whether gradable by CTCAE or not, will also be evaluated for seriousness.
- i. Report all AEs occurring up until 30 days following definitive surgery and all SAEs occurring up until 90 days following definitive surgery, or 30 days following definitive surgery if the subject initiates new anticancer therapy, whichever is earlier.
- j. Vital signs to include temperature, pulse, respiratory rate and blood pressure. Height will be measured at Screening only; weight will be measured at baseline and at each cycle. Vital signs will be collected weekly during Cycle 2 through Cycle 5.
- k. ECOG PS at Screening to be performed within 10 days prior to of the first dose of trial treatment. ECOG performance status will also be performed prior to the administration of each dose of trial treatment at every cycle, at treatment discontinuation, and at follow-up.
- l. For women of childbearing potential, a serum or urine pregnancy test should be performed within 72 hours prior to first dose of trial treatment. If urine pregnancy results are positive or cannot be confirmed as negative, a serum pregnancy test performed by the local study site laboratory will be required. Pregnancy tests (serum and/or urine tests) should be repeated if required by local guidelines.
- m. Blood for menopausal status may be required for certain subjects as described in Section 7.1.3.2.
- n. Coagulation factors (PT/INR and aPTT/PTT) should be tested for all subjects at baseline and monitored closely in subjects receiving anticoagulant therapy during treatment and safety follow-up period.
- o. See Section 7.1.3 for details regarding laboratory parameters to be included.
- p. After Cycle 1, predose lab samples can be collected up to 72 hours prior to the scheduled time point.
- q. Unresolved abnormal labs that are drug-related AEs should be followed until resolution. Labs do not need to be repeated after the end of treatment if labs are within normal range.
- r. Blood for exploratory biomarkers (plasma, serum) is to be collected at screening, predose on Day 1 of Cycles 2, 3, and 6, and at End of Treatment/Early Discontinuation. See Procedures Manual. Any leftover samples from the blood studies will be stored for future biomedical research if the subject signs the FBR consent.
- s. Correlative blood samples for RNA/DNA should be collected at predose on Day 1 of Cycles 1, 2, 3, and 6, and at End of Treatment/Early Discontinuation. See Procedures Manual. Any leftover samples from the blood studies will be stored for future biomedical research if the subject signs the FBR consent.
- t. This sample should be drawn for planned analysis of the association between genetic variants in DNA and drug response. If there is either a documented law or regulation prohibiting collection, or if the IRB/IEC does not approve the collection of the sample for these purposes, then this sample will not be collected at that site. If the sample is collected, leftover extracted DNA will be stored for future biomedical research if the subject signs the FBR consent. If the planned genetic analysis is not approved, but FBR is approved and consent is given, this sample will be collected for the purpose of FBR.
- u. Biopsy and MRI should be conducted between Day 15 through Day 21 of the designated cycle. Leftover tumor tissue will also be stored for FBR if the subject consents. Post-treatment MRI should be conducted within 3-6 weeks following discontinuation of trial treatment and prior to definitive surgery.
- v. For subjects with adequate tumor volume left at the end of Cycle 3 as assessed by the investigator, an additional core needle biopsy will be performed only on subjects who are willing to participate.



- w. Any remaining tumor tissue collected at definitive surgery will be stored for FBR if the subject consents.
- x. FFPE tissue or slides from the subject's initial diagnosis of TNBC should be provided at screening and will be sent to a central pathology laboratory for retrospective confirmation of TNBC diagnosis at the end of the study or at a time point designated by the Sponsor.

## **7.0 TRIAL PROCEDURES**

### **7.1 Trial Procedures**

The Trial Flow Chart - Section 6.0 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 the investigator and or the Sponsor 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.

#### **7.1.1 Administrative Procedures**

##### **7.1.1.1 Informed Consent**

The investigator or qualified designee must obtain documented consent from each potential subject or each subject's legally acceptable representative prior to participating in a clinical trial or Future Biomedical Research.

###### **7.1.1.1.1 General Informed Consent**

Consent must be documented by the subject's dated signature or by the subject's legally acceptable representative's dated signature on a consent form along with the dated signature of the person conducting the consent discussion.

A copy of the signed and dated consent form should be given to the subject before participation in the trial.

The initial informed consent form, any subsequent revised written informed consent form and any written information provided to the subject must receive the IRB/ERC's approval/favorable opinion in advance of use. The subject or his/her legally acceptable representative should 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 or by the subject's legally acceptable representative's dated signature.

Specifics about a trial and the trial population will be added to the consent form template at the protocol level.

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

###### **7.1.1.1.2 Consent and Collection of Specimens for Future Biomedical Research**

The investigator or qualified designee will explain the Future Biomedical Research consent to the subject, answer all of his/her questions, and obtain written informed consent before

performing any procedure related to the Future Biomedical Research sub-trial. A copy of the informed consent will be given to the subject.

#### **7.1.1.2 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.

#### **7.1.1.3 Subject Identification Card**

All subjects will be given a Subject Identification Card identifying them as participants in a research trial. The card will contain trial site contact information (including direct telephone numbers) to be utilized in the event of an emergency. The investigator or qualified designee will provide the subject with a Subject Identification Card immediately after the subject provides written informed consent.

The subject identification card also contains contact information for the emergency unblinding call center so that a health care provider can obtain information about trial medication/vaccination in emergency situations where the investigator is not available.

#### **7.1.1.4 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. Any autoimmune disorders, regardless of onset date, should be recorded. Details regarding the subject's TNBC will be recorded under medical history CRF, see Section 7.1.1.4.1 for further instructions.

##### **7.1.1.4.1 Disease Details**

Details regarding subject's TNBC history and status at baseline must be thoroughly evaluated by the investigator or qualified designee and recorded in the appropriate eCRF including: date of initial diagnosis, stage at diagnosis, tumor grade, primary tumor location and type (i.e. single lesion, multicentric, multifocal), TNM staging at baseline, sentinel lymph node biopsies and results, etc. Refer to Section 5.1 to ensure subject's disease status meets the relevant inclusion and exclusion criteria for study entry.

##### **7.1.1.4.2 Menopausal Status**

The investigator or qualified designee will obtain details regarding the subject's menopausal status as specified (or defined) in Section 7.1.3.2.

#### **7.1.1.5 Prior and Concomitant Medications Review**

##### **7.1.1.5.1 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 30 days prior to the screening visit.

### **7.1.1.5.2 Concomitant Medications**

The investigator or qualified designee will record medication, if any, taken by the subject starting at the screening visit through the Safety Follow-up Visit. All medications related to reportable AEs, SAEs and ECIs, including AEs and SAEs following definitive surgery should be recorded as defined in Section 7.2.

### **7.1.1.6 Assignment of Screening Number**

All consented subjects will be given a unique screening number that will be used to identify the subject for all procedures that occur prior to randomization or treatment allocation. Each subject will be assigned only one screening number. Screening numbers must not be re-used for different subjects.

Any subject who is screened multiple times will retain the original screening number assigned at the initial screening visit.

Specific details on the screening visit requirements (screening/rescreening) are provided in Section 7.1.5.1.

### **7.1.1.7 Assignment of Treatment/Randomization Number**

All eligible subjects will receive a treatment number. The treatment number identifies the subject for all procedures occurring after treatment allocation. Once a treatment number is assigned to a subject, it can never be re-assigned to another subject. A single subject cannot be assigned more than 1 treatment number.

### **7.1.1.8 Trial Compliance (Medication/Diet/Activity/Other)**

Interruptions from the protocol specified treatment for greater than 6 weeks between doses require consultation between the investigator and the Sponsor and written documentation of the collaborative decision on subject management.

Administration of trial medication will be witnessed by the investigator and/or trial staff. The total volume of pembrolizumab or combination product infused will be compared to the total volume prepared to determine compliance with each dose of pembrolizumab or combination product administered. The instructions for preparing and administering pembrolizumab will be provided in the Pharmacy Manual. Refer to the product label for instructions on preparation and administration precautions on combination chemotherapy agents included in the trial: nab-paclitaxel, carboplatin, doxorubicin and cyclophosphamide.

## **7.1.2 Clinical Procedures/Assessments**

### **7.1.2.1 Adverse Event 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 events will be graded and recorded throughout the study and during the follow-up period according to NCI CTCAE Version 4.0 (see Section 12.5). 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 ECI of a potentially immunologic etiology (termed immune-related adverse events, or irAEs).

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

#### **7.1.2.2 12-Lead Electrocardiogram (ECG)**

A 12-lead ECG will be performed using local standard procedures at the time points specified in Section 6.0 – Trial Flow Chart. Clinically significant abnormal findings should be recorded as medical history. Additional assessments may be performed as clinically necessary.

#### **7.1.2.3 Echocardiography (ECHO) or Multigated Acquisition (MUGA) Scan**

An ECHO or MUGA scan will be required at screening for all subjects to determine study eligibility. The assessment method will be at the investigators discretion and per the local SOC. Additional assessments may be performed as clinically necessary.

#### **7.1.2.4 Physical Exam**

##### **7.1.2.4.1 Full Physical Exam**

The investigator or qualified clinical designee will perform a complete physical exam during the screening period. Clinically significant abnormal findings should be recorded as medical history. After study enrollment new clinically significant abnormal findings should be recorded as AEs.

##### **7.1.2.4.2 Directed Physical Exam**

The investigator or qualified clinical designee will perform directed physical exams to assess subject's TNBC status according to the time points as specified in the Trial Flow Chart or as needed according to subject's signs and symptoms. New clinically significant abnormal findings should be recorded as AEs

##### **7.1.2.5 Vital Signs**

The investigator or qualified clinical designee will take vital signs at screening, prior to the administration of each dose of trial treatment, at treatment discontinuation, and at the Follow-up Visit as specified in the Trial Flow Chart. Vital signs should include temperature, pulse, respiratory rate, weight and blood pressure. Height will be measured at screening only. Vital signs should be taken prior to treatment administration.

##### **7.1.2.6 Eastern Cooperative Oncology Group (ECOG) Performance Status**

The investigator or qualified clinical designee will assess ECOG status (Section 12.4) at screening, prior to dosing on Day 1 of each treatment cycle, at discontinuation of trial treatment and at the Follow-up Visit as specified in the Trial Flow Chart.

### **7.1.2.7 Tumor Tissue Biopsy and Sample Collection**

In accordance with the study inclusion criteria, subjects are required to have 2 core needle biopsies (fine needle aspirate not adequate) performed during the Screening Period and agree to have a core needle biopsy performed at the end of Cycle 1 (Days 15-21) if clinically feasible as judged by the investigator (See Section 6.0 – Trial Flow Chart). For subjects with adequate tumor volume left at the end of Cycle 3 as assessed by the investigator, an additional core needle biopsy will be performed only on subjects who agree to participate. Tumor tissue samples obtained from these biopsies will be used for translational research as specified in Section 4.2.3.3.

The Screening biopsy should be performed preferably after subject has met all other eligibility criteria. At least two core biopsies should be obtained and prepared according to the instructions outlined in the Procedures Manual for this trial. If feasible, two core biopsies should be obtained at each of the additional time points. These tumor tissues will be submitted to the designated central laboratory.

If the subject signs the Future Biomedical Research (FBR) consent, any leftover tissue that would ordinarily be discarded at the end of the main study will be retained for FBR as specified in Section 4.2.3.4.

Additionally, archived tumor tissue specimens obtained during subject's initial diagnosis will be collected at Screening for retrospective confirmation of TNBC status by a central pathology vendor.

Detailed instructions for tissue collection, processing and shipment are provided in the Procedures Manual.

### **7.1.2.8 Imaging Disease Assessment**

Subjects must have evidence of non-metastatic disease (M0) based on the assessments from their initial diagnosis. In the event of suspected regional or distant metastasis during Screening, subjects should be thoroughly evaluated as clinically indicated; and those with metastatic disease should be excluded. At Screening, breast MRI will be performed in all subjects for more accurate clinical staging of the primary tumor and axilla lymphadenopathy and to ensure the primary tumor and regional lymph node staging fulfill protocol required criteria (see Section 5.1.2, Inclusion Criteria). Breast MRI performed as part of routine clinical management are acceptable for use as the screening tumor imaging if they are of diagnostic quality and were performed within 28 days prior to the first dose of trial treatment.

After treatment allocation, breast MRI is scheduled at end of Cycle 5 (between Days 15-21) following treatment with the first combination regimen (KNp or KNpCb), and at end of Cycle 9 (between Days 15-21) after completion of the second combination regimen (KAC) but prior to surgery. Additional images will be ordered as clinically indicated, for example with suspected disease progression or metastasis.

### **7.1.2.9 Definitive Surgery**

Approximately 3-6 weeks following discontinuation or completion of study treatments, subjects will undergo definitive surgery per local standard of care. Details regarding date of surgery, type of surgery, tumor resectability, etc., should be recorded in the appropriate

eCRF. Detailed pathological staging per AJCC and assessment of surgical margins will be performed by local pathologist on all the tissues removed during the surgery and recorded in the appropriate eCRF.

For subjects who did not achieve a pCR, tumor tissue samples should be collected and submitted to the designated central laboratory for translational research as specified in Section 4.2.3.3. Any leftover tissue will be archived for FBR if the subject has signed the optional informed consent for FBR as specified in Section 4.2.3.4.

#### **7.1.2.10 Determination of Disease progression**

Measurement of the baseline lesions, changes from the baseline, and overall response will be assessed by the investigator per RECIST 1.1. Due to observed pseudoprogression in a small percentage of subjects treated with pembrolizumab in other cancer indications, irRECIST has been developed to address this issue.

##### **7.1.2.10.1 irRECIST Assessment of Disease**

irRECIST is RECIST 1.1 adapted as described below to account for the unique tumor response seen with immunotherapeutic drugs. irRECIST will be used by site investigator/local radiology review to assess tumor response and progression, and make treatment decisions.

When feasible, subjects should not be discontinued from study treatment until progression is confirmed by the investigator/local radiology assessment. This allowance to continue treatment despite initial radiologic progressive disease (PD) takes into account the observation that some subjects can have a transient tumor flare in the first few months after the start of immunotherapy, and then experience subsequent disease response. The following may present as tumor flare:

- Worsening of existing target lesion(s)
- Worsening of existing non-target lesion(s)
- Development of new lesion(s)

In subjects who have shown initial evidence of radiological PD by RECIST 1.1, the investigator needs to decide whether to continue a subject on study treatment until repeat imaging is obtained (see [Table 10](#)), which should be based on assessing subject's overall clinical condition including performance status, clinical symptoms, and laboratory data. If the subject is clinically stable and can continue on study treatment, repeat scan should be performed in  $\geq 4$  weeks later to confirm PD. Clinical stable status is defined as the following:

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

Any subject deemed **clinically unstable** should be discontinued from trial treatment at site-assessed 1<sup>st</sup> radiologic evidence of PD and is not required to have repeat imaging for PD confirmation.

In determining whether or not the tumor burden has increased or decreased per irRECIST, the investigator should consider all target and non-target lesions as well as any incremental new lesion(s).

Per irRECIST, PD is considered Not Confirmed at repeat imaging if ALL of the following occur:

- Target lesion sum of diameters is < 20 % or < 5 mm absolute increase compared to nadir
- Non-target lesion(s) resulting in initial PD is qualitatively stable or improved
- New lesion(s) resulting in initial PD is qualitatively stable or improved
- No incremental new lesion(s) since last evaluation
- No incremental new non-target lesion progression since last evaluation

If repeat imaging does not confirm PD per irRECIST as assessed by the investigator and the subject continues to be clinically stable, study treatment and tumor imaging assessment may continue per study schedule.

Per irRECIST, PD is considered Confirmed at repeat imaging if ANY of the following occurs:

- Target lesion sum of diameters remains  $\geq$  20% and at least 5 mm absolute increase compared to nadir
- Non-target lesion(s) resulting in initial PD is qualitatively worse
- New lesion(s) resulting in initial PD is qualitatively worse
- Additional new lesion(s) since last evaluation
- Additional new non-target lesion progression since last evaluation

If repeat imaging confirms PD due to any of the scenarios listed above, subjects will be discontinued from study therapy.

Additional details about irRECIST are referenced in Merck TIP Sheet for RECIST 1.1 and irRECIST.



**Table 10 Imaging and Treatment after First Radiologic Evidence of PD**

	<b>Clinically Stable</b>		<b>Clinically Unstable</b>	
	<b>Imaging</b>	<b>Treatment</b>	<b>Imaging</b>	<b>Treatment</b>
1 <sup>st</sup> radiologic evidence of PD by RECIST 1.1	Repeat imaging at $\geq 4$ weeks at site to confirm PD	May continue study treatment at the Investigator's discretion while awaiting confirmatory scan by site	Repeat imaging at $\geq 4$ weeks to confirm PD per physician discretion only	Discontinue treatment
Repeat scan confirms PD by irRECIST at the local site	No additional imaging required	Discontinue treatment	No additional imaging required	N/A
Repeat scan shows SD, PR or CR compared to baseline scan as per RECIST 1.1	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 tumor imaging should occur according to the regular imaging schedule outlined in the protocol

\*: SD, PR and CR for irRECIST are identical to RECIST 1.1

### 7.1.3 Laboratory Procedures/Assessments

Details regarding specific laboratory procedures/assessments to be performed in this trial are provided below. The total amount of blood/tissue to be drawn/collected over the course of the trial (from pre-trial to post-trial visits), including approximate blood/tissue volumes drawn/collected by visit and by sample type per subject can be found in the Procedure Manual.

#### 7.1.3.1 Laboratory Safety Evaluations (Hematology, Chemistry and Urinalysis)

Laboratory tests for hematology, chemistry and urinalysis are specified in [Table 11](#).

Table 11 Laboratory Tests

Hematology	Chemistry	Urinalysis	Other
Hematocrit	Albumin	Blood	Serum $\beta$ -human chorionic gonadotropin ( $\beta$ -hCG) <sup>a</sup>
Hemoglobin	Alkaline phosphatase	Glucose	PT (INR) <sup>d</sup>
Platelet count	Alanine aminotransferase (ALT)	Protein	aPTT/PTT <sup>d</sup>
White Blood Cell - WBC (total and differential)	Aspartate aminotransferase (AST)	Specific gravity	Total triiodothyronine (T3) <sup>e</sup>
Red Blood Cell Count	Bicarbonate <sup>b</sup>	Microscopic exam, if abnormal results are noted	Free thyroxine (FT4)
Absolute Neutrophil Count	Calcium	Urine pregnancy test <sup>a</sup>	Thyroid stimulating hormone (TSH)
Absolute Lymphocyte Count	Chloride		FSH, estradiol <sup>f</sup>
	Creatinine		
	Glucose		
	Lactate Dehydrogenase		
	Phosphorus		
	Potassium		
	Sodium		
	Total Bilirubin		
	Direct Bilirubin, if total bilirubin is elevated above the upper limit of normal		
	Total protein		
	Blood Urea Nitrogen		
	Carbon dioxide (CO <sub>2</sub> or bicarbonate) <sup>b</sup>		
	Uric acid		
	Urea <sup>c</sup>		

<sup>a</sup> Perform on women of childbearing potential only. Urine pregnancy test is preferred. If the urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required.

<sup>b</sup> If considered standard of care in your region. If these tests are not done as part of standard of care in your region then these tests do not need to be performed.

<sup>c</sup> Blood Urea Nitrogen is preferred; if not available urea may be tested.

<sup>d</sup> Coagulation factors (PT/INR and aPTT/PTT) should be tested as part of the screening procedures for all subjects. Any subject receiving anticoagulant therapy should have coagulation factors monitored closely throughout the trial.

<sup>e</sup> Total T3 is preferred; if not available free T3 may be tested.

<sup>f</sup> Blood for menopausal status is only required for some subjects as described in Section 7.1.3.2

Laboratory tests for screening should be performed within 10 days prior to the first dose of trial treatment. After Cycle 1, pre-dose laboratory procedures can be conducted up to 72 hours prior to dosing. Results must be reviewed by the investigator or qualified designee and found to be acceptable prior to each dose of trial treatment.

In cases where a site is not able to obtain the thyroid function testing (T3, FT4, and TSH) results prior to scheduled dosing, review of the thyroid function test results after dosing is acceptable and poses no additional immediate safety risk to subjects.

### **7.1.3.2 Menopausal Status**

The menopausal status (pre- or post-menopausal) for all subjects younger than age 60 must be determined at screening according to the definitions below. The date of the subject's last menstrual period (LMP), bilateral ovariectomy/oophorectomy status (if applicable) and, when indicated serum FSH and estradiol levels, must be assessed and recorded in the eCRFs.

#### Pre-menopausal

- ≤12 months since LMP
- OR**
- Biochemical evidence of pre-menopausal status according to serum FSH and estradiol levels and local institutional guidelines

#### Post-menopausal

- Subject has undergone prior bilateral ovariectomy/oophorectomy
- OR**
- >12 months since LMP **and** no hysterectomy, hormone replacement, estrogen receptor antagonist, chemotherapy or ovarian suppression at any time since LMP
- OR**
- Biochemical evidence of post-menopausal status according to serum FSH and estradiol levels and local institutional guidelines.

### **7.1.3.3 Pregnancy Test**

For women of reproductive potential, a serum or urine pregnancy test should be performed within 72 hours prior to treatment allocation. If urine pregnancy results are positive or cannot be confirmed as negative, a serum pregnancy test performed by the local study site laboratory will be required. Pregnancy tests should be repeated if required by local guidelines.

### **7.1.3.4 Correlative Blood Collections – Samples for Correlative, Genetic, and Exploratory Biomarker Analyses**

Details regarding time points for blood collection to support analysis of exploratory biomarkers presented in Section 4.2.3.3 are outlined in the Study Flow Chart – Section 6.0.

Samples for planned, exploratory genetic analysis of DNA should be drawn unless there is a documented law or regulation prohibiting collection, or unless the IRB/IEC does not approve of the collection.

Blood for correlative biomarker studies should be collected prior to treatment at each specified cycle and at treatment discontinuation.

Detailed instructions for sample collection, processing and shipment are provided in the Procedures Manual.

Sample collection, storage and shipment instructions for Planned Genetic Analysis samples will be provided in the Procedures Manual.

#### **7.1.3.5 Future Biomedical Research Sample Collection**

The following specimens are to be obtained as part of Future Biomedical Research if the subject signs the FBR consent:

- Leftover DNA for future research
- Leftover tumor tissue
- Leftover DNA and RNA from correlative studies
- Leftover plasma and serum from exploratory biomarker studies

#### **7.1.4 Other Procedures**

##### **7.1.4.1 Withdrawal/Discontinuation**

Subjects who discontinue/withdraw from treatment prior to completion of the treatment regimen should be encouraged to continue to be followed for all remaining study visits.

When a subject discontinues/withdraws from participation in the trial, all applicable activities scheduled for the End of Treatment/Early Discontinuation 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 7.2 - Assessing and Recording Adverse Events.

##### **7.1.4.1.1 Withdrawal From Future Biomedical Research**

Subjects may withdraw their consent for Future Biomedical Research and have their specimens and all derivatives destroyed. Subjects may withdraw consent at any time by contacting the principal investigator for the main trial. If medical records for the main trial are still available, the investigator will contact the Sponsor using the designated mailbox (clinical.specimen.management@merck.com), and a form will be provided by the Sponsor to obtain appropriate information to complete specimen withdrawal. Subsequently, the subject's specimens will be removed from the biorepository and be destroyed. A letter will be sent from the Sponsor to the investigator confirming the destruction. It is the responsibility of the investigator to inform the subject of completion of destruction. Any analyses in progress at the time of request for destruction or already performed prior to the request being received by the Sponsor will continue to be used as part of the overall research trial data and results. No new analyses would be generated after the request is received.

In the event that the medical records for the main trial are no longer available (e.g., if the investigator is no longer required by regulatory authorities to retain the main trial records) or the specimens have been completely anonymized, there will no longer be a link between the subject's personal information and their specimens. In this situation, the request for specimen destruction cannot be processed.

#### **7.1.4.2 Blinding/Unblinding**

This is an open label trial; there is no blinding for this trial.

#### **7.1.4.3 Calibration of Critical Equipment**

The investigator or qualified designee has the responsibility to ensure that any critical device or instrument used for a clinical evaluation/test during a clinical trial that provides important information about inclusion/exclusion criteria and/or safety or efficacy parameters shall be suitably calibrated and maintained to ensure that the data obtained is reliable and/or reproducible. Documentation of equipment calibration must be retained as source documentation at the trial site.

Critical Equipment for this trial includes:

- Laboratory equipment – as required for satisfaction of entry criteria and trial assessments and routine safety evaluation of subjects
- Imaging equipment – as required for study objectives
- Drug administration equipment – as required for storage, preparation and administration (infusion) of pembrolizumab

See protocol-specified guidance in the Administrative Binder, Procedures Manual, and Pharmacy Manual.

#### **7.1.5 Visit Requirements**

Visit requirements are outlined in Section 6.0 - Trial Flow Chart. Specific procedure-related details are provided above in Section 7.1 - Trial Procedures.

##### **7.1.5.1 Screening**

Approximately 28 days prior to treatment allocation, potential subjects will be evaluated to determine that they fulfill the entry requirements as set forth in Section 5.1. Screening procedures may be repeated after consultation with the Sponsor.

Results of a test performed prior to the subject signing consent as part of routine clinical management are acceptable in lieu of a screening test if performed within the specified time frame.

Screening procedures are to be completed within 28 days prior to treatment allocation except for the following:

- Laboratory tests and ECOG PS are to be performed within 10 days prior to treatment allocation.
- For women of reproductive potential, a urine and/or serum pregnancy test will be performed within 72 hours prior to treatment allocation.

Subjects may be rescreened twice after initially failing to meet the inclusion/exclusion criteria. Results from assessments performed during the initial screening period are

acceptable in lieu of a repeat screening test if performed within the specified time frame and the inclusion/exclusion criteria is met.

#### **7.1.5.2 Treatment Cycles**

Visit timing requirements during the treatment period are as follows:

- Assessments/procedures should be performed on Day 1 for each cycle unless otherwise specified in the flow chart.
- During Cycles 2-5 where nab-paclitaxel or paclitaxel is administered weekly, assessments/procedures should be performed on Day 1, Day 8, and Day 15.
- Treatment cycles are 3 weeks (21 days).
- The window for each visit is  $\pm 2$  days for Cycles 2-5 and  $\pm 3$  days for Cycles 6-9 unless otherwise noted. Cycle 1 treatment should be no more than 3 days after treatment allocation.
- Biopsies and imaging are performed between Days 15-21 of each specified treatment cycle.

For the full list of all visit assessments/procedures please see Section 6.0 – Trial Flow Chart. Specific procedure-related details are provided above in Section 7.1 – Trial Procedures.

#### **7.1.5.3 Definitive Surgery**

Definitive surgery will be performed per local standard of care approximately 3-6 weeks following discontinuation or completion of study treatment.

#### **7.1.5.4 Post-Treatment Visits**

##### **7.1.5.4.1 End of Treatment or Early Discontinuation Visit**

The End of Treatment or Early Discontinuation visit should occur at any time study treatment is discontinued for any reason. This visit should be conducted between 3-6 weeks following treatment discontinuation but prior to definitive surgery or new therapy. Visit requirements are outlined in Section 6.0 – Trial Flow Chart. Specific procedure-related details are provided in Section 7.1 – Trial Procedures. Additional details regarding subject withdrawal and discontinuation are outlined in Section 5.8.

##### **7.1.5.4.2 Safety Follow-up Visit**

The mandatory Safety Follow-up Visit should be conducted approximately 30 days following definitive surgery. All AEs that occur prior to the Safety Follow-up Visit should be recorded. Subjects with an AE of Grade  $>1$  will be followed until resolution of the AE to Grade 0-1. Serious AEs that occur within 90 days following definitive surgery (or 30 days following definitive surgery if the subject initiates new anticancer therapy, whichever is earlier) should also be followed and recorded.

### **7.1.5.4.3 Follow-up for Disease Status and Survival**

After completion of the Safety Follow-up Visit, the subject will be contacted by telephone every 12 weeks to assess for disease and survival status for 24 months following surgery or until death, withdrawal of consent whichever comes first. Time of disease recurrence, progression, start and stop dates of subsequent anticancer treatments, and reasons for treatments should be recorded in the appropriate eCRF. For a subject who dies during the follow up period, date and cause of death should be recorded in the appropriate eCRF.

The Sponsor may request survival status be assessed at additional time points during the course of the study. For example, these additional time points may be requested prior to: an eDMC safety review, efficacy interim analysis, and/or final analysis. All subjects who are not known to have died prior to the request for these additional survival status time points will be contacted at that time.

## **7.2 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 unfavourable 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 Sponsor's 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.

Sponsor's 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 the Sponsor for human use.

Adverse events may occur during clinical trials, or as prescribed in clinical practice, from overdose (whether accidental or intentional), from abuse and from withdrawal.

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

All adverse events that occur after the consent form is signed but before treatment allocation/randomization must be reported by the investigator if they cause the subject to be excluded from the trial, or are the result of a protocol-specified intervention, including but not limited to washout or discontinuation of usual therapy, diet, placebo treatment or a procedure. From the time of treatment allocation/randomization through 30 days following definitive surgery, all adverse events must be reported by the investigator. Such events will be recorded at each examination on the Adverse Event case report forms/worksheets. The reporting timeframe for adverse events meeting any serious criteria is described in

section 7.2.3.1. The investigator will make every attempt to follow all subjects with non-serious adverse events for outcome.

Electronic reporting procedures can be found in the EDC data entry guidelines. Paper reporting procedures can be found in the Investigator Trial File Binder (or equivalent).

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

### **7.2.1 Definition of an Overdose for This Protocol and Reporting of Overdose to the Sponsor**

For this trial, an overdose will be defined as  $\geq 1000$  mg (5 times the dose) of pembrolizumab and as any dose  $\geq 20\%$  over the prescribed dose for the chemotherapies used in the study. No specific information is available on the treatment of overdose of pembrolizumab. In the event of overdose, pembrolizumab should be discontinued and 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 Sponsor's product or vaccine, the adverse event(s) is reported as a serious adverse event, even if no other seriousness criteria are met.

If a dose of Sponsor's product or vaccine 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 by the investigator within 24 hours to the Sponsor either by electronic media or paper. Electronic reporting procedures can be found in the EDC data entry guidelines. Paper reporting procedures can be found in the Investigator Trial File Binder (or equivalent).

### **7.2.2 Reporting of Pregnancy and Lactation to the Sponsor**

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

Pregnancies and lactations that occur after the consent form is signed but before treatment allocation/randomization must be reported by the investigator if they cause the subject to be excluded from the trial, or are the result of a protocol-specified intervention, including but not limited to washout or discontinuation of usual therapy, diet, placebo treatment or a procedure. Pregnancies and lactations that occur from the time of treatment allocation/randomization through 12 months after the last dose of study medication for subjects who have received cyclophosphamide, and for six months after the last dose of study medication for subjects who did not, or 30 days following cessation of treatment if the subject initiates new anticancer therapy, whichever is earlier, must be reported by the



investigator. All reported pregnancies must be followed to the completion/termination of the pregnancy. Pregnancy outcomes of spontaneous abortion, missed abortion, benign hydatidiform mole, blighted ovum, fetal death, intrauterine death, miscarriage and stillbirth must be reported as serious events (Important Medical Events). If the pregnancy continues to term, the outcome (health of infant) must also be reported.

Such events must be reported within 24 hours to the Sponsor either by electronic media or paper. Electronic reporting procedures can be found in the EDC data entry guidelines. Paper reporting procedures can be found in the Investigator Trial File Binder (or equivalent).

### **7.2.3 Immediate Reporting of Adverse Events to the Sponsor**

#### **7.2.3.1 Serious Adverse Events**

A serious adverse event is any adverse event occurring at any dose or during any use of Sponsor'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 an other important medical event.

**Note:** In addition to the above criteria, adverse events meeting either of the below criteria, although not serious per ICH definition, are reportable to the Sponsor in the same timeframe as SAEs to meet certain local requirements. Therefore, these events are considered serious by the Sponsor for collection purposes.

- Is a new cancer (that is not a condition of the study);
- Is associated with an overdose.

Refer to [Table 12](#) for additional details regarding each of the above criteria.

For the time period beginning when the consent form is signed until treatment allocation/randomization, 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 (reference Section 7.2.3.3 for additional details), that occurs to any subject must be reported within 24 hours to the Sponsor if it causes the subject to be excluded from the trial, or is the result of a protocol-specified intervention, including but not limited to washout or discontinuation of usual therapy, diet, placebo treatment or a procedure.

For the time period beginning at treatment allocation/randomization through 90 days following definitive surgery, or 30 days following definitive surgery if the subject initiates new anticancer therapy, whichever is earlier, any serious adverse event, or follow up to a serious adverse event, including death due to any cause, other than progression of the cancer under study (reference Section 7.2.3.3 for additional details), whether or not related to the Sponsor's product, must be reported within 24 hours to the Sponsor either by electronic media or paper. Electronic reporting procedures can be found in the EDC data entry guidelines. Paper reporting procedures can be found in the Investigator Trial File Binder (or equivalent).

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

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

### **7.2.3.2 Events of Clinical Interest**

Selected non-serious and serious adverse events are also known as Events of Clinical Interest (ECI) and must be reported to the Sponsor.

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

For the time period beginning at treatment allocation/randomization through 30 days following cessation of treatment, any ECI, or follow up to an ECI, whether or not related to the Sponsor's product, must be reported within 24 hours to the Sponsor, either by electronic media or paper. Electronic reporting procedures can be found in the EDC data entry guidelines. Paper reporting procedures can be found in the Investigator Trial File Binder (or equivalent).

Events of clinical interest for this trial include:

1. an overdose of Sponsor's product, as defined in Section 7.2.1 - Definition of an Overdose for This Protocol and Reporting of Overdose to the Sponsor, that is not associated with clinical symptoms or abnormal laboratory results.
2. an elevated AST or ALT lab value that is greater than or equal to 3X the upper limit of normal and an elevated total bilirubin lab value that is greater than or equal to 2X the upper limit of normal and, at the same time, an alkaline phosphatase lab value that is less than 2X the upper limit of normal, as determined by way of protocol-specified laboratory testing or unscheduled laboratory testing.\*

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

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. 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.

### **7.2.3.3 Protocol-Specific Exceptions to Serious Adverse Event Reporting**

Efficacy endpoints as outlined in this section will not be reported to the Sponsor as described in Section 7.2.3 - Immediate Reporting of Adverse Events to the Sponsor.

Specifically, the suspected/actual events covered in this exception include any event that is disease progression of the cancer under study.

The Sponsor will monitor unblinded aggregated efficacy endpoint events and safety data to ensure the safety of the subjects in the trial. Any suspected endpoint, which upon review is not progression of the cancer under study, will be forwarded to global safety as a SAE within 24 hours of determination that the event is not progression of the cancer under study.

### **7.2.4 Evaluating Adverse Events**

An 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.

For studies in which multiple agents are administered as part of a combination regimen, the investigator may attribute each adverse event causality to the combination regimen or to a single agent of the combination. In general, causality attribution should be assigned to the combination regimen (i.e., to all agents in the regimen). However, causality attribution may be assigned to a single agent if in the investigator's opinion, there is sufficient data to support full attribution of the adverse experience to the single agent.

Table 12 Evaluating Adverse Events

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

<b>V4.0 CTCAE Grading</b>	<b>Grade 1</b>	<b>Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.</b>
	<b>Grade 2</b>	<b>Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL.</b>
	<b>Grade 3</b>	<b>Severe or medically significant but not immediately life-threatening; hospitalization or prolongation or hospitalization indicated; disabling; limiting self-care ADL.</b>
	<b>Grade 4</b>	<b>Life threatening consequences; urgent intervention indicated.</b>
	<b>Grade 5</b>	<b>Death related to AE</b>
<b>Seriousness</b>	A serious adverse event is any adverse event occurring at any dose or during any use of Sponsor's 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 for an elective procedure to treat a pre-existing condition that has not worsened is not a serious adverse event. A pre-existing condition is a clinical condition that is diagnosed prior to the use of a Merck product and is documented in the patient's medical history.); 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) (although not serious per ICH definition, is reportable to the Sponsor within 24 hours to meet certain local requirements); or	
	Is an overdose (whether accidental or intentional). Any adverse event associated with an overdose is considered a serious adverse event for collection purposes. 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 †).	
<b>Duration</b>	Record the start and stop dates of the adverse event. If less than 1 day, indicate the appropriate length of time and units	
<b>Action taken</b>	Did the adverse event cause the Sponsor's product to be discontinued?	
<b>Relationship to Sponsor's Product</b>	Did the Sponsor's product cause the adverse event? The determination of the likelihood that the Sponsor's 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. <b>The following components are to be used to assess the relationship between the Sponsor's product and the AE;</b> the greater the correlation with the components and their respective elements (in number and/or intensity), the more likely the Sponsor's product caused the adverse event (AE):	
	<b>Exposure</b>	Is there evidence that the subject was actually exposed to the Sponsor's product such as: reliable history, acceptable compliance assessment (pill count, diary, etc.), expected pharmacologic effect, or measurement of drug/metabolite in bodily specimen?
	<b>Time Course</b>	Did the AE follow in a reasonable temporal sequence from administration of the Sponsor's product? Is the time of onset of the AE compatible with a drug-induced effect (applies to trials with investigational medicinal product)?
	<b>Likely Cause</b>	Is the AE not reasonably explained by another etiology such as underlying disease, other drug(s)/vaccine(s), or other host or environmental factors

<b>Relationship to Sponsor's Product (continued)</b>	<b>The following components are to be used to assess the relationship between the test drug and the AE: (continued)</b>	
	<b>Dechallenge</b>	Was the Sponsor's 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 Sponsor's product; or (3) the trial is a single-dose drug trial; or (4) Sponsor's product(s) is/are only used one time.)
	<b>Rechallenge</b>	Was the subject re-exposed to the Sponsor's 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) Sponsor's 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 SPONSOR'S PRODUCT, OR IF REEXPOSURE TO THE SPONSOR'S PRODUCT POSES ADDITIONAL POTENTIAL SIGNIFICANT RISK TO THE SUBJECT, THEN THE RECHALLENGE MUST BE APPROVED IN ADVANCE BY THE SPONSOR CLINICAL DIRECTOR AS PER DOSE MODIFICATION GUIDELINES IN THE PROTOCOL.
	<b>Consistency with Trial Treatment Profile</b>	Is the clinical/pathological presentation of the AE consistent with previous knowledge regarding the Sponsor's 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.		
<b>Record one of the following</b>	<b>Use the following scale of criteria as guidance (not all criteria must be present to be indicative of a Sponsor's product relationship).</b>	
<b>Yes, there is a reasonable possibility of Sponsor's product relationship.</b>	There is evidence of exposure to the Sponsor's product. The temporal sequence of the AE onset relative to the administration of the Sponsor's product is reasonable. The AE is more likely explained by the Sponsor's product than by another cause.	
<b>No, there is not a reasonable possibility of Sponsor's product relationship</b>	Subject did not receive the Sponsor's product OR temporal sequence of the AE onset relative to administration of the Sponsor's product is not reasonable OR the AE is more likely explained by another cause than the Sponsor's product. (Also entered for a subject with overdose without an associated AE.)	

## 7.2.5 Sponsor 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, i.e., per ICH Topic E6 (R1) Guidelines for Good Clinical Practice.

## 7.3 TRIAL GOVERNANCE AND OVERSIGHT

### 7.3.1 Communication of Cohort Dose Level Adjustment

After 6 and 10 subjects have completed DLT evaluation period for a given dose level in Part 1 of the study, an assessment of DLTs will be conducted according to the rules outlined in Section 5.2.1.2. A meeting (via teleconference or WebEx) will be scheduled between the Sponsor, Principal Investigator and other relevant study personnel to determine the dose level adjustment (if any) that is needed based on the dose finding rules. The results of this evaluation will be communicated to all investigative sites and study personnel and enrollment in each cohort using the new dose level will begin immediately and as applicable.

## 8.0 STATISTICAL ANALYSIS PLAN

This section outlines the statistical analysis strategy and procedures for the study. Changes to analyses made after the protocol has been finalized, but prior to conduct of the final analysis, will be documented in the Clinical Study Report (CSR) for the study. Post hoc exploratory analyses will be clearly identified in the CSR. For this Phase 1b protocol, no separate statistical analysis plan will be issued for this study, with the exception of an analysis plan for the pharmacokinetics analyses.

### 8.1 Statistical Analysis Plan Summary

<b>Study Design Overview</b>	A Phase 1b Open-Label Study to Evaluate Pembrolizumab plus Chemotherapy as Neoadjuvant Treatment for Triple Negative Breast Cancer (TNBC)
<b>Analysis Populations</b>	Safety: All Subjects as Treated (ASaT) Efficacy (secondary): Full Analysis Set (FAS)
<b>Primary Endpoint(s)</b>	Safety: DLT
<b>Key Secondary Endpoints</b>	pCR (defined as ypT0 ypN0) Rate pCR (defined as ypT0/Tis ypN0) Rate
<b>Statistical Methods for Key Efficacy/Immunogenicity/ Pharmacokinetic Analyses</b>	Counts and percentages will be provided for pCR rate separately for each cohort for subjects who are treated with RP2D.  An exact (Clopper-Pearson) 90% CI will be provided for the pCR rate in each cohort.

<b>Treatment Assignment</b>	<p>Subjects are allocated to the following cohorts:</p> <p>Cohort A (KNp/ KAC): Single dose pembrolizumab (K), followed by [pembrolizumab (K) Q3W + nab-paclitaxel (Np) weekly] x 4 cycles (1 cycle = 21 days), followed by KAC Q3W x 4 cycles</p> <p>Cohort B (KNpCb/ KAC): Single dose pembrolizumab (K), followed by [pembrolizumab (K) Q3W + nab-paclitaxel (Np) weekly + carboplatin (Cb) Q3W] x 4 cycles, followed by KAC Q3W x 4 cycles</p> <p>Cohort C (KNpCb / KAC): Single dose pembrolizumab (K), followed by [pembrolizumab (K) Q3W + nab-paclitaxel (Np) weekly + carboplatin (Cb) Q3W] x 4 cycles, followed by KAC Q3W x 4 cycles.</p> <p>Cohort D (KNpCb / KAC): Single dose pembrolizumab (K), followed by [pembrolizumab (K) Q3W + nab-paclitaxel (Np) weekly + carboplatin (Cb) weekly] x 4 cycles, followed by KAC Q3W x 4 cycles.</p> <p>Cohorts E (KTCb / KAC): Single dose pembrolizumab (K), followed by [pembrolizumab (K) Q3W + paclitaxel (T) weekly + carboplatin (Cb) Q3W] x 4 cycles, followed by pembrolizumab + doxorubicin + cyclophosphamide (KAC) Q3W x 4 cycles.</p> <p>Cohort F (KTCb / KAC): Single dose pembrolizumab (K), followed by [pembrolizumab (K) Q3W + paclitaxel (T) weekly + carboplatin (Cb) weekly] x 4 cycles, followed by pembrolizumab + doxorubicin + cyclophosphamide (KAC) Q3W x 4 cycles.</p> <p>If more than one cohort is open for enrollment simultaneously, allocation to a cohort will be made randomly.</p>
<b>Statistical Methods for Key Safety Analyses</b>	<p>Summary statistics (counts, percentage, mean, standard deviation, etc.) will be provided for the safety endpoints as appropriate</p>
<b>Interim Analyses</b>	<p>Two interim analyses are planned in this study. Details are provided in Section 8.7.</p> <ul style="list-style-type: none"> <li>• First Interim Analysis <ul style="list-style-type: none"> <li>○ Timing: after all subjects either have the safety follow up visit (30 days following definitive surgery) or have discontinued the study prior to the safety follow-up visit.</li> <li>○ Purpose: primary analysis for DLT rate and interim efficacy analysis for ORR.</li> </ul> </li> <li>• Second Interim Analysis <ul style="list-style-type: none"> <li>○ Timing: after the last subject is followed for 6 months after definitive surgery, has died, or is lost to follow up, whichever comes first.</li> <li>○ Purpose: safety analysis and interim efficacy analysis for EFS and OS.</li> </ul> </li> <li>• Final Analysis <ul style="list-style-type: none"> <li>○ Timing: after the last subject is followed for 24 months after surgery for events, has died, or is lost to follow up, whichever occurs earlier.</li> <li>○ Purpose: final efficacy analysis for long-term EFS and OS.</li> <li>○</li> </ul> </li> </ul>
<b>Multiplicity</b>	<p>No multiplicity adjustment is planned in this Phase 1b study.</p>
<b>Sample Size and Power</b>	<p>There will be no more than 20 subjects for each dose level, but up to 30 subjects per cohort.</p>

## **8.2 Responsibility for Analyses/In-House Blinding**

The statistical analysis of the data obtained from this study will be the responsibility of the Clinical Biostatistics department of the SPONSOR.

This trial is conducted as an open-label trial, i.e., subjects, investigators, and SPONSOR personnel will be aware of subject treatment assignments after each subject is enrolled and treatment is assigned. If more than one cohort is open for enrollment at the same time, allocation to treatment will be randomly assigned.

Planned interim and final analyses are described in Section 8.7.

## **8.3 Hypotheses/Estimation**

Objectives of the study are stated in Section 3.0.

## **8.4 Analysis Endpoints**

Efficacy and safety endpoints are listed below, followed by the descriptions of the derivations of selected endpoints.

### **8.4.1 Efficacy/Immunogenicity/Pharmacokinetics Endpoints**

Efficacy endpoints and their definitions are presented in Section 8.4.3.

### **8.4.2 Safety Endpoints**

The primary safety endpoint is DLT. Safety will be monitored by cumulative data reviews throughout the trial. The toxicities and grades experienced by subjects who have received study treatment, including AEs, SAEs and ECIs will be summarized. Other safety measures evaluated in all parts of the study include laboratory safety assessments, ECGs, vital signs, and physical examinations.

### **8.4.3 Derivations of Efficacy/Immunogenicity/Pharmacokinetics Endpoints**

Secondary efficacy endpoints and their definitions are presented below.

**Pathological complete response (pCR) Rate (ypT0 ypN0):** is defined as the rate of absence of residual invasive and in situ cancer on hematoxylin and eosin evaluation of the complete resected breast specimen and all sampled regional lymph nodes following completion of neoadjuvant systemic therapy by AJCC staging criteria (7<sup>th</sup> edition) assessed by local pathologist at the time of definitive surgery.

**Pathological complete response (pCR) Rate (ypT0/Tis ypN0):** is defined as the rate of absence of residual invasive cancer on hematoxylin and eosin evaluation of the complete resected breast specimen and all sampled regional lymph nodes following completion of neoadjuvant systemic therapy by AJCC staging criteria (7<sup>th</sup> edition) assessed by local pathologist at the time of definitive surgery.

For subjects who are discontinued from the study treatment and continue with other neoadjuvant treatment not specified by the study prior to the definitive surgery will be classified as not having a pCR in the efficacy analyses, regardless of the results obtained from the surgery.



**Objective Response Rate (ORR):** is defined as the percentage of subjects who have achieved complete response (CR) or partial response (PR) according to RECIST 1.1 by site radiology review. Because imaging will be assessed prior to surgery, a confirmation assessment of CR or PR will not be obtained. Subjects with missing outcome for objective response will be considered non-responders.

**Event Free Survival (EFS):** is the time from the first dose date of study treatment to any of the following events: progression of disease that precludes definitive surgery, disease recurrence (for subjects with complete surgical resection), progression (for subjects with incomplete surgical resection), or death due to any cause. Subjects without documented events will be censored at the date of the last disease status assessment.

**Overall Survival (OS):** is the time from the first dose date of study treatment to death due to any cause. Subjects without documented death at the time of the analysis will be censored at the date of the last follow-up.

#### **8.4.4 Derivations of Safety Endpoints**

Description of safety measures is provided in Section 7.2.

### **8.5 Analysis Populations**

#### **8.5.1 Safety Analysis Populations**

The All-Subjects-as-Treated (ASaT) population will be used for the analysis of safety data in this study. The ASaT population consists of all subjects who received at least one dose of study treatment. In case of treatment administration errors, subjects will be analyzed according to the treatment they actually received.

The DLT evaluation period consists of Day 1 Cycle 1 through end of Cycle 3 (i.e. through 2 cycles of the first combination regimen) as well as Day 1 Cycle 6 through end of Cycle 7 (i.e. through 2 cycles of the second combination regimen).

At least one laboratory or vital sign measurement obtained subsequent to at least one dose of study treatment is required for inclusion in the analysis of each specific parameter. To assess change from baseline, a baseline measurement is also required.

#### **8.5.2 Efficacy Analysis Populations**

The full analysis set (FAS) is defined as all subjects with a baseline evaluable disease by investigator assessment who started with RP2D, regardless of dose modification during the course of the study. The FAS will be the primary population for secondary analyses of efficacy. The subjects with evaluable disease include those who met inclusion criteria 3 and 4 in Section 5.1.2, i.e. subjects with locally advanced non-metastatic TNBC.

## **8.6 Statistical Methods**

### **8.6.1 Statistical Methods for Efficacy Analyses**

This section describes the statistical methods that address the secondary efficacy objectives.

Efficacy assessments will be provided separately for subjects in each cohort. The primary analyses of the efficacy endpoints will be based on FAS subjects in Part 1 and Part 2. Additional supporting analyses using ASaT subjects will also be carried out.

The key efficacy endpoints are pCR rate (ypT0/Tis ypN0) and pCR rate (ypT0 ypN0). Point estimates for each pCR rate and the corresponding exact 90% confidence intervals based on the Clopper-Pearson method will be provided. The 90% CI will be interpreted in the context of a historical pCR rate of 50%. The 50% pCR rate is based on the Phase III study (GeparSepto), in which the pCR (ypT0 ypN0) in the TNBC subgroup was 48.2% in those who received nab-paclitaxel compared with 25.7% in those who received paclitaxel. Another randomized Phase II study (GeparSixto) showed pCR (ypT0 ypN0) rate of 53.2% in those who received addition of weekly carboplatin compared with 36.9% in those who did not. Additional details of these two studies can be found in Section 4.1.1.2 Current and Emerging Neoadjuvant Treatments for TNBC.

The subject's TNBC status used in the primary analysis of pCR rate will be based on the evaluation by the local pathologist. The agreement on the TNBC status evaluated by the local pathologist and retrospectively confirmed by central laboratory will be assessed and if one cohort has more than 10% subjects showing different TNBC status, the primary pCR analyses will be re-done using the central laboratory confirmed result.

Additional efficacy endpoints include ORR, EFS, and OS:

Estimates of ORR and the corresponding exact 90% confidence intervals after completion of the first combination regimen (KNp, KNpCb, or KTCb) and after completion of the second combination regimen (KAC) will be provided using the same approach as pCR rate.

Kaplan-Meier estimates and the corresponding 90% confidence intervals at month 6, month 12, and month 24 following treatment start will be provided for EFS and OS.

### **8.6.2 Statistical Methods for Safety Analyses**

Safety and tolerability will be assessed by clinical review of all relevant parameters including AEs, SAEs, laboratory tests, vital signs, ECG measurements and physical examinations.

DLTs will be listed. DLTs and adverse experiences will be summarized as counts and frequencies by cohort for each dose level for which at least 3 subjects are treated and listed for other dose levels. Laboratory assessments, vital signs, and other safety endpoints will be summarized as appropriate.

Immune-related ECIs (irECIs) that are designated as AEs of special interest will be summarized in separate tables from other AEs. Any AE of unknown etiology associated the combination exposure will be evaluated to determine if it is possibly an ECI of a potentially immunologic etiology (irECI) (see Section 7.2.3.2).

In addition, the broad clinical and laboratory AE categories consisting of the percentage of subjects with any AE, a drug related AE, a serious AE, an AE which is both drug-related and serious, and who discontinued due to an AE will be summarized for dose levels with at least 3 subjects treated and listed for other doses.

### **8.6.3 Summaries of Baseline Characteristics, Demographics, and Other Analyses**

#### **8.6.3.1 Demographic and Baseline Characteristics**

The number and percentage of subjects screened, randomized/allocated, the primary reasons for screening failure, and the primary reason for discontinuation will be displayed. Demographic variables, baseline characteristics, primary and secondary diagnoses, and prior and concomitant therapies will be summarized either by descriptive statistics or categorical tables for ASaT population (by Dose Level and Cohort).

### **8.7 Interim Analyses**

Safety will be evaluated continuously and the number of subjects with a DLT will be assessed for dosing decisions following the time that 6 and 10 subjects are evaluable for DLT of each cohort, however, if dosing decisions can be made according to the pre-specified rules prior to the time that the 6th or 10th subjects are evaluable, the study may proceed according to decisions outlined in Section 5.2.1.2.

First analyses of the primary endpoint (DLT) and two of the secondary efficacy endpoints (pCR rate and ORR) will be evaluated following the time that all subjects either (1) have the safety follow up visit (30 days following definitive surgery) or (2) have discontinued the study prior to the safety follow-up visit. This is expected to happen about 6 months after the last subject is enrolled.

Another analysis of safety and efficacy endpoints (EFS and OS) will be evaluated after the last subject is followed for approximately 6 months after definitive surgery for events, has died, or is lost to follow up, whichever comes first.

Final analysis of long term EFS and OS will be performed after the last subject is followed for approximately 24 months after surgery for events, has died, or is lost to follow up, whichever occurs earlier, to show the long-term clinical benefit.

### **8.8 Multiplicity**

There will be no multiplicity control in this Phase 1b study.

### **8.9 Sample Size and Power Calculations**

The primary purpose of the trial is to investigate the safety and tolerability of neoadjuvant KNp/KAC (Cohort A), KNpCb/KAC (Cohorts B, C, and D), and KTCb/KAC (Cohorts E and F) in adult subjects with locally-advanced TNBC to establish a dose for each combination for further study. The total sample size is based on clinical considerations and not statistical considerations.

Up to 150 subjects will be enrolled, with a maximum of 20 subjects in Cohort A, 10 subjects in Cohort B, and 30 subjects in Cohorts C, D, E or F. As defined in Section 3.2, the efficacy

analyses will include subjects who started with RP2D. Once the RP2D is established for Cohorts C, D, E, and F, additional subjects may be enrolled at the RP2D up to 20 subjects. [Table 13](#) provides information on the sample size and power calculation based on several hypothetical scenarios. Given this is primarily a dose-finding safety study, the secondary efficacy analyses are exploratory in nature and the power calculations are provided only as examples.

Table 13 Sample Size and Power Calculation with Various Scenarios

pCR Rate Under Null Hypothesis	pCR Rate Under Alternative Hypothesis	Sample Size	Power <sup>1</sup>
40%	60%	20	42%
40%	70%	20	77%
50%	60%	20	13%
50%	70%	20	42%

<sup>1</sup>: Based on one-sided alpha level of 0.05.

As described in Section 5.2.1.2, the decisions regarding dose de-escalation will be made in the first 3 Cycles as well as in Cycle 6 and 7 after 6 and 10 subjects are evaluable for DLT at a given dose level. If DLTs are observed in  $\geq 3$  out of the first 6 subjects who are evaluable for DLT, or  $\geq 4$  out of the first 10 subjects who are evaluable for DLT, the dose level will be deemed unacceptably toxic. [Table 14](#) provides the probabilities of observing the above criteria given various assumed true DLT rates in the first 3 Cycles of each combination.

Table 14 Probability of Observing DLTs at the Time of DLT Assessment in the first 3 Cycles

DLT Rate in the First 3 Cycles	Probability <sup>1</sup> of Declaring Dose Unacceptably Toxic	
	After 6 subjects ( $\geq 3/6$ with DLT)	After 10 subjects ( $\geq 4/10$ with DLT if $< 3/6$ have DLT)
10%	1.6%	2.2%
15%	4.7%	7.2%
20%	9.9%	15.4%
25%	16.9%	26.6%
30%	25.6%	39.5%
40%	45.6%	65.4%
50%	65.6%	84.8%

<sup>1</sup>: Based on Binomial distribution of 6 and 10 subjects given the DLT rate in each row.

## 8.10 Subgroup Analyses and Effect of Baseline Factors

No subgroup analyses will be performed.

### **8.11 Compliance (Medication Adherence)**

Drug accountability data for trial treatment will be collected during the study. Percent compliance with drug administration will be calculated for each subject for pembrolizumab (K), nab-paclitaxel (Nb), paclitaxel (T), carboplatin (Cb), doxorubicin (A) and cyclophosphamide (C) separately.

For all doses, percent compliance will be calculated as following:

$$\text{Percent Compliance} = \frac{\text{Number of Doses Taken}}{\text{Number of Doses that Should have been Taken}} \times 100.$$

For nab-paclitaxel, paclitaxel, and carboplatin with weekly dose, “Number of Doses that Should have been Taken” will be calculated as 1 plus the number (integer) of 1-week intervals that fit between the date of the first dose and the date of the last dose of nab-paclitaxel.

For pembrolizumab, carboplatin Q3W, doxorubicin, and cyclophosphamide, “Number of Doses that Should have been Taken” will be calculated as 1 plus the number (integer) of 3-week intervals that fit between the date of the first dose and the date of the last dose of the respective study medication.

### **8.12 Extent of Exposure**

A subject’s extent of exposure to study medication is defined as the total number of doses of combination therapy the subject received.

Extent of Exposure will be summarized for each KNp/KAC, KNpCb/KAC, and KTCb/KAC dose levels with at least 3 subjects enrolled and listed for other dose levels.

## **9.0 LABELING, PACKAGING, STORAGE AND RETURN OF CLINICAL SUPPLIES**

### **9.1 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.

Clinical Supplies will be provided by the Sponsor as summarized in [Table 15](#).

Clinical supplies will be packaged to support enrollment and replacement subjects as required. When a replacement subject is required, the Sponsor or designee needs to be contacted prior to dosing the replacement supplies.

Table 15 Product Descriptions

<b>Product Name &amp; Potency</b>	<b>Dosage Form</b>	<b>Source</b>
Pembrolizumab (MK-3475), 50mg	Powder for Infusion	Provided centrally by the Sponsor
Nab-Paclitaxel, 100mg	Powder for Infusion	Provided centrally by the Sponsor or locally by the trial site, subsidiary, or designee
Nab-Paclitaxel, 250mg	Powder for Infusion	Provided centrally by the Sponsor or locally by the trial site, subsidiary, or designee
Paclitaxel 6 mg/mL, 16.7 mL	Solution for Infusion	Provided centrally by the Sponsor or locally by the trial site, subsidiary, or designee
Carboplatin 10mg/mL, 60mL	Solution for Infusion	Provided centrally by the Sponsor or locally by the trial site, subsidiary, or designee
Doxorubicin 2mg /mL, 100mL	Solution for Infusion	Provided centrally by the Sponsor or locally by the trial site, subsidiary, or designee
Cyclophosphamide, 1g	Powder for Infusion	Provided centrally by the Sponsor or locally by the trial site, subsidiary, or designee

All supplies indicated in [Table 15](#) will be provided per the “Source/Additional Information” column depending on local country operational requirements.

Any commercially available product not included in [Table 15](#) will be provided by the trial site, subsidiary or designee.

Every attempt should be made to source these supplies from a single lot/batch number. The trial site is responsible for recording the lot number, manufacturer, and expiry date for any locally purchased product as per local guidelines unless otherwise instructed by the Sponsor.

## **9.2 Packaging and Labeling Information**

Clinical supplies will be affixed with a clinical label in accordance with regulatory requirements.

All supplies will be provided open label. Pembrolizumab (MK-3475) will be provided as non-kitted single vials or as single vials in a kit box. The other products will be provided as a kit with a single vial.

## **9.3 Clinical Supplies Disclosure**

This trial is open-label; therefore, the subject, the trial site personnel, the Sponsor and/or designee are not blinded. Treatment (name, strength or potency) is included in the label text; random code/disclosure envelopes or lists are not provided.

#### **9.4 Storage and Handling Requirements**

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.

#### **9.5 Discard/Destruction>Returns and Reconciliation**

The investigator is responsible for keeping accurate records of the clinical supplies received from the Sponsor or designee, the amount dispensed to and returned by the subjects and the amount remaining at the conclusion of the trial. For all trial sites, the local country Sponsor personnel or designee will provide appropriate documentation that must be completed for drug accountability and return, or local discard and destruction if appropriate. Where local discard and destruction is appropriate, the investigator is responsible for ensuring that a local discard/destruction procedure is documented.

#### **9.6 Standard Policies**

Trial site personnel will have access to a central electronic treatment allocation/randomization system (IVRS/IWRS system) to allocate subjects, to assign treatment to subjects and to manage the distribution of clinical supplies. Each person accessing the IVRS system must be assigned an individual unique PIN. They must use only their assigned PIN to access the system, and they must not share their assigned PIN with anyone.

### **10.0 ADMINISTRATIVE AND REGULATORY DETAILS**

#### **10.1 Confidentiality**

##### **10.1.1 Confidentiality of Data**

By signing this protocol, the investigator affirms to the Sponsor that information furnished to the investigator by the Sponsor will be maintained in confidence, and such information will be divulged to the institutional review board, ethics review committee (IRB/ERC) or similar or expert committee; affiliated institution and employees, only under an appropriate understanding of confidentiality with such board or committee, affiliated institution and employees. Data generated by this trial will be considered confidential by the investigator, except to the extent that it is included in a publication as provided in the Publications section of this protocol.

##### **10.1.2 Confidentiality of Subject Records**

By signing this protocol, the investigator agrees that the Sponsor (or Sponsor representative), IRB/ERC, or regulatory authority representatives may consult and/or copy trial documents in order to verify worksheet/case report form data. By signing the consent form, the subject agrees to this process. If trial documents will be photocopied during the process of verifying

worksheet/case report form information, the subject will be identified by unique code only; full names/initials will be masked prior to transmission to the Sponsor.

By signing this protocol, the investigator agrees to treat all subject data used and disclosed in connection with this trial in accordance with all applicable privacy laws, rules and regulations.

### **10.1.3 Confidentiality of Investigator Information**

By signing this protocol, the investigator recognizes that certain personal identifying information with respect to the investigator, and all subinvestigators and trial site personnel, may be used and disclosed for trial management purposes, as part of a regulatory submissions, and as required by law. This information may include:

1. name, address, telephone number and e-mail address;
2. hospital or clinic address and telephone number;
3. curriculum vitae or other summary of qualifications and credentials; and
4. other professional documentation.

Consistent with the purposes described above, this information may be transmitted to the Sponsor, and subsidiaries, affiliates and agents of the Sponsor, in your country and other countries, including countries that do not have laws protecting such information. Additionally, the investigator's name and business contact information may be included when reporting certain serious adverse events to regulatory authorities or to other investigators. By signing this protocol, the investigator expressly consents to these uses and disclosures.

If this is a multicenter trial, in order to facilitate contact between investigators, the Sponsor may share an investigator's name and contact information with other participating investigators upon request.

### **10.1.4 Confidentiality of IRB/IEC Information**

The Sponsor is required to record the name and address of each IRB/IEC member that reviews and approves this trial. The Sponsor is also required to document that each IRB/IEC meets regulatory and ICH GCP requirements by requesting and maintaining records of the names and qualifications of the IRB/IEC members and to make these records available for regulatory agency review upon request by those agencies.

## **10.2 Compliance with Financial Disclosure Requirements**

Financial Disclosure requirements are outlined in the US Food and Drug Administration Regulations, Financial Disclosure by Clinical Investigators (21 CFR Part 54). It is the Sponsor's responsibility to determine, based on these regulations, whether a request for Financial Disclosure information is required. It is the investigator's/subinvestigator's responsibility to comply with any such request.

The investigator/subinvestigator(s) agree, if requested by the Sponsor in accordance with 21 CFR Part 54, to provide his/her financial interests in and/or arrangements with the Sponsor to allow for the submission of complete and accurate certification and disclosure statements.



The investigator/subinvestigator(s) further agree to provide this information on a Certification/Disclosure Form, commonly known as a financial disclosure form, provided by the Sponsor. The investigator/subinvestigator(s) also consent to the transmission of this information to the Sponsor in the United States for these purposes. This may involve the transmission of information to countries that do not have laws protecting personal data.

### **10.3 Compliance with Law, Audit and Debarment**

By signing this protocol, the investigator agrees to conduct the trial in an efficient and diligent manner and in conformance with this protocol; generally accepted standards of Good Clinical Practice (e.g., International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use Good Clinical Practice: Consolidated Guideline and other generally accepted standards of good clinical practice); and all applicable federal, state and local laws, rules and regulations relating to the conduct of the clinical trial.

The Code of Conduct, a collection of goals and considerations that govern the ethical and scientific conduct of clinical investigations sponsored by Merck, is provided in Section 12.1 - Merck Code of Conduct for Clinical Trials.

The investigator also agrees to allow monitoring, audits, IRB/ERC review and regulatory authority inspection of trial-related documents and procedures and provide for direct access to all trial-related source data and documents.

The investigator agrees not to seek reimbursement from subjects, their insurance providers or from government programs for procedures included as part of the trial reimbursed to the investigator by the Sponsor.

The investigator shall prepare and maintain complete and accurate trial documentation in compliance with Good Clinical Practice standards and applicable federal, state and local laws, rules and regulations; and, for each subject participating in the trial, provide all data, and, upon completion or termination of the clinical trial, submit any other reports to the Sponsor as required by this protocol or as otherwise required pursuant to any agreement with the Sponsor.

Trial documentation will be promptly and fully disclosed to the Sponsor by the investigator upon request and also shall be made available at the trial site upon request for inspection, copying, review and audit at reasonable times by representatives of the Sponsor or any regulatory authorities. The investigator agrees to promptly take any reasonable steps that are requested by the Sponsor as a result of an audit to cure deficiencies in the trial documentation and worksheets/case report forms.

The investigator must maintain copies of all documentation and records relating to the conduct of the trial in compliance with all applicable legal and regulatory requirements. This documentation includes, but is not limited to, the protocol, worksheets/case report forms, advertising for subject participation, adverse event reports, subject source data, correspondence with regulatory authorities and IRBs/ERCs, consent forms, investigator's curricula vitae, monitor visit logs, laboratory reference ranges, laboratory certification or quality control procedures and laboratory director curriculum vitae. By signing this protocol, the investigator agrees that documentation shall be retained until at least 2 years after the last

approval of a marketing application in an ICH region or until there are no pending or contemplated marketing applications in an ICH region or until at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. Because the clinical development and marketing application process is variable, it is anticipated that the retention period can be up to 15 years or longer after protocol database lock. The Sponsor will determine the minimum retention period and notify the investigator when documents may be destroyed. The Sponsor will determine the minimum retention period and upon request, will provide guidance to the investigator when documents no longer need to be retained. The sponsor also recognizes that documents may need to be retained for a longer period if required by local regulatory requirements. All trial documents shall be made available if required by relevant regulatory authorities. The investigator must consult with and obtain written approval by the Sponsor prior to destroying trial and/or subject files.

ICH Good Clinical Practice guidelines recommend that the investigator inform the subject's primary physician about the subject's participation in the trial if the subject has a primary physician and if the subject agrees to the primary physician being informed.

The investigator will promptly inform the Sponsor of any regulatory authority inspection conducted for this trial.

Persons debarred from conducting or working on clinical trials by any court or regulatory authority will not be allowed to conduct or work on this Sponsor's trials. The investigator will immediately disclose in writing to the Sponsor if any person who is involved in conducting the trial is debarred or if any proceeding for debarment is pending or, to the best of the investigator's knowledge, threatened.

In the event the Sponsor prematurely terminates a particular trial site, the Sponsor will promptly notify that trial site's IRB/IEC.

According to European legislation, a Sponsor must designate an overall coordinating investigator for a multi-center trial (including multinational). When more than one trial site is open in an EU country, Merck, as the Sponsor, will designate, per country, a national principal coordinator (Protocol CI), responsible for coordinating the work of the principal investigators at the different trial sites in that Member State, according to national regulations. For a single-center trial, the Protocol CI is the principal investigator. In addition, the Sponsor must designate a principal or coordinating investigator to review the trial report that summarizes the trial results and confirm that, to the best of his/her knowledge, the report accurately describes the conduct and results of the trial [Clinical Study Report (CSR) CI]. The Sponsor may consider one or more factors in the selection of the individual to serve as the Protocol CI and or CSR CI (e.g., availability of the CI during the anticipated review process, thorough understanding of clinical trial methods, appropriate enrollment of subject cohort, timely achievement of trial milestones). The Protocol CI must be a participating trial investigator.

#### **10.4 Compliance with Trial Registration and Results Posting Requirements**

Under the terms of the Food and Drug Administration Amendments Act (FDAAA) of 2007 and the European Medicines Agency (EMA) clinical trial Directive 2001/20/EC, the Sponsor of the trial is solely responsible for determining whether the trial and its results are subject to the requirements for submission to <http://www.clinicaltrials.gov>, [www.clinicaltrialsregister.eu](http://www.clinicaltrialsregister.eu)

or other local registries. Merck, as Sponsor of this trial, will review this protocol and submit the information necessary to fulfill these requirements. Merck entries are not limited to FDAAA or the EMA clinical trial directive mandated trials. 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.

By signing this protocol, the investigator acknowledges that the statutory obligations under FDAAA, the EMA clinical trials directive or other locally mandated registries are that of the Sponsor and agrees not to submit any information about this trial or its results to those registries.

### **10.5 Quality Management System**

By signing this protocol, the Sponsor agrees to be responsible for implementing and maintaining a quality management system with written development procedures and functional area standard operating procedures (SOPs) to ensure that trials are conducted and data are generated, documented, and reported in compliance with the protocol, accepted standards of Good Clinical Practice, and all applicable federal, state, and local laws, rules and regulations relating to the conduct of the clinical trial.

### **10.6 Data Management**

The investigator or qualified designee is responsible for recording and verifying the accuracy of subject data. By signing this protocol, the investigator acknowledges that his/her electronic signature is the legally binding equivalent of a written signature. By entering his/her electronic signature, the investigator confirms that all recorded data have been verified as accurate.

Detailed information regarding Data Management procedures for this protocol will be provided separately.

### **10.7 Publications**

This trial is intended for publication, even if terminated prematurely. Publication may include any or all of the following: posting of a synopsis online, abstract and/or presentation at a scientific conference, or publication of a full manuscript. The Sponsor will work with the authors to submit a manuscript describing trial results within 12 months after the last data become available, which may take up to several months after the last subject visit in some cases such as vaccine trials. However, manuscript submission timelines may be extended on OTC trials. For trials intended for pediatric-related regulatory filings, the investigator agrees to delay publication of the trial results until the Sponsor notifies the investigator that all relevant regulatory authority decisions on the trial drug have been made with regard to pediatric-related regulatory filings. Merck will post a synopsis of trial results for approved products on [www.clinicaltrials.gov](http://www.clinicaltrials.gov) by 12 months after the last subject's last visit for the primary outcome, 12 months after the decision to discontinue development, or product marketing (dispensed, administered, delivered or promoted), whichever is later.

These timelines may be extended for products that are not yet marketed, if additional time is needed for analysis, to protect intellectual property, or to comply with confidentiality

agreements with other parties. Authors of the primary results manuscript will be provided the complete results from the Clinical Study Report, subject to the confidentiality agreement. When a manuscript is submitted to a biomedical journal, the Sponsor's policy is to also include the protocol and statistical analysis plan to facilitate the peer and editorial review of the manuscript. If the manuscript is subsequently accepted for publication, the Sponsor will allow the journal, if it so desires, to post on its website the key sections of the protocol that are relevant to evaluating the trial, specifically those sections describing the trial objectives and hypotheses, the subject inclusion and exclusion criteria, the trial design and procedures, the efficacy and safety measures, the statistical analysis plan, and any amendments relating to those sections. The Sponsor reserves the right to redact proprietary information.

For multicenter trials, subsequent to the multicenter publication (or after public disclosure of the results online at [www.clinicaltrials.gov](http://www.clinicaltrials.gov) if a multicenter manuscript is not planned), an investigator and his/her colleagues may publish their data independently. In most cases, publication of individual trial site data does not add value to complete multicenter results, due to statistical concerns. In rare cases, publication of single trial site data prior to the main paper may be of value. Limitations of single trial site observations in a multicenter trial should always be described in such a manuscript.

Authorship credit should be based on 1) substantial contributions to conception and design, or acquisition of data, or analysis and interpretation of data; 2) drafting the article or revising it critically for important intellectual content; and 3) final approval of the version to be published. Authors must meet conditions 1, 2 and 3. Significant contributions to trial execution may also be taken into account to determine authorship, provided that contributions have also been made to all three of the preceding authorship criteria. Although publication planning may begin before conducting the trial, final decisions on authorship and the order of authors' names will be made based on participation and actual contributions to the trial and writing, as discussed above. The first author is responsible for defending the integrity of the data, method(s) of data analysis and the scientific content of the manuscript.

The Sponsor must have the opportunity to review all proposed abstracts, manuscripts or presentations regarding this trial 45 days prior to submission for publication/presentation. Any information identified by the Sponsor as confidential must be deleted prior to submission; this confidentiality does not include efficacy and safety results. Sponsor review can be expedited to meet publication timelines.

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## **12.0 APPENDICES**

### **12.1 Merck Code of Conduct for Clinical Trials**

**Merck\***  
**Code of Conduct for Clinical Trials**

#### **I. Introduction**

##### **A. Purpose**

Merck, through its subsidiaries, conducts clinical trials worldwide to evaluate the safety and effectiveness of our products. As such, we are committed to designing, implementing, conducting, analyzing and reporting these trials in compliance with the highest ethical and scientific standards. Protection of subject safety is the overriding concern in the design of clinical trials. In all cases, Merck clinical trials will be conducted in compliance with local and/or national regulations and in accordance with the ethical principles that have their origin in the Declaration of Helsinki.

##### **B. Scope**

Such standards shall be endorsed for all clinical interventional investigations sponsored by Merck irrespective of the party (parties) employed for their execution (e.g., contract research organizations, collaborative research efforts). This Code is not intended to apply to trials which are observational in nature, or which are retrospective. Further, this Code does not apply to investigator-initiated trials which are not under the control of Merck.

#### **II. Scientific Issues**

##### **A. Trial Conduct**

###### **1. Trial Design**

Except for pilot or estimation trials, clinical trial protocols will be hypothesis-driven to assess safety, efficacy and/or pharmacokinetic or pharmacodynamic indices of Merck or comparator products. Alternatively, Merck may conduct outcomes research trials, trials to assess or validate various endpoint measures, or trials to determine subject preferences, etc.

The design (i.e., subject population, duration, statistical power) must be adequate to address the specific purpose of the trial. Research subjects must meet protocol entry criteria to be enrolled in the trial.

###### **2. Site Selection**

Merck selects investigative sites based on medical expertise, access to appropriate subjects, adequacy of facilities and staff, previous performance in Merck trials, as well as budgetary considerations. Prior to trial initiation, sites are evaluated by Merck personnel to assess the ability to successfully conduct the trial.

###### **3. Site Monitoring/Scientific Integrity**

Trial sites are monitored to assess compliance with the trial protocol and general principles of Good Clinical Practice. Merck reviews clinical data for accuracy, completeness and consistency. Data are verified versus source documentation according to standard operating procedures. Per Merck policies and procedures, if fraud, misconduct or serious GCP-non-Compliance are suspected, the issues are promptly investigated. When necessary, the clinical site will be closed, the responsible regulatory authorities and ethics review committees notified and data disclosed accordingly.

##### **B. Publication and Authorship**

To the extent scientifically appropriate, Merck seeks to publish the results of trials it conducts. Some early phase or pilot trials are intended to be hypothesis-generating rather than hypothesis testing. In such cases, publication of results may not be appropriate since the trial may be underpowered and the analyses complicated by statistical issues of multiplicity.

Merck's policy on authorship is consistent with the requirements outlined in the ICH-Good Clinical Practice guidelines. In summary, authorship should reflect significant contribution to the design and conduct of the trial, performance or interpretation of the analysis, and/or writing of the manuscript. All named authors must be able to defend the trial results and conclusions. Merck funding of a trial will be acknowledged in publications.



### **III. Subject Protection**

#### **A. IRB/ERC review**

All clinical trials will be reviewed and approved by an independent IRB/ERC before being initiated at each site. Significant changes or revisions to the protocol will be approved by the IRB/ERC prior to implementation, except that changes required urgently to protect subject safety and well-being may be enacted in anticipation of IRB/ERC approval. For each site, the IRB/ERC and Merck will approve the subject informed consent form.

#### **B. Safety**

The guiding principle in decision-making in clinical trials is that subject welfare is of primary importance. Potential subjects will be informed of the risks and benefits of, as well as alternatives to, trial participation. At a minimum, trial designs will take into account the local standard of care. Subjects are never denied access to appropriate medical care based on participation in a Merck clinical trial.

All participation in Merck clinical trials is voluntary. Subjects are enrolled only after providing informed consent for participation. Subjects may withdraw from a Merck trial at any time, without any influence on their access to, or receipt of, medical care that may otherwise be available to them.

#### **C. Confidentiality**

Merck is committed to safeguarding subject confidentiality, to the greatest extent possible. Unless required by law, only the investigator, sponsor (or representative) and/or regulatory authorities will have access to confidential medical records that might identify the research subject by name.

#### **D. Genomic Research**

Genomic Research will only be conducted in accordance with informed consent and/or as specifically authorized by an Ethics Committee.

### **IV. Financial Considerations**

#### **A. Payments to Investigators**

Clinical trials are time- and labor-intensive. It is Merck's policy to compensate investigators (or the sponsoring institution) in a fair manner for the work performed in support of Merck trials. Merck does not pay incentives to enroll subjects in its trials. However, when enrollment is particularly challenging, additional payments may be made to compensate for the time spent in extra recruiting efforts.

Merck does not pay for subject referrals. However, Merck may compensate referring physicians for time spent on chart review to identify potentially eligible subjects.

#### **B. Clinical Research Funding**

Informed consent forms will disclose that the trial is sponsored by Merck, and that the investigator or sponsoring institution is being paid or provided a grant for performing the trial. However, the local IRB/ERC may wish to alter the wording of the disclosure statement to be consistent with financial practices at that institution. As noted above, publications resulting from Merck trials will indicate Merck as a source of funding.

#### **C. Funding for Travel and Other Requests**

Funding of travel by investigators and support staff (e.g., to scientific meetings, investigator meetings, etc.) will be consistent with local guidelines and practices including, in the U.S., those established by the American Medical Association (AMA).

### **V. Investigator Commitment**

Investigators will be expected to review Merck's Code of Conduct as an appendix to the trial protocol, and in signing the protocol, agree to support these ethical and scientific standards.

\* In this document, "Merck" refers to Merck Sharp & Dohme Corp. and Schering Corporation, each of which is a subsidiary of Merck & Co., Inc. Merck is known as MSD outside of the United States and Canada. As warranted by context, Merck also includes affiliates and subsidiaries of Merck & Co., Inc."

## **12.2 Collection and Management of Specimens for Future Biomedical Research**

### **1. Definitions**

- a. Biomarker: A biological molecule found in blood, other body fluids, or tissues that is a sign of a normal or abnormal process or of a condition or disease. A biomarker may be used to see how well the body responds to a treatment for a disease or condition.<sup>1</sup>
- b. Pharmacogenomics: The investigation of variations of DNA and RNA characteristics as related to drug/vaccine response.<sup>2</sup>
- c. Pharmacogenetics: A subset of pharmacogenomics, pharmacogenetics is the influence of variations in DNA sequence on drug/vaccine response.<sup>2</sup>
- d. DNA: Deoxyribonucleic acid.
- e. RNA: Ribonucleic acid.

### **2. Scope of Future Biomedical Research**

The specimens collected in this trial as outlined in Section 7.1.3.5 – Future Biomedical Research Sample Collection will be used to study various causes for how subjects may respond to a drug/vaccine. Future biomedical research specimen(s) will be stored to provide a resource for future trials conducted by the Sponsor focused on the study of biomarkers responsible for how a drug/vaccine enters and is removed by the body, how a drug/vaccine works, other pathways a drug/vaccine may interact with, or other aspects of disease. The specimen(s) may be used for future assay development and/or drug/vaccine development.

It is now well recognized that information obtained from studying and testing clinical specimens offers unique opportunities to enhance our understanding of how individuals respond to drugs/vaccines, enhance our understanding of human disease and ultimately improve public health through development of novel treatments targeted to populations with the greatest need. All specimens will be used by the Sponsor or those working for or with the Sponsor.

### **3. Summary of Procedures for Future Biomedical Research**

#### **a. Subjects for Enrollment**

All subjects enrolled in the clinical trial will be considered for enrollment in the Future Biomedical Research sub-trial.

#### **b. Informed Consent**

Informed consent for specimens (i.e., DNA, RNA, protein, etc.) will be obtained during screening for protocol enrollment from all subjects or legal guardians, at a trial visit by the investigator or his or her designate. Informed consent for Future Biomedical Research should be presented to the subjects on Visit 1. If delayed, present consent at next possible Subject Visit. Informed consent must be obtained prior to collection of all Future Biomedical Research specimens. Consent forms signed by the subject will be kept at the clinical trial site under secure storage for regulatory reasons.

A template of each trial site's approved informed consent will be stored in the Sponsor's clinical document repository. Each consent will be assessed for appropriate specimen permissions.

c. eCRF Documentation for Future Biomedical Research Specimens

Documentation of patient consent for Future Biomedical Research will be captured in the electronic Case Report Forms (eCRFs). Any specimens for which such an informed consent cannot be verified will be destroyed.

d. Future Biomedical Research Specimen Collections

Collection of specimens for Future Biomedical Research will be performed as outlined in the trial flow chart. In general, if additional blood specimens are being collected for Future Biomedical Research, these will usually be obtained at a time when the subject is having blood drawn for other trial purposes.

**4. Confidential Subject Information for Future Biomedical Research**

In order to optimize the research that can be conducted with Future Biomedical Research specimens, it is critical to link subject' clinical information with future test results. In fact little or no research can be conducted without connecting the clinical trial data to the specimen. The clinical data allow specific analyses to be conducted. Knowing subject characteristics like gender, age, medical history and treatment outcomes are critical to understanding clinical context of analytical results.

To maintain privacy of information collected from specimens obtained for Future Biomedical Research, the Sponsor has developed secure policies and procedures. All specimens will be single-coded per ICH E15 guidelines as described below.

At the clinical trial site, unique codes will be placed on the Future Biomedical Research specimens for transfer to the storage facility. This first code is a random number which does not contain any personally identifying information embedded within it. The link (or key) between subject identifiers and this first unique code will be held at the trial site. No personal identifiers will appear on the specimen tube.

**5. Biorepository Specimen Usage**

Specimens obtained for the Merck Biorepository will be used for analyses using good scientific practices. Analyses utilizing the Future Biomedical Research specimens may be performed by the Sponsor, or an additional third party (e.g., a university investigator) designated by the Sponsor. The investigator conducting the analysis will follow the Sponsor's privacy and confidentiality requirements. Any contracted third party analyses will conform to the specific scope of analysis outlined in this sub-trial. Future Biomedical Research specimens remaining with the third party after specific analysis is performed will be reported to the Sponsor.

**6. Withdrawal From Future Biomedical Research**

Subjects may withdraw their consent for Future Biomedical Research and have their specimens and all derivatives destroyed. Subjects may withdraw consent at any time by contacting the principal investigator for the main trial. If medical records for the main trial are still available, the investigator will contact the Sponsor using the designated

mailbox (clinical.specimen.management@merck.com) and a form will be provided to obtain appropriate information to complete specimen withdrawal. Subsequently, the subject's specimens will be removed from the biorepository and be destroyed. Documentation will be sent to the investigator confirming the destruction. It is the responsibility of the investigator to inform the subject of completion of destruction. Any analyses in progress at the time of request for destruction or already performed prior to the request being received by the Sponsor will continue to be used as part of the overall research trial data and results. No new analyses would be generated after the request is received.

In the event that the medical records for the main trial are no longer available (e.g., if the investigator is no longer required by regulatory authorities to retain the main trial records) or the specimens have been completely anonymized, there will no longer be a link between the subject's personal information and their specimens. In this situation, the request for specimen destruction can not be processed.

## **7. Retention of Specimens**

Future Biomedical Research specimens will be stored in the biorepository for potential analysis for up to 20 years from the end of the main study. Specimens may be stored for longer if a regulatory or governmental authority has active questions that are being answered. In this special circumstance, specimens will be stored until these questions have been adequately addressed.

Specimens from the trial site will be shipped to a central laboratory and then shipped to the Sponsor-designated biorepository. If a central laboratory is not utilized in a particular trial, the trial site will ship directly to the Sponsor-designated biorepository. The specimens will be stored under strict supervision in a limited access facility which operates to assure the integrity of the specimens. Specimens will be destroyed according to Sponsor policies and procedures and this destruction will be documented in the biorepository database.

## **8. Data Security**

Databases containing specimen information and test results are accessible only to the authorized Sponsor representatives and the designated trial administrator research personnel and/or collaborators. Database user authentication is highly secure, and is accomplished using network security policies and practices based on international standards (e.g., ISO17799) to protect against unauthorized access.

## **9. Reporting of Future Biomedical Research Data to Subjects**

No information obtained from exploratory laboratory studies will be reported to the subject, family, or physicians. Principle reasons not to inform or return results to the subject include: Lack of relevance to subject health, limitations of predictive capability, and concerns regarding misinterpretation.

If any exploratory results are definitively associated with clinical significance for subjects while the clinical trial is still ongoing, investigators will be contacted with information. After the clinical trial has completed, if any exploratory results are definitively associated with clinical significance, the Sponsor will endeavor to make such results available

through appropriate mechanisms (e.g., scientific publications and/or presentations). Subjects will not be identified by name in any published reports about this study or in any other scientific publication or presentation.

#### **10. Future Biomedical Research Study Population**

Every effort will be made to recruit all subjects diagnosed and treated on Sponsor clinical trials for Future Biomedical Research.

#### **11. Risks Versus Benefits of Future Biomedical Research**

For future biomedical research, risks to the subject have been minimized. No additional risks to the subject have been identified as no additional specimens are being collected for Future Biomedical Research (i.e., only leftover samples are being retained).

The Sponsor has developed strict security, policies and procedures to address subject data privacy concerns. Data privacy risks are largely limited to rare situations involving possible breach of confidentiality. In this highly unlikely situation there is risk that the information, like all medical information, may be misused.

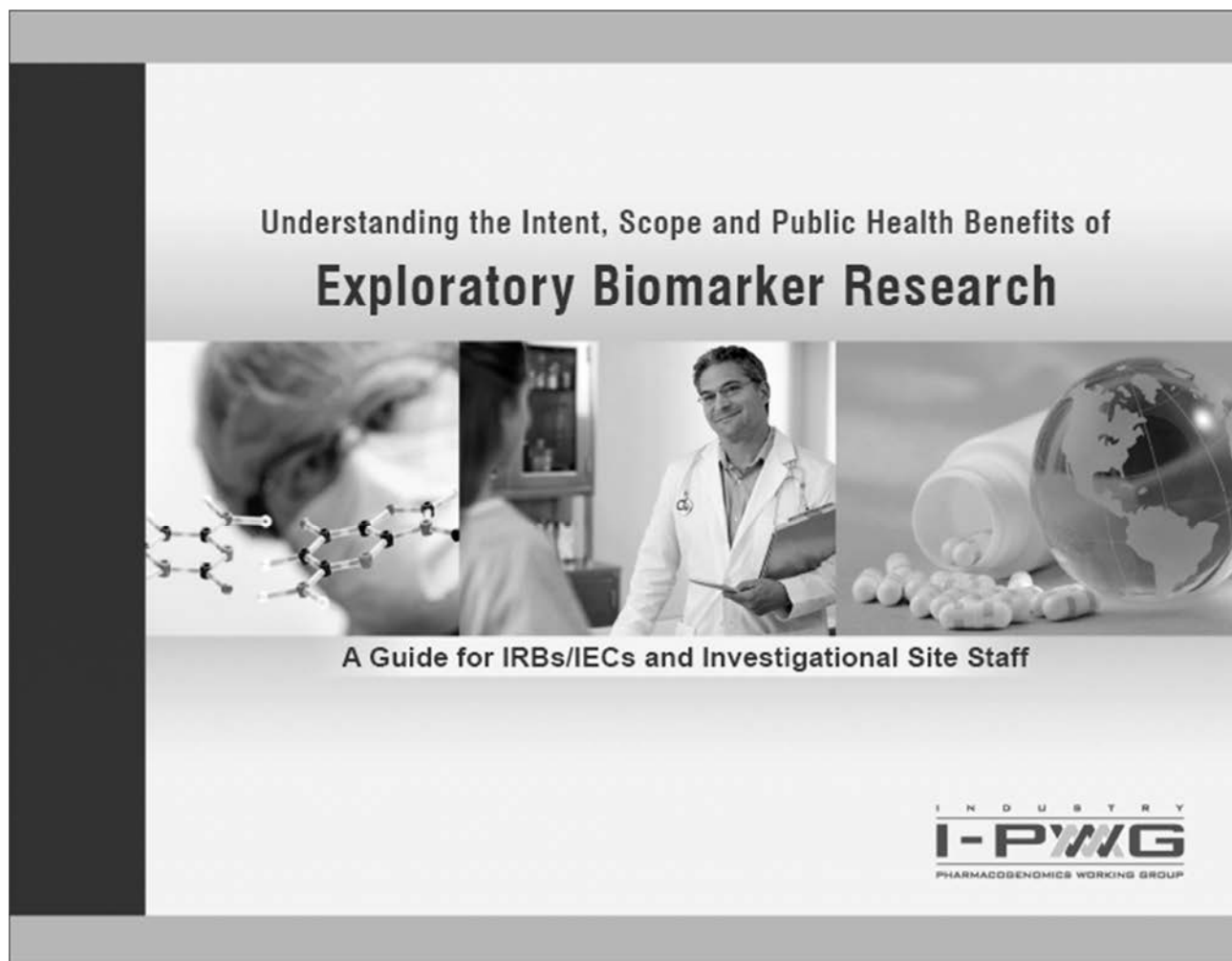
#### **12. Questions**

Any questions related to the future biomedical research should be e-mailed directly to [clinical.specimen.management@merck.com](mailto:clinical.specimen.management@merck.com).

#### **13. References**

1. National Cancer Institute: <http://www.cancer.gov/dictionary/?searchTxt=biomarker>
2. International Conference on Harmonization: DEFINITIONS FOR GENOMIC BIOMARKERS, PHARMACOGENOMICS, PHARMACOGENETICS, GENOMIC DATA AND SAMPLE CODING CATEGORIES - E15; <http://www.ich.org/LOB/media/MEDIA3383.pdf>

### 12.3 Understanding the Intent, Scope and Public Health Benefits of Exploratory Biomarker Research: A Guide for IRBs/IECs and Investigational Site Staff



**This informational brochure is intended for IRBs/IECs and Investigational Site Staff. The brochure addresses issues relevant to specimen collection for biomarker research in the context of pharmaceutical drug and vaccine development.**

Developed by  
The Industry Pharmacogenomics Working Group (I-PWG)  
[www.i-pwg.org](http://www.i-pwg.org)

## 1. What is a Biomarker and What is Biomarker Research?

A biomarker is a "characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention".<sup>1</sup>

Biomarker research, including research on pharmacogenomic biomarkers, is a tool used to improve the development of pharmaceuticals and understanding of disease. It involves the analysis of biomolecules (such as DNA, RNA, proteins, and lipids), or other measurements (such as blood pressure or brain images) in relation to clinical endpoints of interest. Biomarker research can be influential across all phases of drug development, from drug discovery and preclinical evaluations to clinical development and post-marketing studies. This brochure focuses on biomarker research involving analysis of biomolecules from biological samples collected in clinical trials. Please refer to I-PWG Pharmacogenomic Informational Brochure<sup>2</sup> and ICH Guidance E15<sup>3</sup> for additional information specific to pharmacogenomic biomarkers.

## 2. Why is Biomarker Research Important?

### Importance to Patients and Public Health


Biomarker research is helping to improve our ability to predict, detect, and monitor diseases and improve our understanding of how individuals respond to drugs. This research underlies personalized medicine: a tailored approach to patient treatment based on the molecular analysis of genes, proteins, and metabolites.<sup>4</sup> The goal of biomarker research is to aid clinical decision-making toward safer and more efficacious courses of treatment, improved patient outcomes, and overall cost-savings. It also allows for the continued development and availability of drugs that are effective in certain sub-populations when they otherwise might not have been developed due to insufficient efficacy in the broader population.

Recent advances in biomedical technology, including genetic and molecular medicine, have greatly increased the power and precision of analytical tools used in health research and have accelerated the drive toward personalized medicine. In some countries, highly focused initiatives have been created to promote biomarker research (e.g., in the US: [www.fda.gov/oc/initiatives/criticalpath/](http://www.fda.gov/oc/initiatives/criticalpath/); in the EU: [www.imi.europa.eu/index\\_en.html](http://www.imi.europa.eu/index_en.html)).

### Importance to Drug Development

Biomarker research is being used by the pharmaceutical industry to streamline the drug development process. Some biomarkers are used as substitutes or "surrogates" for safety or efficacy endpoints in clinical trials particularly where clinical outcomes or events cannot practically or ethically be measured (e.g., cholesterol as a surrogate for cardiovascular disease).<sup>5</sup> By using biomarkers to assess patient response, ineffective drug candidates may be terminated earlier in the development process in favor of more promising drug candidates. Biomarkers are being used to optimize clinical trial designs and outcomes by identifying patient populations that are more likely to respond to a drug therapy or to avoid specific adverse events.

1



Biomarker research is also being used to enhance scientific understanding of the mechanisms of both treatment response and disease processes, which can help to identify future targets for drug development. Depending on the clinical endpoints in a clinical trial, biomarker sample collection may either be a required or optional component of the trial. However, both mandatory and optional sample collections are important for drug development.

### 3. Importance of Biomarkers to Regulatory Authorities

Regulatory health authorities are increasingly aware of the benefits of biomarkers and how they may be used for drug approval, clinical trial design, and clinical care. Biomarkers have been used to establish risk:benefit profiles. For example, the FDA has modified the US warfarin (Coumadin®) label to include the analysis of *CYP2C9* and *VKORC1* genes to guide dosing regimens. Health authorities such as the FDA (USA), EMEA (European Union), MHLW (Japan), and ICH (International) are playing a key role in advancing this scientific field as it applies to pharmaceutical development by creating the regulatory infrastructure to facilitate this research. Numerous regulatory guidances and concept papers have already been issued, many of which are available through [www.i-pwg.org](http://www.i-pwg.org). Global regulatory authorities have highlighted the importance of biomarker research and the need for the pharmaceutical industry to take the lead in this arena.<sup>3, 6-24</sup>

### 4. How are Biomarkers Being Used in Drug/Vaccine Development?

Biomarker research is currently being used in drug/vaccine development to:

- Explain variability in response among participants in clinical trials
- Better understand the mechanism of action or metabolism of investigational drugs
- Obtain evidence of pharmacodynamic activity (i.e., how the drug affects the body) at the molecular level
- Address emerging clinical issues such as unexpected adverse events
- Determine eligibility for clinical trials to optimize trial design
- Optimize dosing regimens to minimize adverse reactions and maximize efficacy
- Develop drug-linked diagnostic tests to identify patients who are more likely or less likely to benefit from treatment or who may be at risk of experiencing adverse events
- Provide better understanding of mechanisms of disease
- Monitor clinical trial participant response to medical interventions

Biomarker research, including research on banked samples, should be recognized as an important public health endeavor for the overall benefit of society, whether by means of advancement of medical science or by development of safer and more effective therapies.<sup>7</sup> Since the value of collected samples may increase over time as scientific discoveries are made, investment in long-term sample repositories is a key component of biomarker research.



### 5. Biomarkers are Already a Reality in Health Care

A number of drugs now have biomarker information included in their labels.<sup>26</sup> Biomarker tests are already being used in clinical practice to serve various purposes:

**Predictive biomarkers (efficacy)** – In clinical practice, predictive efficacy biomarkers are used to predict which patients are most likely to respond, or not respond, to a particular drug. Examples include: i) *Her2/neu* overexpression analysis required for prescribing trastuzumab (Herceptin<sup>®</sup>) to breast cancer patients, ii) *c-kit* expression analysis prior to prescribing imatinib mesylate (Gleevec<sup>®</sup>) to gastrointestinal stromal tumor patients, and iii) *KRAS* mutational status testing prior to prescribing panitumumab (Vectibix<sup>®</sup>) or cetuximab (Erbix<sup>®</sup>) to metastatic colorectal cancer patients.

**Predictive biomarkers (safety)** – In clinical practice, predictive safety biomarkers are used to select the proper drug dose or to evaluate the appropriateness of continued therapy in the event of a safety concern. Examples include: i) monitoring of blood potassium levels in patients receiving drospirenone and ethinyl estradiol (Yasmin<sup>®</sup>) together with daily long-term drug regimens that may increase serum potassium, and ii) prospective *HLA-B\*57:01* screening to identify those at increased risk for hypersensitivity to abacavir (Ziagen<sup>®</sup>).

**Surrogate biomarkers** – In clinical practice, surrogate biomarkers may be used as alternatives to measures such as survival or irreversible morbidity. Surrogate biomarkers are measures that are reasonably likely, based on epidemiologic, therapeutic, pathophysiologic, or other evidence, to predict clinical benefit. Examples include: i) LDL level as a surrogate for risk of cardiovascular diseases in patients taking lipid-lowering agents such as atorvastatin calcium (Lipitor<sup>®</sup>), ii) blood glucose as a surrogate for clinical outcomes in patients taking anti-diabetic agents, and iii) HIV plasma viral load and CD4 cell counts as sur-

rogates for time-to-clinical-events and overall survival in patients receiving antiretroviral therapy for HIV disease.

**Prognostic biomarkers** – Biomarkers can also help predict clinical outcomes independent of any treatment modality. Examples of prognostic biomarkers used in clinical practice include: i) CellSearch<sup>™</sup> to predict progression-free survival in breast cancer, ii) anti-CCP (cyclic citrullinated protein) for the severity of rheumatoid arthritis, iii) estrogen receptor status for breast cancer, and iv) anti-dsDNA for the severity of systemic lupus erythematosus.

### 6. Biomarker Samples from Clinical Trials: An Invaluable Resource

Adequate sample sizes and high-quality data from controlled clinical trials are key to advancements in biomarker research. Samples collected in clinical trials create the opportunity for investigation of biomarkers related to specific drugs, drug classes, and disease areas. Clinical drug development programs are therefore an invaluable resource and a unique opportunity for highly productive biomarker research. In addition to conducting independent research, pharmaceutical companies are increasingly contributing to consortia efforts by pooling samples, data, and expertise in an effort to conduct rigorous and efficient biomarker research and to maximize the probability of success.<sup>26-27</sup>

### 7. Informed Consent for Collection & Banking of Biomarker Samples

Collection of biological samples in clinical trials must be undertaken with voluntary informed consent of the participant (or legally-acceptable representative). Policies

and regulations for legally-appropriate informed consent vary on national, state, and local levels, but are generally based on internationally recognized pillars of ethical conduct for research on human subjects.<sup>26-31</sup>

#### Optional vs. Required Subject Participation

Depending on the relevance of biomarker research to a clinical development program at the time of protocol development, the biomarker research may be a core required component of a trial (e.g., key to elucidating the drug mechanism of action or confirming that the drug is interacting with the target) or may be optional (e.g., to gain valuable knowledge that enhances the understanding of diseases and drugs). Informed consent for the collection of biomarker samples may be presented either in the main clinical informed consent form or as a separate informed consent form, with approaches varying somewhat across pharmaceutical companies. The relevance of biomarker research to a clinical development program may change over time as the science evolves. The samples may therefore increase in value after a protocol is developed.

#### Consent for Future Research Use

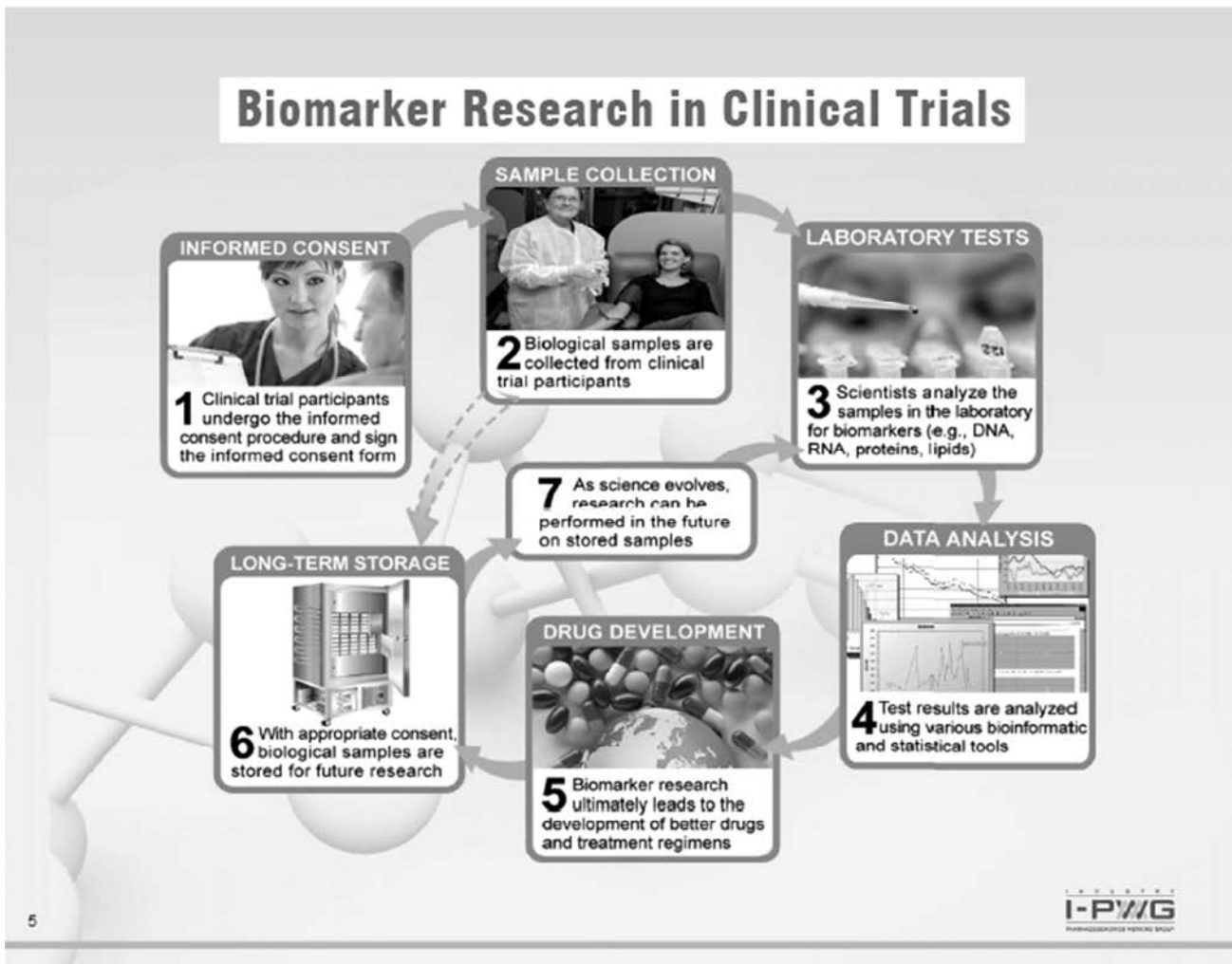
While it can be a challenge to specify the details of the research that will be conducted in the future, the I-PWG holds the view that future use of samples collected for exploratory biomarker research in clinical trials should be permissible when i) the research is scientifically sound, ii) participants are informed of the scope of the intended future research, even if this is broadly defined (see potential uses in Section 4 above), iii) autonomy is respected by providing the option to consent separately to future use of samples or by providing the option to terminate further use of samples upon request (consent withdrawal / sample destruction), and iv) industry standards for confidentiality protection per Good Clinical Practice guidelines are met.<sup>3, 31</sup> Importantly, any research using banked samples should be consistent with the original informed consent, except where otherwise permitted by local law or regulation.

Important elements of informed consent for **future use** of samples include, but are not limited to:<sup>39</sup>

**The scope of research** – Where the scope of the potential future research is broad, participants should be informed of the boundaries of the research. While it may not be possible to describe the exact analytical techniques that will be used, or specific molecules that will be analyzed, it is possible to clearly articulate in reasonable detail the type of research to be conducted and its purpose. Information regarding whether stored samples may be shared with other parties or utilized for commercialization purposes should also be addressed.

**Withdrawal of consent / sample destruction** – The informed consent form should inform participants of their right to withdraw their consent / request destruction of their samples. This should include the mechanisms for exercising that right and any limitations to exercising that right. For example, participants should be informed that it is not possible to destroy samples that have been anonymized.<sup>3</sup> In addition, according to industry standards and regulatory guidance, participants should be informed that data already generated prior to a consent withdrawal request are to be maintained as part of the study data.<sup>38</sup>

**The duration of storage** – The permissible duration of storage may vary according to the nature and uses of the samples and may also vary on national, state, and local levels. The intended duration of storage, including indefinite storage, should be specified.



### 8. Biomarker Sample Collection in Different Countries

Collection of biological samples for biomarker research is straightforward in most jurisdictions. Some countries have specific laws and regulations regarding collection, labeling, storage, export, and/or use of exploratory samples. In addition, some regulations distinguish between DNA and non-DNA samples or between samples used for diagnostic purposes and samples collected for scientific research. Processes for the collection, labeling, storage, export, and/or use of biomarker samples should always adhere to the laws and regulations of the country/region in which those samples are collected.

### 9. Return of Research Results to Study Participants

Policies for the return of biomarker research results to study participants who request them vary among pharmaceutical companies. There are many considerations that pharmaceutical companies weigh when determining their policy regarding the return of biomarker research results to study participants. These include:

- i) the conditions under which biomarker research results were generated (i.e., exploratory research laboratory versus accredited diagnostic laboratory)
- ii) whether the results will have an impact on the medical care of the participant or on a related person, if applicable
- iii) whether genetic counseling is recommended (for genetic results)
- iv) the ability to accurately link the result to the individual from whom the sample was collected
- v) international, national, and local guidelines, policies, legislation, and regulations regarding participants' rights to access data generated on them

Renegar *et al.*, 2008 and Article 29 Data Protection Working Party (an advisory committee to the European Commission on the European Data Protection Directive) have addressed these considerations in detail in relation to pharmacogenomic research data and provided a list of documents addressing the general issue of return of research results.<sup>34-35</sup>

### 10. Benefits and Risks Associated with Biomarker Research

#### Benefits

While it may not always directly benefit the study participant who is providing the samples, biomarker research can improve overall understanding of disease and treatment of future patients receiving therapies developed from such research. Patients are now benefiting from retrospective biomarker research conducted on samples collected from clinical trials and stored for exploratory research. One example is the recent label update to the EGFR antibody drugs cetuximab (Erbix<sup>®</sup>) and panitumumab (Vectibix<sup>®</sup>) which highlights the value of *KRAS* status as a predictive biomarker for treatment of metastatic colorectal cancer with this class of drug.

The humanitarian benefit of human research is recognized by the Nuremberg Code.<sup>28,29</sup> Provided that the degree of risk does not exceed that determined by the humanitarian importance of the problem to be solved, research participants should not be denied the right to contribute to the greater common good.<sup>28,32</sup>

#### Risks

Risks associated with biomarker research are primarily related to the physical aspects of obtaining the sample and to patient privacy concerns.

Physical risks associated with biomarker sample collection in clinical trials can be characterized in two ways: i) negligible additional risk when the biomarker sample is collected as part of a procedure conducted to support

other core trial objectives, and ii) some added risk where the sampling procedure would otherwise have not been performed as a core component of a trial. Risks are also determined by the invasiveness of the sample collection procedure.

Privacy risks are generally those associated with the inappropriate disclosure and misuse of data. Pharmaceutical companies have policies and procedures for confidentiality protection to minimize this risk for all data collected and generated in clinical trials. These may vary across companies, but are based on industry standards of confidentiality and privacy protection highlighted in the following section. Importantly, privacy risks inherent to biomarker data are no greater than other data collected in a clinical trial.

### 11. Privacy, Confidentiality, and Patient Rights

Maintaining the privacy of study participants and the confidentiality of information relating to them is of paramount concern to industry researchers, regulators, and patients. Good Clinical Practice (GCP), the standard adhered to in pharmaceutical clinical research, is a standard that

*"... provides assurance that the data and reported results are credible and accurate, and that the rights, integrity, and confidentiality of trial subjects are protected",*

where confidentiality is defined as, *"The prevention of disclosure, to other than authorized individuals, of a sponsor's proprietary information or of a subject's identity."*

This standard dictates that *"the confidentiality of records that could identify subjects should be protected, respecting the privacy and confidentiality rules in accordance with applicable regulatory requirements."*<sup>21</sup>

Exploratory biomarker research in pharmaceutical development is commonly conducted in research laboratories that are not accredited to perform diagnostic tests used for healthcare decision-making. Therefore, results from exploratory biomarker research usually are not appropriate for use in making decisions about a trial participant's health. In addition, exploratory research data should not be included as part of a participant's medical record accessible for use by insurance companies. Legislation and policies to protect individuals against discrimination based on genetic information continually evolve based on social, ethical, and legal considerations. Examples of such legislation include the Human Tissue Act 2004 (UK) and the Genetic Information Nondiscrimination Act (GINA) 2008 (USA).<sup>26-27</sup>

### 12. Where to Get More Information?

Educational resources related to biomarker and pharmacogenomic research that caters to health care professionals, IRBs/IECs, scientists, and patients are continually being created and are publicly available. Links to many of these resources are available through the I-PWG website: [www.i-pwg.org](http://www.i-pwg.org).

### 13. What is I-PWG?

The Industry Pharmacogenomics Working Group (I-PWG) (formerly the Pharmacogenetics Working Group) is a voluntary association of pharmaceutical companies engaged in pharmacogenomic research. The Group's activities focus on non-competitive educational, informational, ethical, legal, and regulatory topics. The Group provides information and expert opinions on these topics and sponsors educational/informational programs to promote better understanding of pharmacogenomic and other biomarker research for key stakeholders. The I-PWG interacts with regulatory author-



ities and policy groups to ensure alignment. More information about the I-PWG is available at: [www.i-pwg.org](http://www.i-pwg.org).

#### 14. Contributing authors

Monique A. Franc, Teresa Healey, Feng Hong, Ronenn Roubenoff, Jasjit Sarang, Andrea Tyukody Renninger, Amelia Warner

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## 12.4 ECOG Performance Scale

<b>Grade</b>	<b>Description</b>
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all self-care but unable to carry out any work activities; up and about more than 50% of waking hours
3	Capable of only limited self-care; confined to bed or chair more than 50% of waking hours
4	Completely disabled; cannot carry on any self-care; totally confined to bed or chair
5	Dead
Oken M, Creech R, Tormey D, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. <i>Am J Clin Oncol</i> . 1982;5:649-655 <a href="http://ecog-acrin.org/resources/ecog-performance-status">http://ecog-acrin.org/resources/ecog-performance-status</a>	

## **12.5 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>).

## **12.6 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. MRI should be utilized, as per RECIST 1.1, as 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.

## 12.7 Abbreviations

<b>Abbreviation/Term</b>	<b>Definition</b>
AC	Doxorubicin + Cyclophosphamide
AE	Adverse Event
AJCC	American Joint Committee on Cancer
ALT	Alanine Aminotransferase
ASaT	All Subjects as Treated
AST	Aspartate Aminotransferase
β-hCG	β-human Chorionic Gonadotropin
BRCA	Breast Cancer 1
Cb	Carboplatin
CBC	Complete Blood Count
CD8+	Cluster of Differentiation 8 positive
CHF	Congestive Heart Failure
CI	Confidence Interval
CR	Complete Response
CRF	Case Report Form
CSR	Clinical Study Report
CTCs	Circulating Tumor Cells
CTCAE	Common Toxicity Criteria for Adverse Events
CTL	Circulating T Lymphocytes
DL	Dose Level
DLT	Dose-limiting Toxicity
DNA	Deoxyribonucleic acid
ECG	Electrocardiogram
ECI	Events of Clinical Interest
ECOG	Eastern Cooperative Oncology Group
EDC	Electronic Data Capture
eCRFs	Electronic Case Report Forms
EFS	Event-free Survival
EGFR	Epidermal Growth Factor Receptor
ER	Estrogen Receptor
ERC	Ethics Review Committee
FAS	Full Analysis Set
FBR	Future Biomedical Research
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act
FDAMA	Food and Drug Administration Modernization Act
FFPE	Formalin-fixed Paraffin Embedded
FTIH	First Time in Humans
GCP	Good Clinical Practice
HBsAg	Hepatitis B surface Antigen
HCV	Hepatitis C Virus
HER2	Human Epidermal Growth Factor Receptor 2
HGFR	Hepatocyte Growth Factor Receptor
HIV	Human Immunodeficiency Virus
HR	Hormone Receptor
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IgG4	Immunoglobulin G4
IHC	Immunohistochemistry

<b>Abbreviation/Term</b>	<b>Definition</b>
INR	International Normalized Ratio
irAEs	Immune-related Adverse Events
IRB	Institutional Review Board
IV	Intravenous
IVRS	Interactive Voice Response System
IWRS	Integrated Web Response System
K	Pembrolizumab
KM	Kaplan-Meier
KN	KEYNOTE
LMP	Last Menstrual Period
mAb	Monoclonal Antibody
mg	Milligram
mg/m <sup>2</sup>	Milligram per meter squared
mL	Milliliter
MRI	Magnetic Resonance Imaging
mRNA	Messenger Ribonucleic Acid
MSD	Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc.
mTNBC	Metastatic Triple-negative Breast Cancer
MTD	Maximum Tolerated Dose
NCI	National Cancer Institute
NKC	Natural Killer Cell
NMR	Nuclear Magnetic Resonance
Np	Nab-paclitaxel
NSCLC	Non-Small Cell Lung Cancer
NYHA	New York Heart Association
ORR	Objective Response Rate
OS	Overall Survival
OTC	Over-the-counter
pCR	Pathological Complete Response
PD	Progressive Disease
PD-1	Programmed Death Receptor-1
PD-L1	Programmed Death - Ligand 1
PD-L2	Programmed Death - Ligand 2
PFS	Progression-Free Survival
PGt	Pharmacogenetic
PIN	Personal Identification Number
PR	Progesterone Receptor
PR	Partial Response
PS	Performance Status
PT	Prothrombin Time
PTEN	Phosphatase and TEnsin Homolog
Q3W	Every 3 Weeks
Q2W	Every 2 Weeks
RECIST	Response Evaluation Criteria in Solid Tumors
RNA	Ribonucleic Acid
RP2D	Recommended Phase 2 Dose
SAE	Serious Adverse Events
SAP	Statistical Analysis Plan
SD	Stable Disease
SOC	Standard of Care

<b>Abbreviation/Term</b>	<b>Definition</b>
SOP	Standard Operating Procedures
T3	Total triiodothyronine
T4	Free thyroxine
TCGA	The Cancer Genome Atlas
TCR	T Cell Receptor
TILs	Tumor-Infiltrating Lymphocytes
TNBC	Triple-negative Breast Cancer
Tregs	Regulatory T Cells
TSH	Thyroid Stimulating Hormone
ULN	Upper Limit of Normal
WBC	White Blood Cell

### 13.0 SIGNATURES

#### 13.1 Sponsor's Representative

TYPED NAME	
TITLE	
SIGNATURE	
DATE SIGNED	

#### 13.2 Investigator

I agree to conduct this clinical trial in accordance with the design outlined in this protocol and to abide by all provisions of this protocol (including other manuals and documents referenced from this protocol). I agree to conduct the trial in accordance with generally accepted standards of Good Clinical Practice. I also agree to report all information or data in accordance with the protocol and, in particular, I agree to report any serious adverse events as defined in Section 7.0 – Assessing and Recording Adverse Events. I also agree to handle all clinical supplies provided by the Sponsor and collect and handle all clinical specimens in accordance with the protocol. I understand that information that identifies me will be used and disclosed as described in the protocol, and that such information may be transferred to countries that do not have laws protecting such information. Since the information in this protocol and the referenced Investigator’s Brochure is confidential, I understand that its disclosure to any third parties, other than those involved in approval, supervision, or conduct of the trial is prohibited. I will ensure that the necessary precautions are taken to protect such information from loss, inadvertent disclosure or access by third parties.

TYPED NAME	
TITLE	
SIGNATURE	
DATE SIGNED	