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TITLE:

A Phase III, Randomized, Double-blind Study to Evaluate Pembrolizumab plus Chemotherapy vs Placebo plus Chemotherapy as Neoadjuvant Therapy and Pembrolizumab vs Placebo as Adjuvant Therapy for Triple Negative Breast Cancer (TNBC)

IND NUMBER: 124,442
EudraCT NUMBER: 2016-004740-11

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DOCUMENT HISTORY

Document	Date of Issue	Overall Rationale
Amendment 05	01-Jul-2022	Merck Sharp & Dohme Corp. underwent an entity name and address change to Merck Sharp & Dohme LLC, Rahway, NJ, USA. This conversion resulted only in an entity name change and update to the address. The code of conduct for clinical trials was updated to align with the current version.
Amendment 04	26-Feb-2020	The protocol was amended to clarify an adjustment of efficacy boundaries at interim analyses for event-free survival based on the actual number of events observed.
Amendment 03	17-Oct-2018	The protocol was amended to 1) add an analysis of EFS at IA2; and 2) adjust the timing of IA2 accordingly.
Amendment 02	01-May-2018	The protocol was amended to 1) adjust the timing of IA1 to occur after at least 500 subjects have or would have completed surgery; 2) added a second IA (IA2) for pCR; and 3) increase the sample size from ~855 to ~1150 based on a revision to the assumed EFS rate at 36 months in the control arm.
Amendment 01	16-Dec-2016	The protocol was amended to 1) clarify the dose modification guidelines provided for paclitaxel and carboplatin; and 2) incorporate mandatory overdose language for the pembrolizumab program.
Original	05-Dec-2016	Not applicable.

SUMMARY OF CHANGES

PRIMARY REASON(S) FOR THIS AMENDMENT:

Section Number (s)	Section Title(s)	Description of Change (s)	Rationale
Title page 12.1 Throughout	Title page Code of Conduct for Clinical Trials Throughout	Sponsor entity name and address change.	Merck Sharp & Dohme Corp. underwent an entity name and address change to Merck Sharp & Dohme LLC, Rahway, NJ, USA. This conversion resulted only in an entity name change and update to the address.
12.1	Code of Conduct for Clinical Trials	Edits incorporated throughout.	Revisions to align with the current version of the code of conduct.

ADDITIONAL CHANGE(S) FOR THIS AMENDMENT:

No additional changes.

1.0 TRIAL SUMMARY

Abbreviated Title	A Phase III, Randomized, Double-blind Study to Evaluate Pembrolizumab plus Chemotherapy vs Placebo plus Chemotherapy as Neoadjuvant Therapy and Pembrolizumab vs Placebo as Adjuvant Therapy for Triple Negative Breast Cancer (TNBC)
Sponsor Product Identifiers	MK-3475 Pembrolizumab
Trial Phase	III
Clinical Indication	Neoadjuvant and adjuvant treatment for locally-advanced TNBC
Trial Type	Interventional
Type of control	Placebo on a background of chemotherapy
Route of administration	Intravenous
Trial Blinding	Double-blind
Treatment Groups	There are 2 treatment groups in the neoadjuvant and adjuvant therapy phases: • Neoadjuvant Phase o Arm 1: Pembrolizumab + chemotherapy o Arm 2: Placebo + chemotherapy • Adjuvant Phase o Arm 1: Pembrolizumab o Arm 2: Placebo Pembrolizumab: 200 mg fixed dose, intravenously (IV) every 3 weeks (Q3W), in the Neoadjuvant and Adjuvant Treatment Phases Placebo: Normal saline or dextrose IV Q3W dosing in the Neoadjuvant and Adjuvant Treatment Phases **Chemotherapy:** Carboplatin: Area under the curve 5 (AUC 5), IV, Q3W, on Day 1 of Cycles 1-4 or AUC 1.5, IV, weekly, on Days 1, 8, 15 of Cycles 1-4 of the paclitaxel/carboplatin regimen (Treatment 1) Paclitaxel: 80 mg/m^2, IV, weekly, on Days 1, 8, 15 of Cycles 1-4 of the paclitaxel/carboplatin regimen (Treatment 1) Followed by: Doxorubicin: 60 mg/m^2, IV, Q3W, on Day 1 of Cycles 1-4 of the doxorubicin + cyclophosphamide (AC) / Epirubicin + cyclophosphamide (EC) regimen (Treatment 2) or Epirubicin: 90 mg/m^2, IV, Q3W, on Day 1 of Cycles 1-4 of the AC/EC regimen (Treatment 2) Cyclophosphamide: 600 mg/m^2, IV, Q3W, on Day 1 of Cycles 1-4 of the AC/EC regimen (Treatment 2) **Growth factor support:** Granulocyte-colony stimulating factor (G-CSF) should be administered after each cycle of chemotherapy. G-CSF 5 µg/kg/day

	administered subcutaneously (SC) should be initiated at 24 hours postdose and continued until at least 72 hours after the last day of chemotherapy. Pegfilgrastim administered SC as either a single dose of 100 µg/kg (individualized) or a single dose of 6 mg (general approach) at 24 hours after the last day of chemotherapy is also acceptable for the Q3W chemotherapy regimens. Note: each cycle = 21 days
Number of trial subjects	Approximately 1150 subjects will be enrolled.
Estimated duration of trial	The Sponsor estimates that the trial will require approximately 8 years 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 trial for approximately 67 weeks from the time the subject signs the Informed Consent Form (ICF) through completion of study treatment. After a screening phase of ~28 days, each subject will be receiving study treatment based on the randomization schedule for approximately 51 weeks (17 cycles). Each subject will undergo definitive surgery 3-6 weeks after conclusion of the last cycle of the neoadjuvant treatment. *Neoadjuvant Treatment Phase* Subjects who discontinue study treatment during the neoadjuvant period for any reason other than disease progression that precludes definitive surgery (which refers to either local and/or distant disease progression) will enter the long-term follow-up Phase and should be assessed for pCR and disease progression/recurrence. Long term follow-up visits will be scheduled to occur at 3-month intervals (± 1 month) from the date of randomization for the first 2 years, then at 6-month intervals (± 1 month) for Years 3 to 5, and annually thereafter until occurrence of local or/and distant disease progression/ recurrence, death, withdrawal of consent, or the end of the study, whichever occurs first. *Adjuvant Treatment Phase* Subjects who do not start adjuvant treatment after surgery, complete adjuvant study treatment, or discontinue adjuvant study treatment for any reason other than local or distant disease recurrence will enter the Long Term follow-up phase and should be assessed for disease recurrence. Long term follow-up visits will be scheduled to occur at 3-month intervals (± 1 month) from the date of randomization for the first 2 years, then at 6-month intervals (± 1 month) for Years 3 to 5, and annually thereafter until occurrence of local or/and distant recurrence, withdrawal of consent, or the end of the study, whichever occurs first. Imaging assessments for recurrent or metastatic disease will be at the discretion of the subject's treating physician, per local standard of care, or at the time of symptoms.

Randomization Ratio	2:1

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 III, randomized, double-blind study to evaluate pembrolizumab plus chemotherapy vs placebo plus chemotherapy as neoadjuvant therapy and pembrolizumab vs placebo as adjuvant therapy for triple negative breast cancer (TNBC).

A commonly used standard neoadjuvant regimen for TNBC is a weekly taxane (eg, paclitaxel) for 12 weeks followed by an anthracycline (eg, doxorubicin 60 mg/m^2 plus cyclophosphamide at 600 mg/m^2 [AC] or epirubicin 90 mg/m^2 plus cyclophosphamide at 600 mg/m^2 [EC]) every 3 weeks (Q3W) for 4 cycles.

The chemotherapy regimen included in this study is built upon the aforementioned regimens based on the emerging clinical trial data showing that addition of carboplatin enhances efficacy as determined by pathological complete response (pCR) [1], [2]. Pembrolizumab in combination with this regimen will be studied as part of a 2-arm study:

- Arm 1: (KXCb/KA(E)C): Pembrolizumab (K) Q3W + paclitaxel (X) weekly + (carboplatin (Cb) Q3W or weekly) x 4 cycles, followed by pembrolizumab + (doxorubicin or epirubicin) + cyclophosphamide (AC or EC) Q3W x 4 cycles as neoadjuvant therapy prior to surgery; followed by 9 cycles of pembrolizumab Q3W as adjuvant therapy post-surgery.

- Arm 2: (PXCb/PA(E)C): Placebo (P) Q3W + paclitaxel (X) weekly + (carboplatin (Cb) Q3W or weekly) x 4 cycles, followed by placebo + (doxorubicin or epirubicin) + cyclophosphamide (AC or EC) Q3W x 4 cycles as neoadjuvant therapy prior to surgery; followed by 9 cycles of placebo Q3W as adjuvant therapy post-surgery.

  Note: 1 cycle = 21 days

In Arm 1, the dose and schedule of pembrolizumab will be fixed at 200 mg Q3W; and a commonly used AC (or EC) dose/schedule will be used, ie, doxorubicin 60 mg/m^2 (or epirubicin 90 mg/m^2) Q3W plus cyclophosphamide 600 mg/m^2 Q3W. The dose level of paclitaxel is fixed at 80 mg/m^2 weekly in both arms. The dose level for carboplatin is area under the curve (AUC 5) Q3W or (AUC 1.5) weekly in both arms.

In Arm 2, placebo is substituted for pembrolizumab.

Granulocyte-colony stimulating factor (G-CSF) should be administered after each cycle of chemotherapy. G-CSF (5 µg/kg/day) administered subcutaneously (SC) should be initiated at 24 hours postdose and continued until at least 72 hours after the last day of chemotherapy. Pegfilgrastim administered SC as either a single dose of 100 µg/kg (individualized) or a single dose of 6 mg (general approach) at 24 hours after the last day of chemotherapy is also acceptable for the Q3W chemotherapy regimens.

Prior to randomization, the subjects will be stratified based on their nodal status (either positive or negative nodes involved with tumor), tumor size (T1/T2 vs. T3/T4), and carboplatin regimen (Q3W or weekly).

Tumor Biopsy for Confirmation of TNBC Status and Translational Research: Subjects with locally advanced TNBC are required to have a core needle biopsy consisting of at least 2 separate tumor cores, utilizing multiple passes, at screening. A subject's TNBC status for eligibility at Screening will be based on central confirmation in accordance with the inclusion/exclusion criteria described in Section 5.1.2 – Subject Inclusion Criteria and 5.1.3 – Subject Exclusion Criteria. However, a formalin-fixed paraffin-embedded (FFPE) tumor tissue sample or slides obtained at the subject's initial diagnosis maybe submitted to a designated central laboratory for confirmation of the subject's TNBC status if a new biopsy cannot be obtained due to site inaccessibility or a medical contraindication. Note: Sponsor agreement is required for FFPE tumor tissue sample or slides that were obtained greater than 30 days prior to the date that the informed consent was signed.

For subjects with adequate tumor volume at the end of Neoadjuvant Treatment Phase, Treatment 1 Cycle 4 as assessed by the investigator, an optional 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 a pCR, this is optional should a subject choose to participate. 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 –Clinical Procedures/Assessments. A final and optional biopsy will also be performed at the time of recurrence, if applicable, for subjects who agree to participate.

Breast Magnetic Resonance Imaging (MRI): Breast MRIs will be performed in a subset of approximately 150 subjects with locally advanced TNBC who choose to participate. If a subject has consented to participating in the Breast MRI substudy, breast MRIs are performed at screening, during Cycle 4 of Treatment 1 of the Neoadjuvant Treatment Phase (before Neoadjuvant Treatment Phase, Treatment 2 Cycle 1, Day 1), and during Cycle 4 of Treatment 2 of the Neoadjuvant Treatment Phase prior to definitive surgery (See Section 7.1.2.8.1 – Breast MRI for more details). Changes from the baseline will be assessed by the investigator per Response Evaluation Criteria in Solid Tumors (RECIST) 1.1. Breast MRI images will be sent to a designated central vendor for collection, quality review, and independent imaging review.

Definitive surgery: Definitive surgery such as breast conservation surgery (BCS) or mastectomy with or without axillary lymph node dissection will be performed as part of the local standard of care approximately 3-6 weeks following the completion or early discontinuation of the treatments in the Neoadjuvant Treatment Phase. A thorough evaluation of breast cancer status, pathological staging per current American Joint Committee of Cancer (AJCC) Breast Cancer Staging criteria and assessment of surgical margins will be performed by the local pathologist on all the tissues removed during the surgery. Details on management of axillary adenopathy are provided in Table 7.

Radiation: Post-operative radiation therapy is acceptable in accordance to the standard of care as applicable, eg, in cases of BCS, large primary tumor, subset of patients with positive lymph nodes.

Adjuvant Treatment Phase: Following surgery, subjects will enter the adjuvant treatment phase. Subjects will receive either pembrolizumab or placebo (Q3W) for 9 cycles, each cycle lasting 21 days. Treatment in the adjuvant phase should begin approximately 30 to 60 days after definitive surgery. If post-operative radiation therapy is indicated, adjuvant pembrolizumab or placebo may be started either concurrently with radiation therapy or 2 weeks post-radiation therapy.

Safety: Study treatment will continue until completion of study treatment (17 cycles of pembrolizumab/placebo), disease progression in the neoadjuvant phase or until recurrence (local or distance) after surgery, unacceptable adverse event(s), intercurrent illness that prevents further administration of study treatment, investigator's decision to withdraw the subject from study treatment, pregnancy of the subject, noncompliance with study treatment or procedure requirements, consent withdrawal, becoming lost-to-follow-up, death, or administrative reasons that require cessation of treatment. After discontinuation of study treatment, each subject will be followed for 30 days for adverse events (AE) and events of clinical interest (ECIs). Serious AEs (SAEs) will be collected for 90 days after the end of study treatment.

Adverse events 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 12.4).

Safety follow-up will be performed for subjects who complete all protocol-specified treatments or procedures and for those with Early Discontinuations will be outlined in Section 6.0 – Trial Flow Chart and described in more detail in Section 7.1 – Trial Procedures.

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.

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

This study will use an external Data Monitoring Committee (DMC) to monitor safety and efficacy.

2.2 Trial Diagram

The trial design is depicted in Figure 1 and Figure 2.

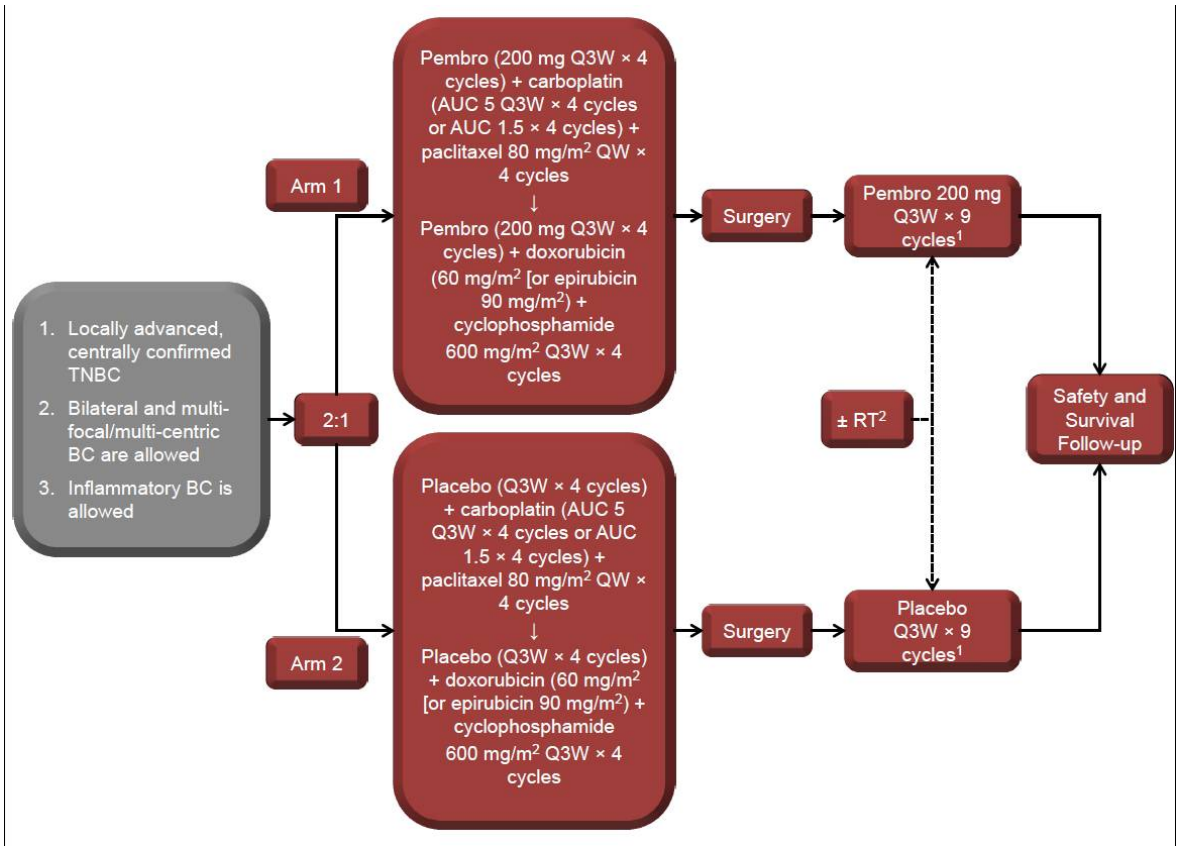
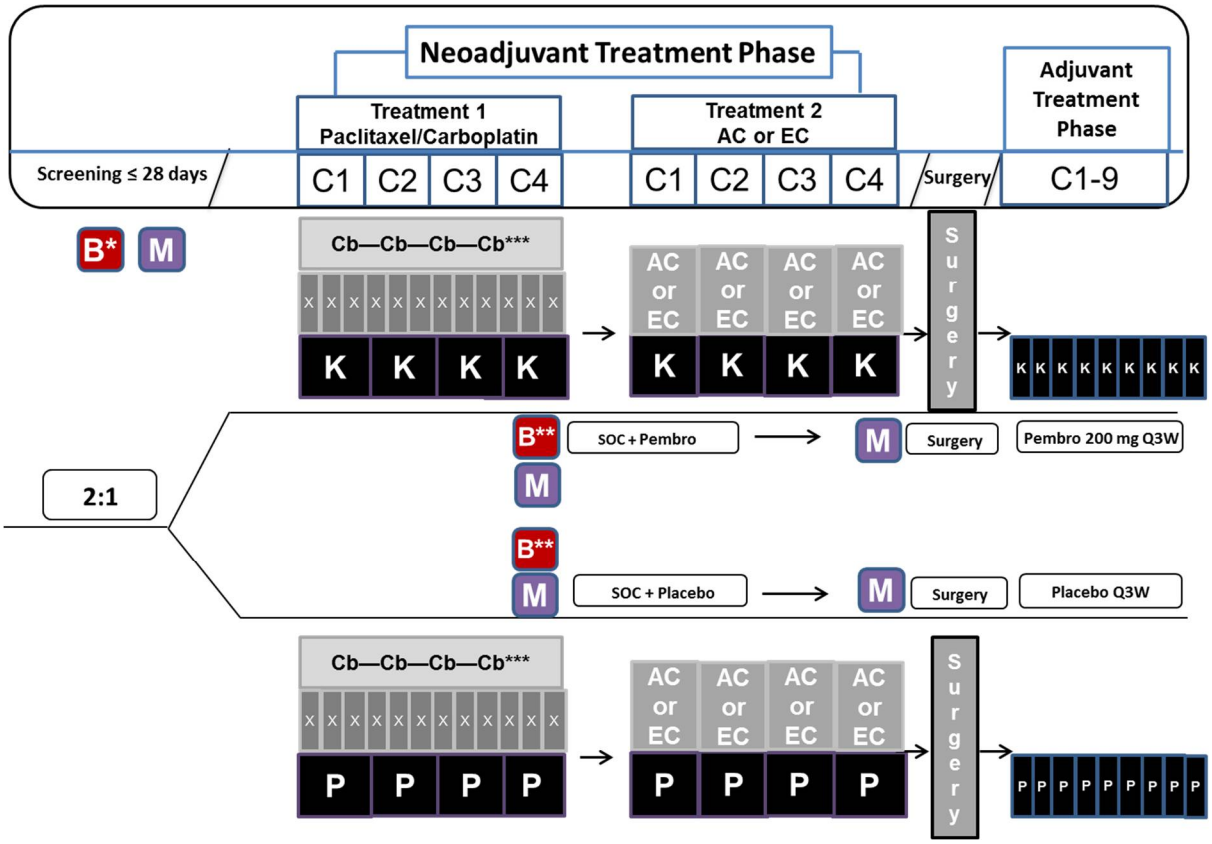


Figure 1 Trial Design Overview

1. No crossover from placebo to pembrolizumab will be permitted.
2. If post-operative radiation therapy is indicated, adjuvant pembrolizumab or placebo may be started either concurrently with radiation therapy or 2 weeks post-radiation therapy.



C = cycle; each cycle is 3 weeks (21 days)
K = pembrolizumab; dosing Q3W on Day 1 of Cycles 1-4 in both the Treatment 1 and Treatment 2 parts of the Neoadjuvant Treatment Phase; and Cycles 1-9 in the Adjuvant Treatment Phase
P = placebo: dosing Q3W on Day 1 of Cycles 1-4 in both the Treatment 1 and Treatment 2 parts of the Neoadjuvant Treatment Phase; and Cycles 1-9 in the Adjuvant Treatment Phase
Cb = carboplatin AUC 5, Q3W on Day 1 of Cycles 1-4 or AUC 1.5, weekly, on Days 1, 8, 15 of Cycles 1-4 of the paclitaxel/carboplatin regimen (Treatment 1)
X = paclitaxel; dosing weekly on Days 1, 8, 15 of Cycles 1-4 of the paclitaxel/carboplatin regimen (Treatment 1)
AC = doxorubicin + cyclophosphamide; dosing Q3W on Day 1 of Cycles 1-4 of the AC or EC regimen (Treatment 2)
EC = epirubicin + cyclophosphamide; dosing Q3W on Day 1 of Cycles 1-4 of the AC or EC regimen (Treatment 2)
B = Biopsy
M = MRI; Breast MRIs will be performed in a subset of subjects with locally advanced TNBC who choose to participate.
* Subjects with locally advanced TNBC are required to have a core needle biopsy consisting of at least 2 separate tumor cores, utilizing multiple passes, at screening.
** An optional biopsy may be performed between Days 15-21 of Cycle 4 (Treatment 1). Additionally, an optional biopsy may be performed at the time of recurrence, if applicable, only on subjects who agree to participate.
*** Carboplatin AUC 5, Q3W, or AUC 1.5, weekly, during the paclitaxel/carboplatin regimen (Treatment 1) will be based on the Investigator's preference.

Figure 2 Trial Design Showing Timing of Dosing and Biopsies

3.0 OBJECTIVE(S) & HYPOTHESIS(ES)

In male and female subjects at least 18 years of age with newly diagnosed, locally advanced, centrally confirmed TNBC:

3.1 Primary Objective(s) & Hypothesis(es)

1) **Objective:** To evaluate the rate of pCR using the definition of ypT0/Tis ypN0 (ie, no invasive residual in breast or nodes; noninvasive breast residuals allowed) as assessed by the local pathologist at the time of definitive surgery in subjects with locally advanced TNBC.

   Hypothesis: Pembrolizumab is superior to placebo, in combination with chemotherapy, as measured by the rate of pCR using the definition of ypT0/Tis ypN0 as assessed by the local pathologist at the time of definitive surgery in subjects with locally advanced TNBC.

2) **Objective**: To evaluate the event-free survival (EFS) as assessed by investigator in subjects with locally advanced TNBC.

   Hypothesis: Pembrolizumab is superior to placebo, as measured by EFS as assessed by the investigator, in subjects with locally advanced TNBC.

The study is considered to have met its primary objective if pembrolizumab is superior to placebo in either pCR or EFS in subjects with locally advanced TNBC at either an interim analysis (IA) or the final analysis (FA).

3.2 Secondary Objective(s) & Hypothesis(es)

1) **Objective**: To evaluate overall survival (OS) in subjects with locally advanced TNBC tumors.

   Hypothesis: Pembrolizumab is superior to placebo, as measured by OS in subjects with locally advanced TNBC.

2) **Objective**: To evaluate the rate of pCR using an alternative definition, ypT0 ypN0 (ie, no invasive or noninvasive residual in breast or nodes) as assessed by the local pathologist at the time of definitive surgery in subjects with locally advanced TNBC and in individuals with programmed death ligand 1 (PD-L1) positive (+) tumors (combined positive score [CPS] ≥1).

3) **Objective:** To evaluate the rate of pCR using the definition of (ypT0/Tis ypN0) (ie, no invasive residual in breast or nodes; noninvasive breast residuals allowed) as assessed by the local pathologist at the time of definitive surgery in individuals with PD-L1 (+) tumors (CPS ≥1).

4) **Objective:** To evaluate the EFS as assessed by investigator in individuals with PD-L1 (+) tumors (CPS ≥1).

5) **Objective:** To evaluate the rate of pCR using an alternative definition, ypT0/Tis (ie, absence of invasive cancer in the breast irrespective of ductal carcinoma in situ or nodal involvement) as assessed by the local pathologist at the time of definitive surgery in subjects with locally advanced TNBC and in individuals with PD-L1 (+) tumors (CPS ≥1).
6) **Objective:** To evaluate overall survival (OS) in individuals with PD-L1 (+) tumors (CPS ≥1).
7) **Objective:** To determine the safety and tolerability of pembrolizumab in combination with neoadjuvant chemotherapy and pembrolizumab as adjuvant therapy in locally advanced TNBC subjects, within and across the neoadjuvant and adjuvant phases.
8) **Objective:** To evaluate health-related quality-of-life (QoL) assessments in TNBC subjects and in subjects with PD-L1 (+) tumors (CPS ≥1) using the European Organisation for Research and Treatment of Cancer (EORTC) QoL Core 30 (QLQ-C30) and EORTC Breast Cancer–Specific QoL Questionnaire (QLQ-BR23) within and across the neoadjuvant and adjuvant treatment phases.

3.3 Exploratory Objectives

1) **Objective**: To evaluate the association between pCR and the objective response rate (ORR) using RECIST 1.1 as assessed by central radiology review after Treatment 1 (Neoadjuvant Phase) or at the time of surgery.
2) **Objective:** To evaluate distant recurrence-free survival (DRFS) post-surgery as assessed by investigator in subjects with locally advanced TNBC and in individuals with PD-L1 (+) tumors (CPS ≥1).
3) **Objective:** To characterize health utilities in subjects with locally advanced TNBC and in subjects with PD-L1 (+) tumors (CPS ≥1) using the European Quality of Life Five-dimension Five-level scale Questionnaire (EuroQol-5 EQ-5D-5L™).
4) **Objective**: To evaluate the rate of Breast Conservation Surgery (BCS) at the time of definitive surgery in subjects with locally advanced TNBC and in individuals with PD-L1 (+) tumors (CPS ≥1).
5) **Objective:** To identify molecular (genomic, metabolic and/or proteomic) biomarkers that may be indicative of clinical response/resistance, safety, pharmacodynamic activity, and/or the mechanism of action of pembrolizumab and other treatments.
6) **Objective:** To evaluate the association between pCR and the ORR using MRI Functional Tumor Volume (FTV) as assessed by central radiology review after Treatment 1 (neoadjuvant phase) and at the time of surgery.
7) **Objective:** To evaluate Residual Cancer Burden (RCB) as assessed by the local pathologist at the time of definitive surgery in subjects with locally advanced TNBC.
8) **Objective:** To correlate extent of tumor-infiltrating lymphocytes (TILs) with pCR rate and EFS.

4.0 BACKGROUND & RATIONALE

4.1 Background

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

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 [3]. Triple-negative breast cancer, or TNBC, which is phenotypically defined by lack of estrogen receptor (ER) and progesterone receptor 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 [4].

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 OS; TNBC is also associated with a higher risk of disease recurrence and higher recurrence in viscera within 5 years of diagnosis [4] [5].

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 [6]. 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 TNBCs [7]. Another finding from molecular characterization is that the majority of Breast Cancer 1 (BRCA)1 germline mutation carriers, when they develop breast cancer, will develop basal-like subtype of TNBC; and the prevalence of BRCA1 in TNBC is around 10-20% [8] [9].

4.1.1.2 Current and Emerging Neoadjuvant Treatments for TNBC

Neoadjuvant chemotherapy—systemic therapy given prior to definite surgery—with an anthracycline/taxane-based regimen has been considered an important and standard part of treatment strategy for patients with locally advanced TNBC for both tumor control and improving the curability rate [10] [11]. 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, as a group, patients with TNBC had a poorer prognosis with significantly higher disease recurrence rate and lower survival rate. The poor long-term outcome in TNBC was found to be driven by those who did not achieve pCR after neoadjuvant chemotherapy.

Patients who achieved pCR demonstrated sustained clinical benefit regardless of breast cancer subtypes [12] [13]. Recently, 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 EFS and OS. Furthermore, this association was found to be strongest in patients with TNBC [14].

Because of the poorer survival for patients that did not achieve pCR after neoadjuvant chemotherapy, there is great interest in examining whether additional therapy after surgery will improve the RFS for this group of patients. The CREATE-X study demonstrated significant improvement in both EFS and OS for patients with HER2-negative breast cancer, positive lymph node and non-pCR, receiving capecitabine compared to controls [15]. In previous studies, the GeparTrio and GeparQuattro, the rate of pCR did not improve with the addition of capecitabine [16] [17]. However, while previous adjuvant studies such as the GEICAM/2003-10, FINXX and/or CBCSG10 did not show a statistically significant improvement in RFS and/or OS with the addition of capecitabine in all patients, there may be a benefit in subsets of patients with TNBC [18], albeit with increased toxicities [19]. Thus, confirmation studies are needed. The current standard of care continues to be observation after surgery for patients who do not obtain pCR with neoadjuvant chemotherapy [11].

The findings that the pCR is correlated with survival have led to increased efforts in identifying new drugs and drug combinations that can deliver higher pCR in TNBC.

Addition of a taxane to anthracycline-base regimen as adjuvant chemotherapy has been shown to improve both DFS and OS in locally-advanced breast cancer [20]. Currently, pCR rate for standard regimen with paclitaxel followed by an anthracycline and cyclophosphamide is about 30% [21]. Because patients without pCR have significantly worse outcomes, efforts are underway to find novel combinations to improve the pCR.

Platinum compounds have been shown significant activity in BRCA-mutated breast cancer, and since BRCA-mutated and sporadic TNBC have similar clinical and biologic profiles, they are being heavily studied in this subtype [22].

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 (AUC 1.5-2) to the triple combination of weekly paclitaxel (80 mg/m^2) plus weekly non-pegylated liposomal doxorubicin (20 mg/m^2) plus Q3W bevacizumab (15 mg/kg) for a total of 6 cycles, showed increased pCR (defined as ypT0 ypN0) from 36.9% to 53.2% (P = 0.005) [1]. However, compared with 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 AUC 2 to AUC 1.5.

In another randomized Phase III study (CALGB 40603) that evaluated the addition of carboplatin or/and bevacizumab to the standard neoadjuvant treatment for TNBC (paclitaxel 80 mg/m^2 weekly for 12 weeks followed by doxorubicin plus cyclophosphamide every 2

weeks [Q2W] for 4 cycles), addition of carboplatin Q3W at AUC 6 to weekly paclitaxel vs. weekly paclitaxel alone, there was 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% [2]. However, similar to the findings in GeparSixto [1], addition of Q3W carboplatin at AUC 6 showed significantly increased Grade 3/4 neutropenia (56% vs. 22%), and Grade 3/4 thrombocytopenia (20% vs. 4%).

Finally, 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% confidence interval [CI], 1.25-1.68, P<0.0001) of not having a pCR in those who patients who received no platinum treatment [23].

While paclitaxel remains the standard of care as part of the anthracycline-based cyclophosphamide regimen, investigators are studying whether other taxanes can be substituted to improve efficacy and/or toxicities.

In a randomized Phase III study (GeparSepto) comparing weekly nab-paclitaxel 150 mg/m^2/ 125 mg/m^2 with weekly paclitaxel 80 mg/m^2 for 12 weeks with both arms followed by epirubicin 90 mg/m^2 plus cyclophosphamide 600 mg/m2 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 [24]. However, the dose was subsequently reduced to 125 mg/m^2 from 150 mg/2 weekly due to toxicity with 400/1200 enrolled subjects receiving the 150 mg/m^2 dose. The combined data showed that the addition of nab-paclitaxel significantly increases the rate of peripheral sensory neuropathy compared to paclitaxel 80 mg/m2 (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).

While the results of the GeparSepto showed promising result, the ETNA study, which compared nab-paclitaxel 125 mg/m2 Day 1, 8, 15 of 4 weeks cycle for 4 cycles to paclitaxel 90 mg/m^2 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. 35.5%) [25]. Furthermore, the nab-paclitaxel-containing regimen has a higher rate of Grade ≥ 3 neutropenia (30.6% vs. 19.7%) and peripheral neuropathy (4.5% vs. 1.8%). Thus, currently, given the higher rate of toxicities and no clear data supporting higher efficacy with nab-paclitaxel, solvent-based paclitaxel remains the standard of care.

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 [26]. 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 [27], [28]. The ability of human cancer to evade the destruction of the immune system has recently been recognized as an emerging hallmark of cancer [29].

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 [30]. 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 [31] [32] [33].

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 [30] [33] [34] [35]. Immune checkpoint inhibiting agents that have been approved by the US Food and Drug Administration (FDA) include ipilimumab, a full human anti-CTLA-4 monoclonal antibody (mAb), pembrolizumab (MK-3475), a humanized mAb targeting PD-1, and nivolumab, a full human mAb targeting PD-1 (see details in Yervoy® US label, Keytruda® US Label, and 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 programmed death – ligand 2 (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 [30], [34], [36]. 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 [30] [33].

The PD-1 receptor-ligand interaction is a major pathway hijacked by tumors to suppress immune control [34]. The normal function of PD-1, expressed on the cell surface of activated T cells under healthy conditions, is to down-modulate unwanted or excessive immune responses, including autoimmune reactions. PD-1 (encoded by the gene Pdcd1) is an immunoglobulin (IgG) superfamily member related to CD28 and cytotoxic CTLA-4, which has been shown to negatively regulate antigen receptor signaling upon engagement of its ligands (PD-L1 and/or PD-L2). The structures of murine PD-1 alone [37], and in complex with its ligands, were first resolved [38] [39], and more recently the nuclear magnetic resonance–based (NMR-based) structure of the human PD-1 extracellular region and analyses of its interactions with its ligands were also reported [40]. PD-1 and family members are type I transmembrane glycoproteins containing an IgG Variable-type (V-type)

domain responsible for ligand binding and a cytoplasmic tail, which is responsible for the binding of signaling molecules. The cytoplasmic tail of PD-1 contains 2 tyrosine-based signaling motifs, an immunoreceptor tyrosine-based inhibition motif (ITIM) and an immunoreceptor tyrosine-based switch motif (ITSM). Following T cell stimulation, PD-1 recruits the tyrosine phosphatases Src homology phosphatase (SHP)-1 and SHP-2 to the ITSM motif within its cytoplasmic tail, leading to the dephosphorylation of effector molecules, such as CD3 zeta (CD3ζ), protein kinase C-theta (PKCθ), and zeta-chain-associated protein kinase 70 kDa (ZAP70), which are involved in the CD3 T cell signaling cascade [41]. The mechanism by which PD-1 down-modulates T cell responses is similar to, but distinct from, that of CTLA-4 [42]. PD-1 was shown to be expressed on activated lymphocytes, including peripheral CD4+ and CD8+ T cells, B cells, T regs and natural killer cells (NKCs) [43]. Expression has also been shown during thymic development on CD4-CD8–double negative T cells [44] as well as subsets of macrophages [45] and dendritic cells [46]. The ligands for PD-1 (PD-L1 and PD-L2) are constitutively expressed or can be induced in a variety of cell types [47]. PD-L1 is expressed at low levels on various nonhematopoietic tissues, most notably on vascular endothelium, whereas PD-L2 protein is only detectably expressed on antigen-presenting cells found in lymphoid tissue or chronic inflammatory environments [47]. Both ligands are type I transmembrane receptors containing both IgV- and IgC-like domains in the extracellular region and short cytoplasmic regions with no known signaling motifs. Binding of either PD-1 ligand to PD-1 inhibits T cell activation triggered through the T cell receptor. PD-L2 is thought to control immune T cell activation in lymphoid organs, whereas PD-L1 serves to dampen unwarranted T cell function in peripheral tissues. Although healthy organs express little (if any) PD-L1, a variety of cancers were demonstrated to express abundant levels of this T cell inhibitor [48] [49], which, via its interaction with the PD-1 receptor on tumor-specific T cells, plays a critical role in immune evasion by tumors [50]. As a consequence, the PD-1/PD-L1 pathway is an attractive target for therapeutic intervention in cancer [51].

4.1.1.4 Targeting PD-1 Immune Checkpoints for TNBC

Several studies have demonstrated that the presence of tumor-infiltrating T-lymphocytes (TILs) correlated with better prognosis in TNBC, independent of systemic therapy [51] [52]. 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 [35]. These findings suggest an active role of acquired immunity in concurring TNBC [53].

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 hormone-receptor-negative, high grade and proliferative tumors [54]. 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 [55]. Recently, it is reported that PD-L1 messenger ribonucleic acid (mRNA) is expressed in nearly 60% of breast tumors, independently of hormone receptor status, and is positively correlated with PD-L1 protein expression and increased TILs [56]. Another study mining The Cancer Genome Atlas ribonucleic acid (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 [57]. 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, clinical pharmacology, and clinical efficacy and safety studies can be found in pembrolizumab clinical IB, the US label, and the Summary of Product Characteristics (SmPC).

Pembrolizumab has demonstrated robust, substantial, and clinically-meaningful benefit in the treatment of a number of solid tumors, based on RECIST 1.1 and immune-related RECIST (irRECIST) recommendations. 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.

4.1.2.1 Summary of Clinical Data Supporting Pembrolizumab Use for Treatment of Metastatic TNBC

4.1.2.1.1 KEYNOTE-012 (KN012)

In Study KN012, a cohort of 32 female patients with metastatic TNBC, with PD-L1 positivity (defined as PD-L1 expression in ≥1% tumor cells or in stroma, using a prototype assay and the 22C3 antibody) was enrolled and received pembrolizumab 10 mg/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, 5 (15.6%) patients experienced at least one drug-related SAE; each of 4 patients experienced one of the following: Grade 3 anemia, headache, aseptic meningitis or pyrexia, and a fifth patient experienced Grade 5 disseminated intravascular coagulation (DIC) with thrombocytopenia and decreased blood fibrinogen. Of the 27 patients with centrally confirmed measurable disease, 1 (3.7%) patient 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), based on RECIST 1.1 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 3 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.

4.1.3 Additional Ongoing Clinical Studies

Two clinical studies are currently investigating the efficacy of single agent pembrolizumab as later line of treatment for mTNBC, namely KEYNOTE-086 (KN086), KEYNOTE-119 (KN119), and 2 clinical studies are investigating the efficacy of combination of pembrolizumab with chemotherapy (KEYNOTE-355 [KN355] and KEYNOTE-173 [KN173]).

- KN086 (NCT02447003): A Phase II Clinical Trial of Pembrolizumab (MK-3475) as Monotherapy for Metastatic Triple Negative Breast Cancer (mTNBC) – (KEYNOTE-086)
- KN119 (NCT02555657): A Randomized, Open-Label, Phase III Clinical Trial of Single Agent Pembrolizumab vs Single Agent Chemotherapy per Physician's Choice for Metastatic Triple Negative Breast Cancer (mTNBC) – (KEYNOTE-119)
- KN173 (NCT02622074): 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)
- KN355 (NCT02819518): A Randomized, Double-Blind, Phase III Study of Pembrolizumab (MK-3475) plus Chemotherapy vs Placebo plus Chemotherapy for Previously Untreated Locally Recurrent Inoperable or Metastatic Triple Negative Breast Cancer – (KEYNOTE-355)

Ongoing clinical studies are also being conducted in melanoma, NSCLC, head and neck cancer, breast cancer, gastric cancer, colorectal cancer, a number of other advanced solid tumor indications, and hematologic malignancies. For further details, please refer to the IB.

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 EFS and OS as shown via large meta-analysis [13]. 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/Modification

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 is 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, head and neck, and NCSLC. Preliminary data have 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 and/or adjuvant setting is warranted.

2. Carboplatin in combination with weekly paclitaxel at 80 mg/m^2 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 2 (the Phase II GeparSixto trial), [1] or carboplatin at AUC 6 Q3W (the Phase III CALGB 40603 trial), [2]. Due to toxicity, in the GeparSixto trial, the dose of carboplatin was reduced to AUC 1.5. 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, $p<0.0001$) [23] compared to those who have received carboplatin. This data provide a good rationale for carboplatin to be included as part of the neoadjuvant combination regimen.

It is worth noting that in the CALGB 40603 study the carboplatin AUC 6 Q3W plus weekly paclitaxel 80 mg/m2 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. Therefore, in this study, paclitaxel 80 mg/m2 and carboplatin AUC 5 Q3W or AUC 1.5 QW 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.

3. 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 (eg, 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 for the Use of Placebo

Normal saline or dextrose infusion Q3W will be used as placebo for pembrolizumab. The use of saline or dextrose placebo in combination with chemotherapy will ensure the objectivity of the investigator. The use of a placebo will test the hypotheses that (1) pembrolizumab and chemotherapy is superior to the combination of placebo and chemotherapy in subjects with locally advanced TNBC, as measured by the rate of pCR based on biopsy results at the time of definitive surgery; and that (2) pembrolizumab and chemotherapy is superior to the combination of placebo and chemotherapy in subjects with locally advanced TNBC, as measured by EFS based on RECIST 1.1.

4.2.2.3 Rationale for Concurrent Post-Operative Radiation and Pembrolizumab

Radiation therapy exerts its anti-tumor effect primarily through single and double-strand breaks resulting in apoptosis, which often leads to tumor necrosis and cessation of cell division. Additionally, radiation of tumors can lead to an antigen-specific tumor response [58]. In locally advanced breast cancer, candidates for post-operative radiation are generally patients who have axillary node-negative disease and underwent BCS, have large tumors, or have significant lymph node involvement.

Preclinical studies in murine models of breast cancer provide strong evidence that addition of radiation to a checkpoint inhibitor leads to a reduction in tumor growth and improvement in survival compared to either treatment modality alone [59]. Trials are currently underway testing the efficacy and safety of combining radiation with pembrolizumab in many tumor types. Preliminary data from a small study in 20 subjects with locally advanced squamous cell carcinoma of the head and neck, demonstrated that the addition of pembrolizumab to cisplatin and radiation did not affect dosing of chemotherapy or radiation [60]. These data suggest that addition of pembrolizumab to radiation is tolerable with no additional risk beyond what was seen previously [60].

4.2.2.4 Starting Dose for This Trial

The optimal duration of pembrolizumab has not been tested. At this time, the recommended duration for treatment is 12 months. Information on the rationale for selecting 200 mg fixed dose Q3W is summarized below.

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

- Clinical data from 8 randomized studies demonstrating flat dose- and exposure-efficacy relationships from 2 mg/kg Q3W to 10 mg/kg every 2 weeks (Q2W)
- Clinical data showing meaningful improvement in benefit-risk including OS at 200 mg Q3W across multiple indications, and

- Pharmacology data showing full target saturation in both systemic circulation (inferred from pharmacokinetic [PK] data) and tumor (inferred from physiologically based pharmacokinetic [PBPK] analysis) at 200 mg Q3W

Among the 8 randomized dose-comparison studies, a total of 2262 subjects were enrolled with melanoma and non-small cell lung cancer, covering different disease settings (treatment naïve, previously treated, PD-L1 enriched and all-comers) and different treatment settings (monotherapy and in combination with chemotherapy). Five studies compared 2 mg/kg Q3W vs. 10 mg/kg Q3W (KN001 B2, KN001 D, KN002, KN010 and KN021), and 3 studies compared 10 mg/kg Q3W vs. 10 mg/kg Q2W (KN001 B3, KN001 F2 and KN006). All of these studies demonstrated flat dose- and exposure-response relationships across the doses studied representing an approximate 5- to 7.5-fold difference in exposure. The 2 mg/kg (or 200 mg fixed-dose) Q3W provided similar responses to the highest doses studied. Subsequently, flat dose-/exposure-response relationships were also observed in other tumor types including head and neck cancer, bladder cancer, gastric cancer and classical Hodgkin Lymphoma, confirming 200 mg Q3W as the appropriate dose independent of the tumor type. These findings are consistent with the mechanism of action of pembrolizumab, which acts by interaction with immune cells, and not via direct binding to cancer cells.

Additionally, pharmacology data clearly show target saturation at 200 mg Q3W. First, PK data in KN001 evaluating target-mediated drug disposition (TMDD) conclusively demonstrated saturation of PD-1 in systemic circulation at doses much lower than 200 mg Q3W. Secondly, a PBPK analysis was conducted to predict tumor PD-1 saturation over a wide range of tumor penetration and PD-1 expression. This evaluation concluded that pembrolizumab at 200 mg Q3W achieves full PD-1 saturation in both blood and tumor.

Finally, population PK analysis of pembrolizumab, which characterized the influence of body weight and other subject covariates on exposure, has shown that the fixed-dosing provides similar control of PK variability as weight based dosing, with considerable overlap in the distribution of exposures from the 200 mg Q3W fixed dose and 2 mg/kg Q3W dose. Supported by these PK characteristics, and given that fixed-dose has advantages of reduced dosing complexity and reduced potential of dosing errors, the 200 mg Q3W fixed-dose was selected for evaluation across all pembrolizumab protocols.

4.2.2.5 Maximum Dose/Exposure for This Trial

The maximum and the target dose regimen for Arm 1 of the study will be KXCb/KA(E)C followed by K post surgery. The maximum and the target dose regimen for Arm 2 of the study will be PXCb/PA(E)C followed by P post surgery. The rationale can be found in Section 4.2.2.3. The maximum dose for Pembrolizumab will be 200 mg. For chemotherapy treatment, the maximum dose for each chemotherapy drug will be as follows: carboplatin: AUC 5 or AUC 1.5; paclitaxel: 80 mg/m^2; doxorubicin: 60 mg/m^2 or epirubicin: 90 mg/m^2; cyclophosphamide: 600 mg/m^2.

Two randomized trials have tested carboplatin in combination with weekly paclitaxel 80 mg/m^2 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 [2]; the Phase II GeparSixto study combined weekly carboplatin at AUC1.5 or 2 with weekly paclitaxel [1]. The response rate for weekly carboplatin (1.5-2AUC), tested in the GeparSixto trial, 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 [61].

4.2.2.6 Rationale for Dose Interval and Trial Design

The standard neoadjuvant treatment is typically 4 cycles of taxane (12 × weekly dosing) followed by 4 cycles of anthracycline/cyclophosphamide combination (eg, doxorubicin 60 mg/m^2 or epirubicin 90 mg/m^2 Q3W + cyclophosphamide 600 mg/m^2 Q3W). This trial will test the new combination using the same dosing interval and schedule.

4.2.2.7 Rationale for Selection of Stratification Factors

Factors that affect clinical outcome of patients with newly diagnosed breast cancer include age, performance status, lymph node involvement and potentially tumor size. The likelihood of achieving T0/Tis is higher with smaller tumor regardless of lymph node status [62], [63]. In a pooled analysis of TNBC neoadjuvant breast cancer trials, decreased pCR rates were observed for larger tumor (OR 0.78; 95% CI, 0.64 to 0.95; P =.013) [13]. Similar observations were seen in German breast cancer trials, where smaller tumors (T1 or T2) are also more likely to obtain a pCR [21]. Finally, tumor size is prognostic of distance-recurrence free survival in a multivariate analysis of EORTC 10994/BIG 1-00 Phase III trial (hazard ratio [HR] = 3.62 (95% CI, 1.66-7.89) and HR = 2.80 (95% CI, 0.62-12.64) for T3 and T4 vs T1/T2, respectively. The p-value of overall effect of Tumor Size =0.0048) [64]. Based on these observations, stratification for T1/T2 vs. T3/T4 will be applied.

Similarly, subjects with lymph node involvement (N+) at the time of initial breast cancer diagnosis generally have more aggressive, and possibly of different biology, disease than subjects without lymph node involvement (N0). In a recent prospective Neoadjuvant Breast Symphony Trial (NBRST) study, pCR is more like to be achieved in N0 patients (HR=2.09, multivariate P< 0.001) [65]. Furthermore, in a pooled analysis, the JBCRG (Japanese Breast Cancer Research Group) showed significantly poorer outcome for patients with N+ (HR of 2.29 and 3.05 for DFS and OS, respectively) [66]. Because of the strong association between lymph node status and outcome, stratification for N0 vs N+ at initial diagnosis will be applied.

Weekly carboplatin (AUC 1.5-2) was tested in the GeparSixto trial, a randomized Phase II study with the addition of weekly paclitaxel (80 mg/m^2), weekly non-pegylated liposomal doxorubicin (20 mg/m^2) and Q3W bevacizumab (15 mg/kg). The response rate was 53% within the range of Q3W carboplatin, suggesting the equivalency between weekly and every 3 week dosing of carboplatin in the CALGB 40603 [1] [2]. However, some data suggested that weekly dosing may be more tolerable [61]. As such, potential difference in tolerability may affect the ability of patients to complete prescribed regimens and ultimately efficacy outcome.

4.2.3 Rationale for Endpoints

4.2.3.1 Efficacy Endpoints

pCR and EFS are proposed as dual-primary endpoints for KN522 following the FDA guidance on "Pathological Complete Response in Neoadjuvant Treatment of High-Risk Early-Stage Breast Cancer". Patients who achieved pCR have demonstrated sustained clinical benefit regardless of breast cancer subtypes. Recently, 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 [12] [13].

Following the single trial model referred to in the above FDA guidance, patients entering the study that supported accelerated approval will be followed for survival endpoints such as EFS or OS. As such, EFS is proposed as a dual-primary efficacy endpoint with pCR.

4.2.3.2 Safety Endpoints

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 ECI are important endpoints for safety and tolerability evaluations.

4.2.3.3 Planned Exploratory Biomarker Research

Cancer immunotherapies represent an important and novel class of anti-tumor agents. However, the mechanism of action of these exciting new therapies is not completely understood and much remains to be learned regarding how best to leverage these new drugs in treating patients. Thus, to aid future patients, it is important to investigate the determinants of response or resistance to cancer immunotherapy as well as determinants of adverse events in the course of our clinical trials. These efforts will identify novel predictive/pharmacodynamic biomarkers and generate information that will better guide single-agent and combination therapy with immuno-oncology drugs. To identify novel biomarkers, we will collect biospecimens (blood components, tumor material, etc.) to support analyses of cellular components (eg, protein, deoxyribonucleic acid [DNA], RNA, metabolites) and other circulating molecules. Investigations may include but are not limited to:

Germline (blood) Genetic Analyses (eg, SNP Analyses, Whole Exome Sequencing, Whole Genome Sequencing)

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. Furthermore, it is important to evaluate germline DNA variation across the genome in order to interpret tumor-specific DNA mutations. Finally, microsatellite instability (MSI) may be evaluated as this is an important biomarker for some cancers (ie, colorectal cancer).

Genetic (DNA) Analyses from Tumor

The application of new technologies, such as next generation sequencing, has provided scientists the opportunity to identify tumor-specific DNA changes (ie, mutations, methylation status, microsatellite instability). Key molecular changes of interest to immune-oncology drug development include the mutational burden of tumors and the clonality of T-cells in the tumor microenvironment. Increased mutational burden (sometimes referred to as a "hyper-mutated" state) may generate neo-antigen presentation in the tumor microenvironment. To conduct this type of research, it is important to identify tumor-specific mutations that occur across all genes in the tumor genome. Thus, genome-wide approaches may be used for this effort. Note that in order to understand tumor-specific mutations; it is necessary to compare the tumor genome with the germline genome. Microsatellite instability (MSI) may also be evaluated as this is an important biomarker for some cancers (ie, colorectal cancer).

Tumor and Blood RNA Analyses

Both genome-wide and targeted messenger RNA (mRNA) expression profiling and sequencing in tumor tissue and in blood may be performed to define gene signatures that correlate to clinical response to treatment with pembrolizumab or other immunotherapies. Pembrolizumab induces a response in tumors that likely reflects an inflamed/ immune phenotype. Specific immune-related gene sets (such as those capturing interferon-gamma transcriptional pathways) may be evaluated and new signatures may be identified. Individual genes related to the immune system may also be evaluated (eg, IL-10). MicroRNA profiling may also be pursued.

Proteomics and Immunohistochemistry using Blood or Tumor

Tumor and blood samples from this study may undergo proteomic analyses (eg, PD-L1 immunohistochemistry [IHC]). PD-L1 protein level in tumor sections, assessed by IHC, has been shown to correlate with response to pembrolizumab in patients with NSCLC, and an IVD device has been developed for use with pembrolizumab in NSCLC. Preliminary data indicate that this association may also be true in additional cancer types (ie, TNBC, H&N, and gastric). Additional tumor or blood-derived proteins may also correlate with response to pembrolizumab. Therefore, tumor tissue may be subjected to proteomic analyses using a variety of platforms that could include but are not limited to immunoassays, liquid chromatography/mass spectrometry. This approach could identify novel protein biomarkers that could aid in patient selection for pembrolizumab (MK-3475) therapy.

Other Blood Derived Biomarkers

In addition to expression on the tumor tissue, PD-L1 and other tumor derived proteins can be shed from tumor and released into the blood. Assays such as enzyme-linked immunoassay measure such proteins in serum. Correlation of expression with response to pembrolizumab therapy may identify new approaches for predictive biomarkers in blood, representing a major advance from today's reliance on assessing tumor biomarkers. This research would serve to develop such assays for future clinical use.

Translational Research

The tumor microenvironments before treatment and after the combinations will be characterized, and this may include the presence and changes of TILs, immune-related mRNA expression signatures, and PD-L1 expression. In addition, tumor genetic profiling such as genetic testing for mutational burden based on tumor samples collected at Screening will be performed. Additional translational research may include T cell clonality, neo-antigen expression, presence and changes in circulating tumor markers such as circulating tumor DNA (ctDNA), and serum microRNA (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.

4.2.3.4 Future Biomedical Research

The Sponsor will conduct Future Biomedical Research on specimens consented 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, depending on which specimens are consented for future biomedical research.

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/retaining 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 are presented in Section 12.2 – Collection and Management of Specimens for Future Biomedical Research.

4.3 Benefit/Risk

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

Additional potential benefits are addressed in Section 4.1.2 – Summary of Pembrolizumab Clinical Activities, which details responses to pembrolizumab in the TNBC cohort of the multi-cohort Phase Ib study, KEYNOTE-012, which enrolled subjects with PD-L1 (+) (in ≥1% of tumor cells or in stroma, by IHC) tumors. A total of 32 female subjects with a median age of 50.5 years (range: 29 to 72 years) and PD-L1 (+) mTNBC were enrolled in the study. Most of these subjects had received and progressed on multiple lines of therapy for advanced disease. The median number of prior lines of systemic therapy for metastatic disease was 2, with 46.9% of subjects having received ≥3 lines. Of the 27 subjects with centrally confirmed measurable disease, one subject (3.7%) had a CR, 4 subjects (14.8%) had a confirmed PR, 25.9% had SD, and 44.4% had PD based on RECIST 1.1 as assessed by the central imaging vendor. As of 23 Mar 2015, the median DOR had not been reached (range: 15.0 to 47.3+ weeks), and 3 subjects (1 CR; 2 PR) were still on treatment after at least

15 months. Similar to pembrolizumab studies in other tumor types, the most common AEs included fatigue (17.9%), decreased appetite (12.8%), hypothyroidism (12.8%), and arthralgia (10.3%). Five subjects (15.6%) experienced at least one drug-related SAE; each of 4 subjects experienced one of the following: Grade 3 anemia, headache, aseptic meningitis or pyrexia, and a fifth subject experienced Grade 5 DIC with thrombocytopenia and decreased blood fibrinogen in the setting of rapidly progressive disease.

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

5.0 METHODOLOGY

5.1 Entry Criteria

5.1.1 Diagnosis/Condition for Entry into the Trial

Male and female subjects at least 18 years of age with newly diagnosed, locally advanced, centrally confirmed TNBC, as defined by the most recent American Society of Clinical Oncology (ASCO)/College of American Pathologists (CAP) guidelines, 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 willing and able to provide written informed consent for the trial. The subject may also provide consent for Future Biomedical Research. However, the subject may participate in the main trial without participating in Future Biomedical Research.
2. Be a male or female subject ≥18 years of age on day of signing informed consent.
3. Have centrally confirmed TNBC, as defined by the most recent ASCO/CAP guidelines.
4. Have previously untreated locally advanced non-metastatic (M0) TNBC defined as the following combined primary tumor (T) and regional lymph node (N) staging per current AJCC staging criteria for breast cancer staging criteria as assessed by the investigator based on radiological and/or clinical assessment:
    - T1c, N1-N2
    - T2, N0-N2
    - T3, N0-N2
    - T4a-d, N0-N2

    Note: bilateral tumors (ie, synchronous cancers in both breasts) and/or multi-focal (ie, 2, separate lesions in the same quadrant)/multi-centric (ie, 2 separate lesions in different quadrants) tumors are allowed, as well as inflammatory breast cancer, and the tumor with the most advanced T stage should be used to assess the eligibility. If

the subject has either bilateral or multi-focal/multi-centric disease, TNBC needs to be confirmed for each breast/focus.

5. Provide a core needle biopsy consisting of at least 2 separate tumor cores from the primary tumor at screening to the central laboratory.

   Note: Sponsor agreement is required for FFPE tumor tissues samples or slides that were obtained greater than 30 days prior to the date that the informed consent was signed.

6. Have Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 performed within 10 days of treatment initiation.
7. Demonstrate adequate organ function as defined in Table 1. All screening labs should be performed within 10 days of treatment initiation.

Table 1 Adequate Organ Function Laboratory Values

Organ System	Laboratory Value
Hematological	
Absolute neutrophil count (ANC)	≥1,500 cells/μL without granulocyte colony-stimulating factor (G-CSF) support within 2 weeks prior to the first dose of study treatment
Platelet count	≥100,000/μL without transfusion within 2 weeks prior to the first dose of study treatment
Hemoglobin	≥9 g/dL or ≥5.6 mmol/L without transfusion or EPO dependency
Renal	
Serum creatinine **OR** Calculated creatinine clearance (CrCl) (calculated per institutional standard)	≤1.5 X upper limit of normal (ULN) **OR** ≥50 mL/min
Hepatic	
Total bilirubin	≤1.5 X ULN **OR** Direct bilirubin ≤ULN for subjects with total bilirubin levels >1.5 X ULN
Aspartate aminotransferase [AST (SGOT)] and alanine aminotransferase [ALT (SGPT)]	≤2.5 X ULN
Albumin	≥3.0 g/dL
Lactate dehydrogenase (LDH)	<2.5 X ULN
Coagulation	
International Normalized Ratio (INR) or prothrombin time (PT)	≤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)	≤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

8. Have left ventricular ejection fraction (LVEF) of ≥50% or ≥ institution lower limit of normal (LLN) as assessed by echocardiogram (ECHO) or multigated acquisition (MUGA) scan performed at screening.
9. Males and female subjects of childbearing potential (Section 5.7.2 – Contraception) 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 6 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.
10. (Female subject of childbearing potential) Have a negative urine or serum pregnancy test within 72 hours prior to receiving the first dose of study medication. If the urine test is positive or borderline 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 a history of invasive malignancy ≤5 years prior to signing informed consent except for adequately treated basal cell or squamous cell skin cancer or in situ cervical cancer.
2. Has received prior chemotherapy, targeted therapy, and radiation therapy within the past 12 months.
3. Has received prior therapy with an anti-PD-1, anti-PD-L1, or anti-PD-L2 agent or with an agent directed to another co-inhibitory T-cell receptor (eg, CTLA-4, OX-40, CD137) or has previously participated in MK-3475 clinical trials.
4. Is currently participating in or has participated in an interventional clinical trial with an investigational compound or device within 4 weeks of the first dose of treatment in this current trial.

   Note: subject should be excluded if 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.

   Note: Seasonal influenza vaccines for injection are generally inactivated flu vaccines and are allowed; however intranasal influenza vaccines (eg, FluMist®) are live attenuated vaccines, and are not allowed.
6. Has an active autoimmune disease that has required systemic treatment in past 2 years (ie, with use of disease modifying agents, corticosteroids or immunosuppressive drugs). Replacement therapy (eg, thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency) is not considered a form of systemic treatment.

7. Has a diagnosis of immunodeficiency or is receiving systemic steroid therapy (ie, dosing exceeding 10 mg daily of prednisone or equivalent) 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 (eg, HBsAg reactive) or Hepatitis C (eg, HCV RNA [qualitative] is detected).
10. Has a history of (non-infectious) pneumonitis that required steroids or current pneumonitis.
11. Has an active infection requiring systemic therapy.
12. 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
13. Has a history or current evidence of any condition, therapy, lab abnormality or other circumstance that might expose the subject to risk by participating in the trial, confound the results of the trial, or interfere with the subject's participation for the full duration of the trial.
14. Has known psychiatric or substance abuse disorders that would interfere with cooperation with the requirements of the trial.
15. 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 6 months after the last dose of study medication for subjects who have not.
16. Has a known hypersensitivity to the components of the study therapy or its analogs.
17. Has a known history of active TB (*Bacillus* Tuberculosis)

5.2 Trial Treatment(s)

The treatments to be used in this trial are outlined below in Table 2.

Table 2 Trial Treatment

Drug	Dose/ Potency	Dose Frequency	Route of Administration	Dosing Time of each 3-week cycle	Use
Pembrolizumab (MK-3475)	200 mg	Q3W	IV infusion	Day 1 of Cycles in the Neoadjuvant and Adjuvant Phases of the study for a total of 17 cycles	Experimental
Carboplatin	AUC5 (or AUC1.5)	Q3W (or Weekly)	IV Infusion	Day 1 of Cycles 1-4 of Treatment 1 (or weekly, on Days 1, 8, 15 of Cycles 1-4 of Treatment 1)	Chemotherapy background treatment
Paclitaxel	80 mg/m^2	Weekly	IV Infusion	Days 1, 8, 15 of Cycles 1-4 of Treatment 1	
Doxorubicin (or Epirubicin)	60 mg/m^2 (90 mg/m^2)	Q3W	IV Injection	Day 1 of Cycles 1-4 of Treatment 2	
Cyclophos-phamide	600 mg/m^2	Q3W	IV Infusion	Day 1 of Cycles 1-4 of Treatment 2	
Placebo (normal saline or dextrose)	NA	Q3W	IV infusion	Day 1 of Cycles in the Neoadjuvant and Adjuvant Phases of the study for a total of 17 cycles	Placebo for Pembrolizumab
Filgrastim (G-CSF)	5 µg/kg/day	Per SOC	Subcutaneous injection	Administered 24 hours after chemotherapy and for at least 72 hours after the last dose of chemotherapy.	Prophylaxis for neutropenia
Pegfilgastrim (G-CSF)	100 µg/kg (individualized) or 6 mg (general approach)	Per SOC	Subcutaneous injection	Administered 24 hours as a single dose after chemotherapy	Prophylaxis for neutropenia
Radiation therapy[1]	Variable	Variable	Standard fractionation	Variable	Radiation therapy background treatment

Abbreviations: AUC = area under the concentration-time curve; BID = twice daily; IV = intravenous; Q3W = every 3 weeks; SOC = standard of care.
1. Administered per the local standard of care as applicable (eg, in cases of BCS, large primary tumor, subset of subjects with positive lymph nodes).

Trial Treatment should begin within 3 days of randomization.

All supplies indicated in Table 2 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 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.

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)

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

The dose amount required for paclitaxel, doxorubicin, epirubicin and cyclophosphamide will be calculated based on milligrams per square meter of body surface area (mg/m^2).

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

5.2.1.2 Dose Modification

5.2.1.2.1 Dose Modification and Toxicity Management Guidelines for 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 on 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 3.

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

General instructions:

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

irAEs	Toxicity grade or conditions (NCI CTCAE v4.0)	Action taken to pembrolizumab	irAE management with corticosteroid and/or other therapies	Monitor and follow-up
Pneumonitis	Grade 2	Withhold	• Administer corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper	• Monitor subjects for signs and symptoms of pneumonitis • Evaluate subjects with suspected pneumonitis with radiographic imaging and initiate corticosteroid treatment • Add prophylactic antibiotics for opportunistic infections
	Grade 3 or 4, or recurrent grade 2	Permanently discontinue		
Diarrhea / colitis	Grade 2 or 3	Withhold	• Administer corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper	• Monitor subjects 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). • Subjects with ≥Grade 2 diarrhea suspecting colitis should consider GI consultation and performing endoscopy to rule out colitis. • Subjects 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.
	Grade 4 or recurrent grade 3 colitis	Permanently discontinue		

irAEs	Toxicity grade or conditions (NCI CTCAE v4.0)	Action taken to pembrolizumab	irAE management with corticosteroid and/or other therapies	Monitor and follow-up
AST / ALT elevation or Increased Bilirubin	Grade 2	Withhold	• Administer corticosteroids (initial dose of 0.5-1 mg/kg prednisone or equivalent) followed by taper	• Monitor with liver function tests (consider weekly or more frequently until liver enzyme value returned to baseline or is stable
	Grade 3 or 4	Permanently discontinue	• Administer corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper	
Type 1 diabetes mellitus (T1DM) or Hyperglycemia	Newly onset T1DM or Grade 3 or 4 hyperglycemia associated with evidence of β-cell failure	Withhold	• Initiate insulin replacement therapy for subjects with T1DM • Administer anti-hyperglycemic in subjects with hyperglycemia	• Monitor subjects for hyperglycemia or other signs and symptoms of diabetes.
Hypophysitis	Grade 2	Withhold	• Administer corticosteroids and initiate hormonal replacements as clinically indicated.	• Monitor for signs and symptoms of hypophysitis (including hypopituitarism and adrenal insufficiency)
	Grade 3 or 4	Withhold or permanently discontinue[1]		
Hyperthyroidism	Grade 2	Continue	• Treat with non-selective beta-blockers (eg propranolol) or thionamides as appropriate	• Monitor for signs and symptoms of thyroid disorders.
	Grade 3 or 4	Withhold or Permanently discontinue[1]		
Hypothyroidism	Grade 2-4	Continue	• Initiate thyroid replacement hormones (eg levothyroxine or liothyronine) per standard of care	• Monitor for signs and symptoms of thyroid disorders.

irAEs	Toxicity grade or conditions (NCI CTCAE v4.0)	Action taken to pembrolizumab	irAE management with corticosteroid and/or other therapies	Monitor and follow-up
Nephritis and renal dysfunction	Grade 2	Withhold	• Administer corticosteroids (prednisone 1-2 mg/kg or equivalent) followed by taper.	• Monitor changes of renal function
	Grade 3 or 4	Permanently discontinue		
Myocarditis	Grade 1 or 2	Withhold	• Based on severity of AE administer corticosteroids	• Ensure adequate evaluation to confirm etiology and/or exclude other causes
	Grade 3 or 4	Permanently discontinue		
All Other irAEs	Intolerable/ persistent Grade 2	Withhold	• Based on type and severity of AE administer corticosteroids	• Ensure adequate evaluation to confirm etiology and/or exclude other causes
	Grade 3	Withhold or discontinue based on the type of event. Events that require discontinuation include and not limited to: Guillain-Barré Syndrome, encephalitis		
	Grade 4 or recurrent Grade 3	Permanently discontinue		

Abbreviations: AE = adverse event; ALT = alanine aminotransferase; AST = aspartate aminotransferase; CTCAE = Common Terminology Criteria for Adverse Events; GI = gastrointestinal; IV = intravenous; irAE = immune-related adverse event; NCI = National Cancer Institute; T1DM – type 1 diabetes mellitus.

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

NOTE:

For subjects 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).

5.2.1.2.2 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 4.

Table 4 Pembrolizumab Infusion Reaction Dose modification and Treatment Guidelines

NCI CTCAE Grade	Treatment	Premedication at Subsequent Dosing
Grade 1 Mild reaction; infusion interruption not indicated; intervention not indicated	Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator.	None
Grade 2 Requires therapy or infusion interruption but responds promptly to symptomatic treatment (eg, antihistamines, NSAIDs, narcotics, IV fluids); prophylactic medications indicated for ≤24 hrs	**Stop Infusion.** Additional appropriate medical therapy may include but is not limited to: • IV fluids • Antihistamines • NSAIDs • Acetaminophen • Narcotics Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator. If symptoms resolve within 1 hour of stopping drug infusion, the infusion may be restarted at 50% of the original infusion rate (eg 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 1.5 h (±30 minutes) prior to infusion of pembrolizumab with: • Diphenhydramine 50 mg PO (or equivalent dose of antihistamine). • Acetaminophen 500-1000 mg PO (or equivalent dose of analgesic).

NCI CTCAE Grade	Treatment	Premedication at Subsequent Dosing
Grades 3 or 4 **Grade 3:** Prolonged (ie, not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae (eg, renal impairment, pulmonary infiltrates) **Grade 4:** Life-threatening; pressor or ventilatory support indicated	**Stop Infusion.** Additional appropriate medical therapy may include but is not limited to: • 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. **Subject is permanently discontinued from further study drug treatment.**	No subsequent dosing
Abbreviations: CTCAE = Common Terminology Criteria for Adverse Events; IV = intravenous; NCI = National Cancer Institute; NSAIDS = nonsteroidal anti-inflammatory drugs; PO = by mouth. 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 NCI CTCAE v4.0 at http://ctep.cancer.gov		

Dose Modification Guideline During Concurrent Radiation and Pembrolizumab Administration

For radiation-induced dermatitis, hold pembrolizumab for ≥Grade 3 AEs and resume when desquamation is no longer moist. Standard skin therapy and analgesics should be used in accordance with local practice. Adjust radiation delivery as necessary when treatment is resumed. For dose modification guideline for pembrolizumab/placebo during concurrent treatment with radiation, see “All other irAEs” in Table 3.

Other Allowed Dose Interruptions 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 6 weeks of the scheduled interruption, unless otherwise discussed with the Sponsor. The reason for interruption should be documented in the subject's study record.

5.2.1.2.3 Dose Modifications for Chemotherapy Agents

Suggested dose modifications for paclitaxel and carboplatin are detailed in Table 5 and for doxorubicin (or epirubicin) and cyclophosphamide Table 6.

Granulocyte-colony stimulating factor (G-CSF) should be administered after each cycle of chemotherapy. G-CSF (5 µg/kg/day) administered subcutaneously (SC) should be initiated at 24 hours postdose and continued until at least 72 hours after the last day of chemotherapy.

Pegfilgrastim administered SC as either a single dose of 100 µg/kg (individualized) or a single dose of 6 mg (general approach) at 24 hours after the last day of chemotherapy is also acceptable for the Q3W chemotherapy regimens. The period between the end of the last dose of Treatment 1 and the first dose of Treatment 2 during the neoadjuvant phase should not exceed 3 weeks unless due to toxicity(ies). Sponsor consultation is needed if the duration between Treatment 1 and Treatment 2 is longer than 3 weeks. Local guidelines and practices should be followed, if different than the recommendations outlined in Table 5 and Table 6.

Table 5 Dose Modification Guideline for Paclitaxel and Carboplatin

Toxicities	Grade or actual value	Paclitaxel alone or with Carboplatin
Hematological		
Neutropenia	≥1000/mm^3 Grade 2/Grade 1	No change to paclitaxel and carboplatin
	<1000/mm^3 Grade 3/Grade 4	Hold paclitaxel and/or carboplatin until ANC ≥1000/mm^3. Administer G-CSF until ANC ≥1000/ mm^3. Resume paclitaxel and/or carboplatin based on timing of recovery: • <3 weeks: Dose-reduce paclitaxel to 70 mg/m^2 and/or carboplatin to AUC 4 (Q3W dosing) or AUC 1.1 (QW dosing) for all subsequent cycles. • ≥3 weeks: Stop paclitaxel and /or carboplatin (see general instruction below)
Febrile neutropenia	ANC ≤1000/mm^3, fever ≥38.5°C Grade 3 and Grade 4	Hold paclitaxel and/or carboplatin until resolved (ANC >1000/mm^3, fever <38.5°C, and resolution of any signs of infection). Administer G-CSF until ANC ≥1000/ mm^3. Resume paclitaxel and or carboplatin according to number of episodes: • First episode: Reduce paclitaxel to 70 mg/m^2 and/or carboplatin to AUC 4 (Q3W dosing) or AUC 1.1 (QW dosing) for all subsequent doses. • Second episode: Discontinue paclitaxel and/or carboplatin (see general instruction below)
Thrombocytopenia	75-<100,000/mm^3 Grade 1	Hold paclitaxel and/or carboplatin until ≥100,000/mm^3, resume treatment based on timing of recovery: • ≤1 week — no change to paclitaxel and carboplatin. • >1 but <3 weeks — Reduce paclitaxel to 70 mg/m^2 and/or carboplatin to AUC 4 (Q3W dosing) or AUC 1.1 (QW dosing) for all subsequent doses. • ≥3 weeks: Discontinue paclitaxel and/or carboplatin (see general instruction below)
	<75,000/mm^3 ≥Grade 2	Hold paclitaxel and/or carboplatin until ≥100,000/mm^3. • Reduce paclitaxel to 70 mg/m^2 and/or carboplatin to AUC 4 (Q3W dosing) or AUC 1.1 (QW dosing) for all subsequent doses. • Stop paclitaxel and/or carboplatin if held for ≥3 weeks in a row, (see general instruction below)

Toxicities	Grade or actual value	Paclitaxel alone or with Carboplatin
Anemia	All grades	No change to paclitaxel and carboplatin • Iron studies should be done and iron should be replaced as indicated. • Red blood cell transfusions can be given at the investigator's discretion.
Nausea/Vomiting	Grade 1 or 2	No change to paclitaxel and carboplatin
	≥Grade 3	Hold paclitaxel and/or carboplatin until resolved to ≤Grade 1. • Resume paclitaxel and/or carboplatin at previous dose with modification of premedication • Second episode ≥Grade 3 despite with maximum supportive care, reduce paclitaxel to 70 mg/m^2 and/or carboplatin to AUC 4 (Q3W dosing) or AUC 1.1 (QW dosing) for all subsequent cycles
Mucositis/Stomatitis	Grade 1 or 2	No change to paclitaxel and carboplatin
	≥Grade 3	Hold paclitaxel and /or carboplatin until resolved to ≤Grade 1. • Resume paclitaxel and /or carboplatin at previous dose with modification of premedication • Second episode ≥Grade 3 despite with maximum supportive care, reduce paclitaxel to 70 mg/m^2 and/or carboplatin to AUC 4 (Q3W dosing) or AUC 1.1 (QW dosing) for all subsequent cycles
Neurotoxicity	Grade 1–2	No change to paclitaxel and carboplatin
	Grade 3	Hold paclitaxel and /or carboplatin until neuropathy improves to ≤Grade 2. • Resume paclitaxel dose reduced to 70 mg/m^2 and/or carboplatin to AUC 4 (Q3W dosing) or AUC 1.1 (QW dosing) for all subsequent doses. • Discontinue paclitaxel and/or carboplatin if held for ≥3 weeks in a row, (see general instruction below)
	Grade 4	• Discontinue paclitaxel and/or carboplatin if held for ≥3 weeks in a row, (see general instruction below)
Hepatic	Grade 1	• No change to paclitaxel and/or carboplatin
	≥Grade 2 or 3	• Bilirubin fractionation should be performed if total bilirubin >1.5xULN. Dose may continue if isolated bilirubinemia is mostly indirect such as in subject with Gilbert • Hold paclitaxel and/or carboplatin until resolve to Grade 1 and resume the dose at previous level • Discontinue paclitaxel and/or carboplatin if held for ≥3 weeks in a row, (see general instruction below)
	Grade 4	• Discontinue paclitaxel and/or carboplatin (see general instruction below) Note all concurrent ALT/AST >3×ULN and Total bilirubin >2×ULN should be discontinued and evaluated for potential Hy's law

Toxicities	Grade or actual value	Paclitaxel alone or with Carboplatin
Anaphylaxis /hypersensitivity	Mild	• Complete paclitaxel or carboplatin infusion, observe until symptom resolved
	Moderate	• Stop infusion and treat per standard practice • Resume infusion at half of the infusion speed if symptom resolve • Stop if symptom recurs
	Severe	• Stop infusion immediately and discontinue treatment (see general instruction below)
Other significant toxicities excluding fatigue, alopecia and leukopenia at discretion of the investigators	Grade 2	• Hold paclitaxel and/or carboplatin until resolve to ≤Grade 1 • Resume at the previous dose and increase supportive care measure, if available
	≥Grade 3	• Hold paclitaxel and/or carboplatin, and discuss with sponsor medical monitor for further instructions • If ≥Grade 3 toxicity recurs upon rechallenge, discontinue treatment permanently

Table 6 Dose Modification Guidelines for Doxorubicin and Cyclophosphamide (AC) or Epirubicin and Cyclophosphamide (EC)

Toxicities	Grade or actual value	Doxorubicin and cyclophosphamide, epirubicin and cyclophosphamide
Hematological		
Neutropenia	≥1000/mm^3 (Grade 2/Grade 1)	No change to AC or EC •
	<1000/mm^3 Grade 3/Grade 4	Hold AC or EC until ANC ≥1000/mm^3. Administer G-CSF until ANC ≥1000/ mm^3. Resume AC or EC based on timing of recovery: • <3 weeks: Reduce AC or EC by 20% for all subsequent cycles. • ≥3 weeks: discontinue AC or EC (see general instruction below)
Febrile neutropenia	ANC ≤1000/mm^3, fever ≥38.5°C Grade 3 and Grade 4	Hold AC or EC until resolved (ANC >1000/mm^3, fever <38.5°C, and resolution of any signs of infection. Administer G-CSF until ANC ≥1000/ mm^3. Resume AC or EC according to number of episodes: • First episode: Reduce AC or EC by 20% for all subsequent cycles • Second episode: Discontinue AC or EC (see general instruction below)
Thrombocytopenia	75–<100,000/mm^3 Grade 1	Hold AC or EC until ≥100,000/mm^3, resume AC or EC based on timing of recovery: • ≤1 week — no change to AC or EC. • >1 but <3 weeks — Reduce AC or EC by 20% for all subsequent cycles • ≥3 weeks: Discontinue AC or EC (see general instruction below)
	<75,000/mm^3 ≥Grade 2	Hold AC or EC until ≥100,000/mm^3. • Reduce AC or EC by 20% for all subsequent cycles • Discontinue AC or EC if held for ≥3 weeks in a row, (see general instruction below)

Toxicities	Grade or actual value	Doxorubicin and cyclophosphamide, epirubicin and cyclophosphamide
Anemia	All grades	No change to AC or EC • Iron studies should be done and iron should be replaced as indicated. • Red blood cell transfusions can be given at the investigator's discretion.
Nausea/Vomiting	Grade 1 or 2	No change to AC or EC
	≥Grade 3	Hold AC or EC until resolved to ≤Grade 1. • Resume AC or EC at previous dose with modification of premedication • Second episode ≥Grade 3 despite with maximum supportive care, reduce AC or EC by 20% for all subsequent cycles
Mucositis/Stomatitis	Grade 1 or 2	No change to AC or EC
	≥Grade 3	Hold AC or EC until resolved to ≤Grade 1. • Resume AC or EC at previous dose with modification of premedication • Second episode ≥Grade 3 despite with maximum supportive care, reduce AC or EC by 20% for all subsequent cycles
Hepatic	Grade 1	• No change to AC or EC
	≥Grade 2 or 3	• Hold AC or EC until resolve to Grade 1 and resume the dose at previous level • Discontinue AC or EC if held for ≥3 weeks in a row, (see general instruction below)
	Grade 4	• Discontinue AC or EC (see general instruction below) Note all concurrent ALT/AST >3×ULN and Total bilirubin >2×ULN should be discontinued and evaluated for potential Hy's law
Cardiac toxicity	Grade 1 or 2	• No change to AC or EC
	≥Grade 3	• Discontinue doxorubicin or epirubicin (see general instruction below)
Anaphylaxis/ hypersensitivity	Mild	• Complete AC or EC infusion, observe until symptom resolved
	Moderate	• Stop infusion and treat per standard practice • Resume infusion at half of the infusion speed if symptom resolve • Stop if symptom recurs
	Severe	• Stop infusion immediately and discontinue treatment (see general instruction below)
Other significant toxicities excluding fatigue, alopecia and leukopenia at discretion of the investigators	Grade 2	• Hold AC or EC until resolve to ≤Grade 1 • Resume at the previous dose and increase supportive care measure, if available
	≥Grade 3	• Hold AC or EC and discuss with sponsor medical monitor for further instructions • If ≥Grade 3 toxicity recurs upon rechallenge, discontinue treatment permanently

Instruction on Discontinuation of a Component or Entire Regimen

During the first part of the combination therapy, if 1 or more than 1 component must be discontinued due to toxicity, the investigator can select 1 of the following options at his/her own discretion for the subject (Table 5 and Table 6):

- If paclitaxel is discontinued due to toxicity related to paclitaxel,
    - Stop the first part of the neoadjuvant chemotherapy (pembrolizumab + carboplatin [KCb] [or placebo + carboplatin [PCb]); start and complete the KAC or KEC (or PAC/PEC) regimen as planned per protocol, then followed by surgery. Subjects can resume pembrolizumab or placebo in the adjuvant phase as planned in the protocol.
- If only carboplatin is discontinued due to carboplatin toxicity,
    - Continue with KX/PX or X followed by KAC or KEC (or PAC/PEC) as planned per protocol, then followed by surgery. Subjects can resume pembrolizumab or placebo in the adjuvant phase as planned in the protocol.
- If only pembrolizumab/placebo is discontinued due to pembrolizumab/placebo toxicity,
    - Continue with carboplatin and/or paclitaxel regimen alone as planned per protocol, then start and complete the AC or EC regimen as planned per protocol, then followed by surgery. Subjects will not resume pembrolizumab or placebo in the adjuvant phase.

During the second part of the combination therapy KAC or KEC (or PAC/PEC), if one or more than one component should be discontinued, the investigator can select 1 of the following options at his/her own discretion for the subject:

- If doxorubicin (or epirubicin) and/or cyclophosphamide are discontinued due to doxorubicin (or epirubicin) and/or cyclophosphamide toxicity,
    - Discontinue all study treatment including pembrolizumab and proceed with surgery. Subjects can resume pembrolizumab or placebo in the adjuvant phase as planned in the protocol.
- If only pembrolizumab/placebo is discontinued due to pembrolizumab/placebo toxicity,
    - Continue doxorubicin (or epirubicin) and cyclophosphamide for the remaining cycles as planned per protocol, and followed by surgery. Subjects will not resume pembrolizumab or placebo in the adjuvant phase.

Subjects who are discontinued from the study treatment and continue with another neoadjuvant treatment prior to the definitive surgery will be evaluable for pCR and EFS endpoints.

Note: if pembrolizumab is discontinued during the Neoadjuvant Treatment Phase due to toxicity, no pembrolizumab is to be given after surgery.

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.

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 Section 6 – Trial Flow Chart.

Refer to the product label for detailed instructions on preparation and administration precautions on combination chemotherapy agents included in the trial: paclitaxel, carboplatin, doxorubicin, epirubicin, 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 Cycles 2-4 of the Neoadjuvant Treatment Phase (Treatment 1) every 3 weeks (± 2 days); and for Cycles 1-4 of the Neoadjuvant Treatment Phase (Treatment 2) and Cycle 1-9 of the Adjuvant Treatment Phase, every 3 weeks (± 3 days). Trial treatments should be administered in accordance with the schedules provided in Section 6 – Trial Flow Chart.

On Day 1 of each Cycle, 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 (ie, 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 Paclitaxel

Paclitaxel, at a dose level of 80 mg/m^2, will be administered on Days 1, 8, and 15 during Cycles 1-4 of the paclitaxel/carboplatin regimen (Treatment 1) as IV infusion as instructed per product label.

When paclitaxel is administered on the same day together with pembrolizumab/placebo and carboplatin, paclitaxel should be administered after pembrolizumab/placebo but prior to the administration of carboplatin. Additional premedication should be administered as per standard practice.

5.2.2.3 Carboplatin

Carboplatin at AUC 5 (maximum dose of 750 mg) will be administered on Day 1 of Cycles 1-4 or AUC 1.5 (maximum dose of 225 mg), IV, weekly, on Days 1, 8, 15 of Cycles 1-4 of the paclitaxel/carboplatin regimen (Treatment 1) as an IV infusion as instructed per product label immediately following the administration of paclitaxel. Additional premedication should be administered as per standard practice.

If the dose of carboplatin is reduced to either AUC 4 (Q3W) or AUC 1.1 (QW) (Table 5), the maximum dose should not exceed 600 mg or 165 mg, respectively.

5.2.2.4 Cyclophosphamide

Cyclophosphamide at a dose level of 600 mg/m^2 will be administered intravenously as instructed per product label on Day 1 of Cycles 1-4 of the AC or EC regimen (Treatment 2) following the administration of pembrolizumab/placebo. Additional premedication should be administered as per standard practice.

5.2.2.5 Doxorubicin

Doxorubicin at a dose level of 60 mg/m^2 should be administered IV push on Day 1 of Cycles 1-4 of the AC regimen (Treatment 2) as instructed per product label following the administration of pembrolizumab. Additional premedication should be administered as per standard practice. Doxorubicin should be avoided for subjects who had previous exposure to doxorubicin of more than 200 mg/m^2.

5.2.2.6 Epirubicin

Epirubicin at a dose level of 90 mg/m^2 should be administered IV push as instructed per product label on Day 1 of Cycles 1-4 of the EC regimen (Treatment 2) following the administration of pembrolizumab. Additional premedication should be administered as per standard practice.

5.2.2.7 Radiation Therapy

Post-operative radiation therapy is acceptable according to the applicable standard of care (eg, cases of BCS, large primary tumor, some positive lymph node disease).

5.2.3 Trial Blinding

A double-blinding technique will be used. Pembrolizumab and placebo will be prepared and/or dispensed in a blinded fashion by an unblinded pharmacist or qualified trial site personnel. The subject and the investigator who is involved in the treatment or clinical evaluation of the subjects are unaware of the group assignments.

See Section 7.1.4.2, Blinding/Unblinding, for a description of the method of unblinding a subject during the trial, should such action be warranted.

5.3 Randomization or Treatment Allocation

Treatment allocation/randomization will occur centrally using an interactive voice response system / integrated web response system (IVRS/IWRS). There are 2 treatment arms. Subjects will be assigned randomly in a 2:1 ratio to pembrolizumab and placebo, respectively, after stratification as described in Section 5.4 – Stratification. The choice of QW carboplatin or Q3W carboplatin should be determined prior to randomization, and carboplatin is the stratification factor. The choice of doxorubicin or epirubicin should be determined at the initiation of Treatment 2.

5.4 Stratification

Treatment allocation/randomization will be stratified according to the following factors:

1. Nodal status: Positive vs. Negative
2. Tumor size: T1/T2 vs. T3/T4.
3. Choice of carboplatin (Cb): Q3W vs. Weekly

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. Note: the use of GnRH therapy (eg, goserelin acetate [Zolodex®]) for ovarian preservation and bisphosphonates or rank ligand inhibitors to prevent osteopenia or osteoporosis is allowed during chemotherapy.

Supportive care is permitted for managing drug-related toxicities. See guidelines in Section 5.6 –Rescue Medications & Supportive Care for more details.

All prior medications received within 30 days before the screening visit, and all new concomitant medications given from the screening visit through the Adjuvant Phase safety follow-up visit should be recorded. After the Adjuvant Phase safety follow-up visit, record all medications administered for the treatment of SAEs and ECIs as defined in Section 7.2. – Assessing and Recording Adverse Events.

5.5.2 Prohibited Concomitant Medications

Subjects are prohibited from receiving the following therapies from the time of screening until completion of all study therapy:

- Immunotherapy not specified in this protocol
- Chemotherapy not specified in this protocol
- Investigational agents not specified in this protocol
- Radiation therapy except as described in Section 2.1. Post-operative radiation therapy is acceptable according to the standard of care, as applicable.
- 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 (eg, 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 (eg, to IV contrast dye) is permitted.*

Subjects who are discontinued from the study treatment and continue with another neoadjuvant treatment prior to the definitive surgery will be evaluable 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.

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 adverse events with potential immunologic etiology are outlined along with the dose modification

guidelines in Section 5.2.1.2 (Table 3). 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 3 in Section 5.2.1.2.1 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.

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

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

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

OR

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

OR

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

Female and male subjects of reproductive potential must agree to avoid becoming pregnant (or getting their partner pregnant) while receiving study drug and for 12 months after the last dose of study drug for subjects who have received cyclophosphamide, and for 6 months after the last dose of study medication for subjects who have not, by complying with one of the following:

1. practice abstinence† from heterosexual activity;

OR

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

Acceptable methods of contraception are‡:

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 ethics review committees (ERCs)/international review boards (IRBs). Periodic abstinence (eg, calendar, ovulation, sympto-thermal, post-ovulation methods) 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 6 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 Use in 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 (eg, 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

5.8.1 Discontinuation of Treatment

Discontinuation of treatment does not represent withdrawal from the trial.

As certain data on clinical events beyond treatment discontinuation may be important to the study, they must be collected through the subject's last scheduled follow-up, even if the subject has discontinued treatment. Therefore, all subjects who discontinue trial treatment prior to completion of the treatment will still continue to participate in the trial as specified in Section 6.0 - Trial Flow Chart and Section 7.1.5.6 – Discontinued Subjects Continuing to be Monitored in the Trial.

Subjects may discontinue treatment at any time for any reason or be dropped from treatment at the discretion of the investigator should any untoward effect occur. In addition, a subject may be discontinued from treatment by the investigator or the Sponsor if treatment is inappropriate, the trial plan is violated, or for administrative and/or other safety reasons. Specific details regarding procedures to be performed at treatment discontinuation are provided in Section 7.1.4 – Other Procedures.

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

○ The subject or subject's legally acceptable representative requests to discontinue treatment.

- Unacceptable adverse experiences as described in Section 7.2 – Assessing and Recording Adverse Events.
- 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.
- The subject has a confirmed positive serum pregnancy test
- Noncompliance with trial treatment or procedure requirements
- Pembrolizumab or placebo must be discontinued for recurrent Grade 2 pneumonitis.

The Early Discontinuation and Safety Follow-up visit procedures are listed in Section 6 – Trial Flow Chart and Section 7.1.5 – Visit Requirements. Following completion of treatment, each subject will be followed for 30 days for any adverse events (SAEs will be collected for 90 days after completion of treatment or 30 days following completion of treatment if the subject initiates new anticancer therapy, whichever is earlier, as described in Section 7.2.3.1 – Serious Adverse Events).

Discontinuation from treatment is "permanent." Once a subject is discontinued, he/she shall not be allowed to restart treatment.

5.8.2 Withdrawal from the Trial

A subject must be withdrawn from the trial if the subject or subject's legally acceptable representative withdraws consent from the trial.

If a subject withdraws from the trial, they will no longer receive treatment or be followed at scheduled protocol visits.

Specific details regarding procedures to be performed at the time of withdrawal from the trial including the procedures to be performed should a subject repeatedly fail to return for scheduled visits and/or if the study site is unable to contact the subject, as well as specific details regarding withdrawal from Future Biomedical Research are outlined in Section 7.1.4 – Other Procedures.

5.9 Subject Replacement Strategy

A subject who discontinues from trial treatment or withdraws from 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, withdraws

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

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

1. The study may be stopped early for futility or safety at the recommendation of the external DMC.
2. Quality or quantity of data recording is inaccurate or incomplete as assessed by the Sponsor
3. Poor adherence to protocol and regulatory requirements
4. Incidence or severity of adverse drug reaction in this or other studies indicates a potential health hazard to subjects
5. 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.

Statistical criteria for stopping the study are provided in Section 8.0– Statistical Analysis Plan.

Enrollment will not be halted during the planned safety and efficacy IAs.

Further recruitment in the study or at (a) particular study site(s) may be stopped due to insufficient compliance with the protocol, GCP, and/or other applicable regulatory requirements or procedure-related problems or if the number of discontinuations for administrative reasons is too high.

6.0 TRIAL FLOW CHART

Trial Period:	Screening Phase	Neoadjuvant Treatment Phase[a]									30 Day Safety Follow-up[b]	Definitive Surgery	30 Day Safety Follow-Up (Post Definitive Surgery)[b]	Adjuvant Treatment Phase[a]	30 Day Safety Follow-Up[b]	Early Discon Visit[c]	Long-term Follow-up[d]	Survival Follow-up
		Treatment 1 (Paclitaxel/Carboplatin)					Treatment 2 (AC or EC)											
Treatment Cycle:	Screening	C1 D1	C1 D8	C1 D15	C2-C4 D1	C2-C4 D8, D15	C1 D1	C2 D1	C3 D1	C4 D1				C1-C9 D1				
Scheduling Window (Days)	-28 to -1	+3	±2	±2	±2	±2	±3	±3	±3	±3	±3	Surgery	±3	±3	±3		± 1 month	± 1 month
Informed Consent[e]	X																	
Informed Consent for FBR	X[f]																	
Inclusion/Exclusion Criteria	X																	
Subject Identification Card	X																	
Demographics and Medical History	X																	
Prior and Concomitant Medication Review[g]	X	X			X		X	X	X	X	X		X	X	X	X		
Treatment allocation/ /randomization via IVRS[h]		X																
Post-study Anticancer Therapy Status																	X	X
Survival Status[i]		⟷												X	X	X	X	X
Pathological tumor staging													X[ff]					
Pembrolizumab/ Placebo		X			X		X	X	X	X				X				
Paclitaxel 80 mg/m^2		X	X	X	X	X												
Carboplatin AUC 5[j]		X			X													

Trial Period:	Screening Phase	Neoadjuvant Treatment Phase[a]									30 Day Safety Follow-up[b]	Definitive Surgery	30 Day Safety Follow-Up (Post Definitive Surgery)[b]	Adjuvant Treatment Phase[a]	30 Day Safety Follow-Up[b]	Early Discon Visit[c]	Long-term Follow-up[d]	Survival Follow-up
		Treatment 1 (Paclitaxel/Carboplatin)					Treatment 2 (AC or EC)											
Treatment Cycle:	Screening	C1 D1	C1 D8	C1 D15	C2-C4 D1	C2-C4 D8, D15	C1 D1	C2 D1	C3 D1	C4 D1				C1-C9 D1				
Scheduling Window (Days)	-28 to -1	+3	±2	±2	±2	±2	±3	±3	±3	±3	±3	Surgery	±3	±3	±3		± 1 month	± 1 month
Carboplatin AUC1.5[j]		X	X	X	X	X												
Doxorubicin 60 mg/m^2 or Epirubicin 90 mg/m^2							X	X	X	X								
Cyclophosphamide 600 mg/m^2							X	X	X	X								
Radiation therapy (if indicated)														X[gg]				
Review Adverse Events[k]	X	X	X	X	X	X	X	X	X	X	X		X	X	X[l]	X[l]		
12-Lead ECG (Locally performed)	X						X[m]				X	X[kk]		X[kk]	X	X		
MUGA or ECHO for LVEF Assessment	X						X[m]				X	X[kk]		X[kk]	X[kk]	X[kk]		
Full Physical Examination	X																	
Directed Physical Examination		X			X		X	X	X	X	X		X	X	X	X	X	
Vital Signs, Height and Weight[n]	X	X	X	X	X	X	X	X	X	X	X		X	X	X	X	X	
ECOG Performance Status[o]	X	X			X		X	X	X	X	X		X	X	X	X	X	
Pregnancy Test – Urine or Serum β-HCG[p]	X																	

Trial Period:	Screening Phase	Neoadjuvant Treatment Phase[a]									30 Day Safety Follow-up[b]	Definitive Surgery	30 Day Safety Follow-Up (Post Definitive Surgery)[b]	Adjuvant Treatment Phase[a]	30 Day Safety Follow-Up[b]	Early Discon Visit[c]	Long-term Follow-up[d]	Survival Follow-up
		Treatment 1 (Paclitaxel/Carboplatin)					Treatment 2 (AC or EC)											
Treatment Cycle:	Screening	C1 D1	C1 D8	C1 D15	C2-C4 D1	C2-C4 D8, D15	C1 D1	C2 D1	C3 D1	C4 D1				C1-C9 D1				
Scheduling Window (Days)	-28 to -1	+3	±2	±2	±2	±2	±3	±3	±3	±3	±3	Surgery	±3	±3	±3		± 1 month	± 1 month
Blood for menopausal status (if applicable)[q]	X																	
ePROs[r]		X					X			X				X (C1, C5, C9)		X	X	
PT/INR and aPTT/ PTT[s,u]	X										X		X		X	X		
CBC with Differential[t,u,v]	X[v]		X	X	X	X	X	X	X	X	X	X[jj]	X	X	X	X	X	
Chemistry Panel[t,u,v]	X[v]		X	X	X	X	X	X	X	X	X	X[jj]	X	X	X	X	X	
Urinalysis[t,u,v]	X[v]				X		X			X	X	X[jj]	X		X	X	X	
T3, FT4 and TSH[t,u,v]	X[v]						X				X		X		X	X	X	
Cortisol[t, u, hh]	X											X						
Troponin and BNP[t, u, ii]	X											X						
LDH	X										X		X		X	X		
Breast MRI[w]	X[w]						X[w]					X[w]						
Assessment of disease progression/ recurrence[x]					X		X	X	X	X	X	X	X	X	X	X	X	X
Blood for Plasma Biomarker Analyses[y]		X			X[y]		X									X		
Blood for Serum Biomarker Analyses[y]		X			X[y]		X									X		
Blood for RNA Analyses[z]		X			X[z]		X			X						X		

Trial Period:	Screening Phase	Neoadjuvant Treatment Phase[a]									30 Day Safety Follow-up[b]	Definitive Surgery	30 Day Safety Follow-Up (Post Definitive Surgery)[b]	Adjuvant Treatment Phase[a]	30 Day Safety Follow-Up[b]	Early Discon Visit[c]	Long-term Follow-up[d]	Survival Follow-up
		Treatment 1 (Paclitaxel/Carboplatin)					Treatment 2 (AC or EC)											
Treatment Cycle:	Screening	C1 D1	C1 D8	C1 D15	C2-C4 D1	C2-C4 D8, D15	C1 D1	C2 D1	C3 D1	C4 D1				C1-C9 D1				
Scheduling Window (Days)	-28 to -1	+3	±2	±2	±2	±2	±3	±3	±3	±3	±3	Surgery	±3	±3	±3		± 1 month	± 1 month
Blood for Genetic Analyses[aa]		X																
pCR assessment												X						
Core tumor tissue biopsy for translational research	X					X[bb]						X[cc]					X[dd]	
Definitive surgery												X[cc]						
FFPE tissue or slides for TNBC status[ee]	X																X[dd]	

AC = doxorubicin + cyclophosphamide; AUC = Area under the curve; CBC = Complete Blood Count; Discon = discontinuation; DNA = deoxyribonucleic acid; EC = epirubicin + cyclophosphamide; ECG = electrocardiogram; ECHO = Echocardiogram; ECOG = Eastern Cooperative Oncology Group; ePRO = Electronic Patient Reported Outcomes; FBR = Future Biomedical Research; FFPE = formalin-fixed paraffin-embedded; FT4=Free thyroxine 4; HCG = human chorionic gonadotropin; IVRS = Integrated Web Response System; LDH = Lactate Dehydrogenase; LVEF = Left ventricular ejection fraction; MRI = magnetic resonance imaging; MUGA = Multigated Acquisition; NCI = National Cancer Institute; pCR = Pathological Complete Response; PT/INR = Prothrombin Time/International Normalized Ratio; aPTT/PTT= Activated Prothrombin Time/Partial thromboplastin time; RNA = ribonucleic acid; T3 = Triiodothyronine; TNBC = Triple-negative Breast Cancer; TSH = Thyroid stimulating hormone.

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 paclitaxel or weekly carboplatin) unless otherwise specified. Each treatment cycle is 3 weeks (21 days). If the treatment is delayed, all procedures should be performed based on the new dosing schedule. The Adjuvant Treatment Phase is expected to start 30 to 60 days after definitive surgery, and if performed outside of this window, sponsor consultation will be required. Post-definitive surgery, pembrolizumab or placebo will be given in the Adjuvant Treatment Phase, as assigned during allocation/randomization. No crossover from placebo to pembrolizumab will be permitted.

b. The 30-Day Safety Follow-Up visit should be performed after the Neoadjuvant Treatment Phase, after definitive surgery, and after the Adjuvant Treatment Phase. If surgery is scheduled to occur less than 30 days after the end of Neoadjuvant Treatment Phase, the Safety Follow-up Visit should occur before surgery. If an Early Discontinuation Visit occurs, then every attempt should be made to perform a 30-Day Safety Follow-Up visit (30 days ± 3 days). After surgery, the 30-Day Safety Follow-Up visit can be skipped if Cycle 1 of the Adjuvant Treatment Phase begins within 30 days ±3 days post definitive surgery.

c. The Early Discontinuation Visit should be conducted if subject discontinues all protocol-specified treatment after Treatment 1 Cycle 1 through the Adjuvant Treatment Phase. Every attempt should be made to have an Early Discontinuation visit during the Long-term Follow-Up phase of the study for subjects who discontinue before the next protocol-specified visit.

Trial Period:	Screening Phase	Neoadjuvant Treatment Phase[a]									30 Day Safety Follow-up[b]	Definitive Surgery	30 Day Safety Follow-Up (Post Definitive Surgery)[b]	Adjuvant Treatment Phase[a]	30 Day Safety Follow-Up[b]	Early Discon Visit[c]	Long-term Follow-up[d]	Survival Follow-up
		Treatment 1 (Paclitaxel/Carboplatin)					Treatment 2 (AC or EC)											
Treatment Cycle:	Screening	C1 D1	C1 D8	C1 D15	C2-C4 D1	C2-C4 D8, D15	C1 D1	C2 D1	C3 D1	C4 D1				C1-C9 D1				
Scheduling Window (Days)	-28 to -1	+3	±2	±2	±2	±2	±3	±3	±3	±3	±3	Surgery	±3	±3	±3		± 1 month	± 1 month

d. Long-term Follow-up visits will be scheduled to occur at 3-month intervals (± 1 month) from the date of randomization for the first 2 years, then at 6-month intervals (± 1 month) for Years 3 to 5, and annually thereafter until occurrence of local or/and distant disease progression/ recurrence, death, withdrawal of consent, or the end of the study, whichever occurs first. Subjects should be assessed for either pCR and disease progression/recurrence (if discontinued during the Neoadjuvant Treatment Phase) or disease recurrence (if discontinued during the Adjuvant Treatment Phase). Additional tests/investigations/imaging assessments for recurrent or metastatic disease (eg, bone/liver scan) will be at the discretion of subject's treating physician per local standard of care or at the time of symptoms. Subjects who have recurrence or metastatic disease at any time during the Neoadjuvant, Adjuvant Treatment Phase, or during Long-term Follow-Up will be followed up by telephone every 6 months (± 1 month) for overall survival until consent withdrawal from trial, becoming lost to follow-up, death or end of the study, whichever is earlier.

e. Written consent must be obtained prior to performing any protocol-specified procedures. If the signature falls outside of the 28-day screening window, the consent form does not need to be resigned. 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 (eg, within 28 days prior to the first dose of trial treatment).

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 Laboratory Manual and Section 12.2 – Collection and Management of Specimens for Future Biomedical Research.

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 after the Adjuvant Treatment Phase, or Early Discontinuation, whichever is earlier. Record all medications taken for AEs as defined in Section 7.2 – Assessing and Recording Adverse Events.

h. Site personnel will access the IVRS prior to dosing on Treatment 1 Cycle 1, Day 1 to obtain the subject's allocation/randomization number; treatment must be given within 3 days following allocation//randomization (+ 3 days). See Section 7.1.5.2 – Treatment Cycles for more details.

i. If a subject does not return for protocol-specified visit assessments in the Long-term Follow-Up period, all attempts should be made to contact the subject via telephone for Survival Status, further explained in Section 7.1.5.4.3 – Long-term Follow-Up for Disease Status and Survival. If a subject ends treatment in the Neoadjuvant or Adjuvant Treatment Phases for disease progression/recurrence, the subject should be followed every 6 months (± 1 month) via telephone for Survival Status. Updated disease and survival status may be requested by the Sponsor at any time during the course of the study. Upon Sponsor notification, all subjects who do not/will not have a scheduled study visit or study contact during the Sponsor defined time period will be contacted for their disease and survival status (excluding subjects that have a death event previously recorded).

j. Carboplatin dosing will be AUC 5, IV, Q3W, on Day 1 of Cycles 1-4 **or** AUC 1.5, IV, weekly, on Days 1, 8, 15 of Cycles 1-4 of the paclitaxel/carboplatin regimen (Treatment 1) based on the investigator's preference.

k. 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.

l. Report all AEs occurring up until 30 days following Cycle 9 (Adjuvant Treatment Phase) and all SAEs occurring up until 90 days following Cycle 9 (Adjuvant Treatment Phase) until resolution or if the subject initiates new anticancer therapy, whichever is earlier.

Trial Period:	Screening Phase	Neoadjuvant Treatment Phase[a]									30 Day Safety Follow-up[b]	Definitive Surgery	30 Day Safety Follow-Up (Post Definitive Surgery)[b]	Adjuvant Treatment Phase[a]	30 Day Safety Follow-Up[b]	Early Discon Visit[c]	Long-term Follow-up[d]	Survival Follow-up
		Treatment 1 (Paclitaxel/Carboplatin)					Treatment 2 (AC or EC)											
Treatment Cycle:	Screening	C1 D1	C1 D8	C1 D15	C2-C4 D1	C2-C4 D8, D15	C1 D1	C2 D1	C3 D1	C4 D1				C1-C9 D1				
Scheduling Window (Days)	-28 to -1	+3	±2	±2	±2	±2	±3	±3	±3	±3	±3	Surgery	±3	±3	±3		± 1 month	± 1 month

m. After Treatment 1 Cycle 4, and prior to dosing the subject with AC or EC (Treatment 2, Cycle 1), the 12-lead ECG and MUGA/ECHO must be performed to ensure adequate cardiac function.

n. 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 during treatment cycle.

o. ECOG performance status 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 30-Day follow-up visits, and at the Early Discontinuation visit and in the Long-term Follow-Up visits for the first 2 years.

p. 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. Monthly pregnancy testing should be conducted as per local regulations where applicable.

q. Blood for menopausal status may be required for certain subjects as described in Section 7.1.3.3 – Menopausal Status.

r. The electronic Patient Reported Outcomes (ePROs) include EORTC QLQ-C30, EORTC QLQ-BR23, and EQ-5D™. During Long-term Follow-Up, ePROs should be performed every 12 months for 2 years, or until disease progression/recurrence, whichever is earlier.

s. Coagulation factors (PT/INR and aPTT/PTT) should be tested within 10 days of treatment initiation and at the time points specified. Additional testing to be conducted as clinically indicated for subjects taking anticoagulant therapy.

t. After Treatment 1 Cycle 1, pre-dose lab samples can be collected up to 72 hours prior to the scheduled time point.

u. Screening laboratory samples will be collected within 10 days prior to study treatment initiation.

v. 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.

w. The Breast MRI study is optional. A breast MRI will be obtained at screening, during Cycle 4 of Treatment 1 of the Neoadjuvant Treatment Phase (before Neoadjuvant Treatment Phase, Treatment 2 Cycle 1, Day 1), and during Cycle 4 of Treatment 2 of the Neoadjuvant Treatment Phase (before definitive surgery) for subjects who have chosen to participate.

x. Assessment includes (per local or institutional guidelines): disease progression that precludes definitive surgery, local or distant recurrence, development of a second primary malignancy, or death. Results are to be recorded in the electronic data capture (EDC) system. Upon Sponsor notification, all subjects who do not/will not have a scheduled study visit or study contact during the Sponsor-defined time period will be contacted for their disease status.

y. Blood for exploratory biomarkers (plasma, serum) is to be collected at pre-dose on Day 1 of Cycles 1, 2 and 3 of Treatment 1 (paclitaxel/carboplatin), and Day 1 of Cycle 1 of Treatment 2 (AC/EC), and at Early Discontinuation visit. See Laboratory Manual. Any leftover samples from the blood studies will be stored for future biomedical research, if the subject signs the FBR consent.

Trial Period:	Screening Phase	Neoadjuvant Treatment Phase[a]									30 Day Safety Follow-up[b]	Definitive Surgery	30 Day Safety Follow-Up (Post Definitive Surgery)[b]	Adjuvant Treatment Phase[a]	30 Day Safety Follow-Up[b]	Early Discon Visit[c]	Long-term Follow-up[d]	Survival Follow-up
		Treatment 1 (Paclitaxel/Carboplatin)					Treatment 2 (AC or EC)											
Treatment Cycle:	Screening	C1 D1	C1 D8	C1 D15	C2-C4 D1	C2-C4 D8, D15	C1 D1	C2 D1	C3 D1	C4 D1				C1-C9 D1				
Scheduling Window (Days)	-28 to -1	+3	±2	±2	±2	±2	±3	±3	±3	±3	±3	Surgery	±3	±3	±3		± 1 month	± 1 month

z. Blood for RNA Analyses should be collected at pre-dose on Day 1 of Cycles 1, 2, and 3 of Treatment 1 (paclitaxel/carboplatin), pre-dose on Day 1 of Cycles 1 and 4 of Treatment 2 (AC/EC), and at the Early Discontinuation visit. See Laboratory Manual. Any leftover samples from the blood studies will be stored for future biomedical research, if the subject signs the FBR consent.

aa. This sample should be drawn for planned analysis of the association between genetic variants in DNA and drug response. Refer to Section 7.1.3.7 for additional information.

bb. For subjects with adequate tumor volume left at the end of the Neoadjuvant Treatment Phase, Treatment 1 Cycle 4, as assessed by the investigator, an optional core needle biopsy will be performed only on subjects who are willing to participate.

cc. An optional tumor tissue sample will also be collected at definitive surgery for subjects who have not achieved a pathological complete response (pCR); tumor tissue collected at definitive surgery will be stored for FBR, if the subject consents.

dd. Optional, if recurrence.

ee. During screening, formalin-fixed paraffin-embedded (FFPE) tumor tissue samples or slides obtained at subject's initial diagnosis maybe submitted to a designated central laboratory for confirmation of subject's TNBC status, only if a new biopsy cannot be obtained due to site inaccessibility or a medical contraindication. Sponsor agreement is required for FFPE tumor tissue sample or slides that were obtained greater than 30 days prior to the date that the informed consent was signed.

ff. Detailed pathological staging of all tumor tissue collected during definitive surgery for determination of pCR.

gg. Adjuvant pembrolizumab or placebo may be started either concurrently with radiation therapy or 2 weeks post-radiation therapy.

hh. Cortisol to be determined in the morning.

ii. Troponin (I or T) and BNP to be measured at screening and then prior to surgery.

jj. Samples for CBC with differential, chemistry panel, and urinalysis do not need to be collected if the safety follow-up visit occurred within 14 days of definitive surgery.

kk. The 12-lead ECG and MUGA or ECHO (using the same method throughout the study) must be performed in the 30- days safety follow- up visit after completion of neoadjuvant treatment or before surgery (if scheduled earlier) in the frame of cardiac risk assessment prior to surgery, prior to dosing in Cycle 4 and Cycle 8 of the adjuvant treatment phase, and at either the 30-day follow- up visit after adjuvant or at discontinuation visit (whichever occurs first) to ensure adequate cardiac function. Additional assessments to be performed as clinically indicated.

6.1 Pharmacokinetic Evaluations

Trial Period:	**Screening Phase**	**Neoadjuvant Treatment Phase**																**30 Day Safety Follow-up[a]**	**Early Discon Visit[b]**
		Treatment 1 (Paclitaxel/Carboplatin)												**Treatment 2 (AC or EC)**					
Treatment Cycle:	Screening	C1D1	C1 D8	C1 D15	C2 D1	C2 D8	C2 D15	C3 D1	C3 D8	C3 D15	C4 D1	C4 D8	C4 D15	C1 D1	C2 D1	C3 D1	C4 D1		
Scheduling Window (Days)	-28 to -1	+3	±2	±2	±2	±2	±2	±2	±2	±2	±2	±2	±2	±3	±3	±3	±3	±3	
Pembrolizumab PK and ADA[c]		X			X						X			X	X		X	X	X

ADA = Anti-Drug Antibody; PK = Pharmacokinetics

Note: The Japanese subjects participating in the PK study will continue to have PK/ADA collected until all scheduled samples have been collected.

a. The 30-Day Safety Follow-Up visit should be performed after the Neoadjuvant Treatment Phase.

b. The Early Discontinuation Visit should be conducted if subject discontinues all protocol-specified treatment after Treatment 1 Cycle 1 through the Adjuvant Treatment Phase. Every attempt should be made to have an Early Discontinuation visit during the Long-term Follow-Up phase of the study for subjects who discontinue before the next protocol-specified visit.

c. Pre-dose trough PK samples will be collected within 24 hours before infusion of study treatment on Day 1 of Cycles 1, 2, 4 of Treatment 1 and Treatment 2 of the Neoadjuvant Treatment Phase. Trough PK samples will also be collected at discontinuation of pembrolizumab/placebo and 30 days after discontinuation of pembrolizumab/placebo (see Section 7.1.3.2 – Pharmacokinetic Evaluations).

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. If there are changes to the subject's status during the trial (e.g., health or age of majority requirements), the investigator or qualified designee must ensure the appropriate consent is in place.

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. At the time of treatment allocation/randomization, site personnel will add the treatment/randomization number to the Subject Identification Card.

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 a separate Electronic Case Report Form (eCRF), see Section 7.1.1.4.1 – Disease Details for further instructions.

7.1.1.4.1 Disease Details

Details regarding subject's TNBC diagnosis 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 (ie, single lesion, multi-centric, multifocal), TNM staging at baseline, primary and sentinel lymph node biopsies and results, etc. Refer to Section 5.1 – Entry Criteria to ensure subject's disease status meets the relevant inclusion and exclusion criteria for study entry.

7.1.1.4.1.1 Management of the Axilla

The management of axillary adenopathy will be performed as shown in Table 7.

Table 7 Management of Axillary Adenopathy

cN Status	Surgical Approach
cN0	SLNB after NACT preferred to optimally assess pCR, but SLNB (pre NACT allowed)
cN0 and SLNB negative prior to NACT	No further treatment required post NACT
cN0 and SLNB positive prior to NACT	ALND post NACT
cN0 and SLNB negative post NACT	No further treatment required
cN0 and SLNB positive post NACT	ALND
cN+	If ycN0 after NACT SLNB or ALND allowed
	If yCN+ after NACT ⟹ ALND

Abbreviations: ALND = Axillary lymph node dissection; cN+= Palpable and/or sonographically suspicious lymph nodes; cN0 = Node-negative disease; NACT = neoadjuvant chemotherapy; pCR = pathological complete response; SLNB = sentinel-lymph-node biopsy, yCN0= node-negative disease after chemotherapy.

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 7.1.3.3 – Menopausal Status.

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 screening visit.

7.1.1.5.2 Concomitant Medications

The investigator or qualified designee will record all concomitant medication, if any, taken by the subject within 30 days before the first dose of trial treatment through the Adjuvant Treatment Phase Safety Follow-up Visit. All medications related to reportable AEs, SAEs and ECIs, including AEs and SAEs following the Adjuvant Treatment Phase, 30-day Safety Follow-up Visit, and Early Discontinuation visit should be recorded as defined in Section 7.2 – Assessing and Recording Adverse Events.

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 – Screening.

7.1.1.7 Assignment of Treatment/Randomization Number

All eligible subjects will be randomly allocated and will receive a treatment/randomization number. The treatment/randomization number identifies the subject for all procedures occurring after treatment allocation/randomization. Once a treatment/randomization 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/randomization number.

Study treatment should begin on the day of randomization or, at most, within 3 days post randomization.

7.1.1.8 Trial Compliance (Medication)

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 monitored by the investigator and/or trial staff. The total volume of pembrolizumab alone and/or combination product infused will be compared to the total volume prepared to determine compliance with each dose of pembrolizumab and/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: paclitaxel; carboplatin; doxorubicin (or epirubicin); and cyclophosphamide. Normal saline will be substituted for pembrolizumab in Arm 2.

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 Appendix 12.4). 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 or placebo all AEs of unknown etiology associated with pembrolizumab exposure should be evaluated to determine if it is possibly an irAEs.

Any AE, either directly or indirectly related to surgery or the medication required to perform surgery and its sequelae should be reported.

Please refer to Section 7.2 – Assessing and Recording Adverse Events for detailed information regarding the assessment and recording of AEs.

7.1.2.2 Cardiac Evaluation

Subjects must meet pre-specified LVEF requirements to be eligible for the study (Section 5.1). Cardiac function should be monitored during the neoadjuvant period, prior to surgery, and during the adjuvant period by 12-lead electrocardiogram (ECG), LVEF monitoring (MUGA or ECHO), and/or laboratory evaluation of troponin (I or T) and brain natriuretic peptide (BNP), as specified in the SoA (Section 6.0); additional cardiac assessments should be performed as clinically indicated. Special attention to cardiac function should be given prior to surgery. Increased vigilance is recommended for subjects with risk factors for cardiovascular disease, such as hypertension, diabetes, obesity, smoking history and past cardiac history, and for subjects who are ≥60 years old. If cardiac monitoring reveals an LVEF drop to <50%, LVEF should be reassessed after 3 weeks, or sooner if so required by institutional guidelines. If repeat testing confirms a significant LVEF drop, study treatment (including surgery) should be withheld, a cardiology consultation should be obtained and therapy for left ventricular dysfunction should be instituted as indicated. In such cases, cardiac clearance should be obtained prior to resumption of study treatment or surgery.

7.1.2.3 Physical Examination

7.1.2.3.1 Full Physical Examination

The investigator or qualified clinical designee will perform a complete physical examination during the screening period. Clinically significant abnormal findings should be recorded as medical history. Post randomization, full physical examinations should be performed at the discretion of the physician according to the subject's signs and symptoms.

7.1.2.3.2 Directed Physical Examination

The investigator or qualified clinical designee will perform directed physical examinations to assess subject's TNBC status according to the time points as specified in Section 6.0 – Trial Flow Chart as needed according to subject's signs and symptoms. New clinically significant abnormal findings should be recorded as AEs.

7.1.2.4 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 the 30-Day Safety Follow-Up visits, at Early Discontinuation and Long-term Follow-Up visits as specified in Section 6.0 – 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.

7.1.2.5 Eastern Cooperative Oncology Group Performance Status

The investigator or qualified clinical designee will assess ECOG performance status (Section 6.0 – Trial Flow Chart and Appendix 12.3 – ECOG Performance Status Scale) at screening, prior to dosing on Day 1 of each treatment cycle, at the 30-Day Safety Follow-Up visits, Early Discontinuation visit and Long-term Follow-up visits as specified in Section 6.0 – Trial Flow Chart.

7.1.2.6 Patient Reported Outcomes

The electronic Patient Reported Outcomes (ePROs) EORTC QLQ-C30, EORTC QLQ-BR23, and EQ-5D™ questionnaires will be administered by trained study site personnel and completed electronically by the subjects themselves.

It is strongly recommended that ePROs are administered prior to administration of study medication, adverse event evaluation, and disease status notification. The ePROs are completed in the following order: EQ-5D™, then EORTC QLQ-C30, and last the EORTC Breast Cancer–Specific Quality of Life Questionnaire (EORTC QLQ-BR23) at the time points specified in Section 6.0 – Trial Flow Chart.

The ePROs are administered as follows:

- Neoadjuvant Treatment Phase
  - On Day 1 of Cycle 1 of Treatment 1
  - On Day 1 of Cycles 1 and 4 of Treatment 2
- Adjuvant Treatment Phase
  - On Day 1 of Cycles 1, 5, and 9
- At the Early Discontinuation Visit
- Long-term Follow-up Visits, ePROs will occur every 12 months for 2 years or until PD, whichever is earlier.

7.1.2.7 Tumor Tissue Biopsy and Sample Collection

In accordance with the study inclusion criteria, subjects with locally advanced TNBC are required to have a core needle biopsy consisting of at least 2 separate tumor cores, utilizing multiple passes (fine needle aspirate not adequate) performed during the Screening Period for confirmation of TNBC by a central lab.

During screening, FFPE tumor tissue samples or slides obtained at the subject's initial diagnosis maybe submitted to a designated central laboratory for confirmation of the subject's TNBC status, only if a new biopsy cannot be obtained due to site inaccessibility or a medical contraindication. Note: Sponsor agreement is required for FFPE tumor tissue sample or slides that were obtained greater than 30 days prior to the date that the informed consent was signed.

For subjects with adequate tumor volume left at the end of the Neoadjuvant Treatment Phase, Treatment 1 Cycle 4, as assessed by the investigator, an optional 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 – Planned Exploratory Biomarker Research.

Tumor tissue samples will also be collected at definitive surgery for subjects who have not achieved a pCR, this is optional for subjects who choose to participate.

A final and optional biopsy will also be performed at the time of recurrence, if applicable, for subjects who agree to participate. 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 – Future Biomedical Research.

Biopsies should be obtained and prepared according to the instructions outlined in the Laboratory Manual for this trial. If feasible, at least two separate core biopsies should be obtained at each of the additional time points. These tumor tissues will be submitted to the designated central laboratory.

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

7.1.2.8 Imaging Disease Assessment

Subjects must have evidence of M0 disease 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.

Imaging (eg, CT, MRI, Bone Scan) will be performed at the discretion of the investigator, as per the local institution's standard of care. Disease assessment will be performed per RECIST 1.1, if applicable, and data recorded on the appropriate eCRF.

7.1.2.8.1 Breast Magnetic Resonance Imaging

Breast MRI will be performed in a subset of approximately 150 subjects with locally advanced TNBC who choose to participate 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 – Subject Inclusion Criteria).

If a subject has consented to participating in the Breast MRI, an MRI should be scheduled for three time points:

- At Screening (prior to first dose of study drug),
- During Cycle 4 of Treatment 1 of the Neoadjuvant Treatment Phase (before Neoadjuvant Treatment Phase Treatment 2 Cycle 1, Day 1), and

- During Cycle 4 of Treatment 2 of the Neoadjuvant Treatment Phase (before definitive surgery).

Changes in the MRI from the baseline will be assessed by the investigator per RECIST 1.1 (See Appendix 12.5).

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.

Breast MRI images will be sent to a designated central vendor for collection, quality review, and independent imaging review.

Central imaging vendor will be used to determine from the FTV from dynamic contrast-enhanced (DCE) MRI images of the breast. The SER breast MRI protocol was based on technique developed at UCSF and used in the ACRIN 6657 multi-center clinical trial [67].

7.1.2.9 Definitive Surgery

Approximately 3-6 weeks following completion of the Neoadjuvant Treatment Phase or Early Discontinuation, subjects will undergo definitive surgery per local standard of care. Details regarding date of surgery, type of surgery, tumor resectability etc. will be recorded in the appropriate eCRF. Detailed pathological staging per current AJCC staging criteria and assessment of surgical margins will be performed by the local pathologist on all the tissues removed during the surgery and recorded in the appropriate eCRF.

All pathologists reviewing and interpreting surgical specimens for assessment of pCR are required to be blinded to treatment assignment. Details on management of axillary adenopathy are provided in Table 7.

All trial pathologists will be required to complete formal training. A pathology guidance document will be provided outlining standard guidelines for localization of tumor bed, handling of lymph nodes and pathological evaluation of specimens. Regional pathologist(s) will be available to serve as an adjudicator or consultant for cases for in which the site pathologist is uncertain of pCR outcome.

For subjects who did not achieve a pCR, optional tumor tissue samples should be collected and submitted to the designated central laboratory for translational research as specified in Section 4.2.3.3 – Planned Exploratory Biomarker Research. 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 – Future Biomedical Research.

7.1.2.10 Determination of Disease Progression

7.1.2.10.1 Assessment of PD – MRI Substudy

For the individuals who choose to participate to receive the Breast MRIs at the protocol-specific time points, a measurement of the baseline lesions, changes from the baseline, and

objective response will be assessed by the investigator per RECIST 1.1. Central confirmation assessment of CR or PR will not be obtained.

Imaging assessments for recurrent or metastatic disease will be at the discretion of the subject's treating physician, per local standard of care, or at the time of symptoms except for subjects participating in the MRI substudy. For subjects who recur after completing therapy, Sponsor will collect on the appropriate eCRFs any new therapies started at the time of subject's recurrence. The Sponsor may also request images from the imaging assessments to be sent for independent imaging review; and may request for tumor tissue (if subject signs a consent form) to be sent to the central lab for future testing.

7.1.2.10.2 Determination of PD During the Neoadjuvant Period

Immunotherapeutic agents such as pembrolizumab may produce anti-tumor effects by potentiating endogenous cancer-specific immune responses. The response patterns seen with such an approach may extend beyond the typical time course of responses seen with cytotoxic agents, and can manifest as a clinical response after an initial increase in tumor burden or even the appearance of new lesions.

If physical examination shows PD during the neoadjuvant period, the disease should be evaluated by radiologic imaging. Tumor assessment by imaging may be repeated by the site ≥4 weeks later in order to confirm PD with the option of continuing treatment as per protocol while awaiting radiographic confirmation of progression. If repeat imaging shows a reduction in the tumor burden compared to the initial imaging assessment demonstrating PD, study treatment may be continued at the investigator's discretion. If repeat imaging confirms PD, the subject is to be discontinued from study treatment (Section 7.1) and subsequent treatment options are at the investigator's discretion. The disease can also be confirmed histologically, cytologically, or surgically. In cases where discordant results regarding PD are obtained by physical examination, imaging, biopsy, and/or surgery, surgical results will overrule those obtained from biopsy, imaging, and physical examination (in the hierarchy defined here). The date of progression in these cases will be backdated to the earliest date when progression was objectively diagnosed. If subjects have surgery, all surgical data will be collected independent of whether surgery was considered definitive or not.

7.1.2.10.3 Determination of Recurrence During and Following the Adjuvant Period

The diagnosis of breast cancer recurrence should be based on radiologic evidence while histological or cytological confirmation should be obtained whenever possible. In cases where discordant results regarding recurrence are obtained by physical examination, imaging, biopsy, and/or surgery, surgical results will overrule those obtained from biopsy, imaging, and physical examination (in the hierarchy defined here). The recurrence of the disease should be backdated to the earliest date when recurrence was objectively diagnosed and not to the date of occurrence of the first symptom(s) (if there are any).

For subjects who recur after completing therapy, any new therapies started at the time of subject's recurrence will be collected on the appropriate eCRFs. The Sponsor may also request images from the imaging assessments be sent for independent imaging review; and may request tumor tissue (if the subject signs a consent form) be sent to the central laboratory for future testing.

7.1.2.10.4 Determination of Secondary Primary Malignancy

The diagnosis of a second primary cancer must be confirmed by biopsy (or by cytology). If a biopsy cannot be performed, the second primary malignancy must be confirmed by 2 radiological imaging assessments obtained at least 4 weeks apart. All second primary malignancies are to be reported whenever they occur during the study time period. Subjects diagnosed with a second primary malignancy, but with no evidence of breast cancer recurrence, will remain on study and continue on study treatment, if the investigator considers this to be in the best interest of the subject. The secondary primary malignancy, once confirmed, should be dated based on the confirmatory histological assessment and not to the date of occurrence of the first symptom(s) (if there are any).

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 screening to post-treatment-discontinuation visits), including approximate blood/tissue volumes drawn/collected by visit and by sample type per subject can be found in Laboratory Manual.

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

Laboratory tests for hematology, chemistry and urinalysis to be performed locally are specified in Table 8.

Table 8 Laboratory Tests

Hematology	Chemistry	Urinalysis	Other
Hematocrit	Albumin	Blood	Serum β-human Chorionic Gonadotropin (β-hCG)[a]
Hemoglobin	Alkaline Phosphatase	Glucose	PT (INR)[b]
Platelet Count	Alanine Aminotransferase (ALT)	Protein	aPTT/PTT[b]
White Blood Cell - WBC (total and differential)	Aspartate Aminotransferase (AST)	Specific Gravity	Total Triiodothyronine (T3)[c]
Red Blood Cell Count	Carbon Dioxide (CO_2 or Bicarbonate)[d]	Microscopic exam, if abnormal results are noted	Free Thyroxine (FT4)
Absolute Neutrophil Count	Calcium	Urine Pregnancy Test[a]	Thyroid Stimulating Hormone (TSH)
Absolute Lymphocyte Count	Chloride		FSH, Estradiol[e]
	Creatinine or Creatinine clearance (CrCl)		Blood for pharmacokinetics (PK) and anti-drug antibody (ADA)[f]
	Glucose		
	Lactate Dehydrogenase (LDH)		
	Phosphorus		
	Potassium		
	Sodium		
	Total Bilirubin		
	Direct Bilirubin, if Total Bilirubin is elevated above the upper limit of normal		
	Total Protein		
	Blood Urea Nitrogen or Urea[g]		
	Uric Acid		
	Cortisol[h]		
	Troponin[i]		
	BNP[i]		

a. 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. The serum or urine pregnancy test should be performed within 72 hours prior to first dose of trial treatment
b. Coagulation factors (PT/INR and aPTT/PTT) should be tested as part of the screening procedures and at the time points specified in the Trial Flow Chart (Section 6.0). Additional testing to be conducted as clinically indicated for subjects taking anticoagulant therapy.
c. Total T3 is preferred; if not available free T3 may be tested.
d. 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.
e. Blood for menopausal status is only required for some subjects as described in Section 7.1.3.3 – Menopausal Status.
f. Blood for PK will be performed on Japanese subjects and a subset of non-Japanese subjects, who choose to participate in the PK study.
g. Blood urea nitrogen is preferred; if not available urea may be tested.
h. Cortisol is to be determined in the morning at screening.
i. Troponin and BNP measured at screening and then as indicated in the Trial Flow Chart (Section 6.0).

Laboratory tests for screening should be performed within 10 days of treatment initiation. A serum or urine pregnancy test should be performed within 72 hours prior to first dose of trial treatment. After the Neoadjuvant Treatment Phase, Treatment 1 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.

Coagulation factors (prothrombin time [PT]/International Normalized Ratio [INR] and activated partial thromboplastin time [aPTT]/partial thromboplastin time [PTT]) should be tested for subjects with locally advanced TNBC at baseline and at the time points specified in the Trial Flow Chart. Additional testing to be conducted as clinically indicated for subjects taking anticoagulant therapy.

7.1.3.2 Pharmacokinetic Evaluations

The accumulation of robust PK and ADA data has allowed for the adequate characterization of the clinical pharmacology of pembrolizumab across indications. The collection of PK and ADA samples in no longer required. Blood samples for PK and ADA collected prior to Amendment 02 may be stored. Analysis will be performed only if required.

Note: The Japanese subjects participating in the PK study will continue to have PK/ADA collected until all scheduled samples have been collected (Section 6.1).

7.1.3.3 Menopausal Status

The menopausal status (pre- or post-menopausal) for women with locally advanced TNBC 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.

7.1.3.4 Pregnancy Test

For women of reproductive 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 should be repeated if required by local guidelines.

7.1.3.5 Male Sterility

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

7.1.3.6 Blood Collections Samples for Exploratory Biomarker and RNA Analyses

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

7.1.3.7 Planned Genetic Analysis Sample Collection

Sample collection, storage and shipment instructions for Planned Genetic Analysis samples will be provided in the Laboratory Manual. Samples should be collected for planned analysis of associations between genetic variants in germline/tumor DNA and drug response. If a documented law or regulation prohibits (or local IRB/IEC does not approve) sample collection for these purposes, then such samples should not be collected at the corresponding sites. Leftover DNA extracted from planned genetic analysis samples will be stored for future biomedical research only if subject signs the FBR consent.

7.1.3.8 Future Biomedical Research Samples

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 RNA
- Leftover plasma and serum from exploratory biomarker studies

7.1.4 Other Procedures

7.1.4.1 Withdrawal/Discontinuation

Subjects who discontinue 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 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. 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@MSD.com). Subsequently, the subject's consent for Future Biomedical Research will be withdrawn. A letter will be sent from the Sponsor to the investigator confirming the withdrawal. It is the responsibility of the investigator to inform the subject of completion of withdrawal. Any analyses in progress at the time of request for withdrawal 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 withdrawal cannot be processed.

7.1.4.2 Subject Blinding/Unblinding

STUDY TREATMENT IDENTIFICATION INFORMATION IS TO BE UNMASKED ONLY IF NECESSARY FOR THE WELFARE OF THE PARTICIPANT. EVERY EFFORT SHOULD BE MADE NOT TO UNBLIND.

For emergency situations where the investigator or delegate needs to identify the drug used by a subject and/or the dosage administered, he/she will contact the emergency unblinding call center by telephone and make a request for emergency unblinding. As requested by the investigator or delegate the emergency unblinding call center will provide the information to him/her promptly and report unblinding to the sponsor. Prior to contacting the emergency unblinding call center to request unblinding of a subject’s treatment assignment, the investigator or delegate must enter the toxicity grade of the adverse experiences observed, the relation to study drug, the reason thereof, etc., in the medical chart etc.

For studies that require non-emergency unblinding as part of the study design (eg, disease progression) to support treatment decisions, instructions in Section 7.1.4.2 should be followed. The emergency unblinding center should not be used for this purpose.

Subjects whose treatment assignment has been unblinded by the investigator/delegate and/or non-study treating physician should continue to be monitored in the trial.

Additionally, the investigator must go into the IVRS system and perform the unblind in the IVRS system to update drug disposition. In the event that the emergency unblinding call center is not available for a given site in this trial, IVRS/IWRS should be used for emergency unblinding in the event that this is required for subject safety.

Treatment identification information is to be unmasked ONLY if necessary for the welfare of the subject. Every effort should be made not to unblind the subject unless necessary.

In the event that unblinding has occurred, the circumstances around the unblinding (e.g., date, reason and person performing the unblinding) must be documented promptly, and the Sponsor Clinical Director notified as soon as possible. Once an emergency unblinding has taken place, the principal investigator, site personnel, and Sponsor personnel may be unblinded so that the appropriate follow-up medical care can be provided to the subject.

An End of Treatment and Unblinding call will be performed in IVRS/IWRS.

Discontinuation of treatment and subsequent unblinding due to disease progression, as described above, does not represent withdrawal from the trial.

7.1.4.2.1 Non-Emergency Unblinding

In case of PD or recurrence as assessed by the investigator; the investigator may choose to end the protocol-specified treatment, unblind the subject, and begin treatment with a regimen other than those components used in this protocol. In this circumstance, unblinding to pembrolizumab versus placebo administration may occur on an individual basis and only after consultation with the Clinical Director. Every effort should be made not to unblind the subject unless necessary.

7.1.4.3 Calibration of Equipment

The investigator or qualified designee has the responsibility to ensure that any device or instrument used for a clinical evaluation/test during a clinical trial that provides information about inclusion/exclusion criteria and/or safety or efficacy parameters shall be suitably calibrated and/or 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.

7.1.5 Visit Requirements

7.1.5.1 Screening

Approximately 28 days prior to treatment allocation/randomization, 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/randomization except for the following:

- Laboratory tests and ECOG performance status 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 receiving the first dose of study medication.

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 the Neoadjuvant Treatment Phase, Cycles 1-4 where 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 ± 2 days for Cycle 1 Day 8-Cycle 4 Day 15 of the Neoadjuvant Treatment Phase (Treatment 1: paclitaxel and carboplatin regimen) and ± 3 days for Cycle 1-4 of the Neoadjuvant Treatment Phase (Treatment 2: AC or EC regimen) and Cycle 1-9 of the Adjuvant Treatment Phase, unless otherwise noted. The first Cycle 1 treatment should be no more than 3 days after treatment allocation/randomization.

In the Neoadjuvant Treatment Phase, there are 2 treatment parts: Treatment 1 (pembrolizumab + paclitaxel/carboplatin or placebo + paclitaxel/carboplatin) and Treatment 2 (pembrolizumab + AC or EC, or placebo + AC or EC). Post-definitive surgery, the following treatment (Adjuvant Treatment Phase) will be given: pembrolizumab or placebo, as assigned during allocation/randomization. No crossover from placebo to pembrolizumab will be permitted.

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.

7.1.5.2.1 Neoadjuvant Treatment Phase

Visit timing requirements during the Neoadjuvant Treatment Phase are as follows:

- Assessments/procedures are performed on Day 1 of each cycle prior to dosing of any study treatment (or prior to weekly dosing of paclitaxel), unless otherwise specified.
- Each treatment cycle is 3 weeks (21 days).
- If the treatment is delayed, all procedures should be performed based on the new dosing schedule.

7.1.5.2.2 Adjuvant Treatment Phase

The Adjuvant Treatment Phase is expected to start 30 to 60 days after definitive surgery and if performed outside of this window, Sponsor consultation will be required. If the subject is found to have disease progression prior to surgery, they will not proceed to the adjuvant treatment phase.

If post-operative radiation therapy is indicated, adjuvant pembrolizumab or placebo may be started either concurrently with radiation therapy or 2 weeks post-radiation therapy.

7.1.5.3 Definitive Surgery

Definitive surgery either with BCS or mastectomy with or without axillary lymph node dissection will be performed per local standard of care approximately 3-6 weeks following discontinuation or completion of study treatment in the Neoadjuvant Treatment Phase. See Table 7 for guidance regarding axilla lymph node management.

Post-operative radiation therapy is acceptable according to the applicable standard of care, eg, in cases of BCS, large primary tumor, some positive lymph node disease.

7.1.5.4 Post-Treatment Visits

7.1.5.4.1 Early Discontinuation Visit

The Early Discontinuation Visit should be conducted if subject discontinues all protocol-specified treatment after Treatment 1 Cycle 1 through the Adjuvant Treatment Phase. If the Discontinuation Visit occurs 30 days from the last dose of study treatment, at the time of the mandatory Safety Follow-Up Visit, procedures listed in the Early Discontinuation should be performed. Complete the appropriate Early Discontinuation Visit electronic Case Report Forms (eCRFs).

Every attempt should be made to have an Early Discontinuation visit during the Long-term Follow-Up phase of the study for subjects who discontinue before the next protocol-specified visit. 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 – Subject Withdrawal/Discontinuation Criteria.

7.1.5.4.2 Safety Follow-up Visits

Mandatory Safety Follow-up Visits should be conducted approximately 30 days (±3 days) following end of the Neoadjuvant Treatment Phase, Definitive Surgery, and Adjuvant Treatment Phase. If surgery is scheduled to occur less than 30 days after the end of Neoadjuvant Treatment Phase, the Safety Follow-up Visit should occur before surgery. If an Early Discontinuation visit occurs, then every attempt should be made to perform a 30-Day Safety Follow-Up visit (30 days ± 3 days).

All AEs that occur prior to the Safety Follow-up Visit should be recorded. Subjects with an AE Grade >1 will be followed until resolution of the AE to Grade 0-1. All SAEs 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 Long-term Follow-up for Disease Status and Survival

Neoadjuvant Treatment Phase

Subjects who discontinue study treatment during the neoadjuvant period for any reason other than disease progression that precludes definitive surgery (which refers to either local and/or distant disease progression) will enter the long-term follow-up Phase and should be assessed for pCR and disease progression/recurrence. Long-term follow-up visits will be scheduled to occur at 3-month intervals (± 1 month) from the date of randomization for the first 2 years, then at 6-month intervals (± 1 month) for Years 3 to 5, and annually thereafter until occurrence of local or/and distant disease progression/ recurrence, death, withdrawal of consent, or the end of the study, whichever occurs first.

Adjuvant Treatment Phase

Subjects who do not start adjuvant treatment after surgery, complete adjuvant study treatment, or discontinue adjuvant study treatment for any reason other than local or distant disease recurrence will enter the Long-term follow-up phase and should be assessed for disease recurrence. Long term follow-up visits will be scheduled to occur at 3-month intervals (± 1 month) from the date of randomization for the first 2 years, then at 6-month intervals (± 1 month) for Years 3 to 5, and annually thereafter until occurrence of local or/and distant recurrence, withdrawal of consent, or the end of the study, whichever occurs first.

Additional tests/investigations/imaging assessments for recurrent or metastatic disease (eg bone/liver scan) will be at the discretion of subject's treating physician per local standard of care or at the time of symptoms. The Section 6.0 – Trial Flow Chart summarizes the trial procedures to be performed at each visit.

At the time of recurrence, the Sponsor may request X-rays/computed tomography (CT)/MRI assessments to be sent for independent imaging review by a central vendor; and may request for tumor tissue (if subject signs a consent form) to be sent to the central lab for future testing.

ePROs will be collected every 12 months for the first 2 years or until progression/recurrence, whichever is earlier for all subjects who enter the Long-term Follow-up Phase.

If a subject does not return for protocol-specified visit assessments in the Long-term Follow-Up period, all attempts should be made to contact the subject via telephone for Survival Status every 6 months (± 1 month). If a subject ends treatment in the Neoadjuvant or Adjuvant Treatment Phases for disease progression, the subject should be followed every 6 months ± 1 month via telephone for Survival Status.

The subject will be contacted by the site to assess for disease and survival status until disease progression or death, withdrawal of consent for the trial, whichever comes first. Date 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.

7.1.5.4.4 Unscheduled Visit

Subjects who experience a toxicity that requires discontinuation of all components (ie, pembrolizumab + carboplatin + paclitaxel) of the Neoadjuvant Treatment Phase, Treatment 1 cycles (after Cycle 1 Day 1), the subject should be observed for recovery prior to initiation of the Neoadjuvant Treatment Phase, Treatment 2 cycles (ie, pembrolizumab (placebo) + doxorubicin (or epirubicin) + cyclophosphamide).

Results from assessments performed during the Unscheduled Visit are acceptable in lieu of repeating assessments during the Neoadjuvant Treatment Phase, Treatment 2 Cycle 1 Day 1 visit, if performed within 3 days prior to Treatment 2, Cycle 1 Day 1 dosing.

Toxicities requiring dose modifications are outlined in Section 5.2.1 – Dose Selection/Modification.

7.1.5.5 Survival Status

To ensure current and complete survival data is available at the time of database locks, updated disease and survival status may be requested during the course of the study by the Sponsor. For example, updated survival status may be requested prior to but not limited to an external DMC review, IA and/or FA. Upon Sponsor notification, all subjects who do not/will not have a scheduled study visit or study contact during the Sponsor-defined time period will be contacted for their disease and survival status.

7.1.5.6 Discontinued Subjects Continuing to be Monitored in the Trial

Subjects who discontinue treatment will be followed up by telephone every 6 months (±1 month) for OS until consent withdrawal from trial, becoming lost to follow-up, death or end of the study, whichever comes first.

Date of disease recurrence or metastatic progression, start and stop dates of subsequent anti-cancer treatments, and reasons for treatments should be recorded in the appropriate eCRF. For subjects who die during the follow-up period, the date and cause of death should be recorded in the appropriate eCRF.

7.1.6 Medical Resource Utilization and Health Economics

Medical resource utilization and health economics data, associated with medical encounters, will be collected in the CRF by the investigator and study-site personnel for all subjects throughout the study. Protocol-mandated procedures, tests, and encounters are excluded.

The data collected may be used to conduct exploratory economic analyses and will include:

- All-cause hospitalizations and emergency room visits, from the time of treatment allocation/randomization through 90 days following cessation of study treatment, or 30 days following cessation of study treatment, if the subject initiates new anticancer therapy, whichever is earlier.

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 cessation of treatment, all adverse events must be reported by the investigator. Such events will be recorded at each examination on the Adverse Event case report forms/worksheets. The reporting timeframe for adverse events meeting any serious criteria is described in section 7.2.3.1. 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 Electronic Data Capture (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 ≥1000 mg (5 times the dose) of pembrolizumab and as any dose ≥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 120 days following cessation of Sponsor's product, or 30 days following cessation of trial 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).

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 should be reported to the Sponsor.

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 9 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 cessation of trial treatment, or 30 days following cessation of trial treatment if the subject initiates new anticancer therapy, whichever is earlier, any serious adverse event, or follow up to a serious adverse event, including death due to any cause other than progression of the cancer under study (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).

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 9 Evaluating Adverse Events

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

V4.0 CTCAE Grading	**Grade 1**	**Mild; asymptomatic or mid symptoms; clinical or diagnostic observations only; intervention not indicated.**
	Grade 2	**Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL.**
	Grade 3	**Severe or medically significant but not immediately life-threatening; hospitalization or prolongation or hospitalization indicated; disabling; limiting self-care ADL.**
	Grade 4	**Life threatening consequences; urgent intervention indicated.**
	Grade 5	**Death related to AE**
Seriousness	A serious adverse event is any adverse event occurring at any dose or during any use of 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 an MSD 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 †).	
Duration	Record the start and stop dates of the adverse event. If less than 1 day, indicate the appropriate length of time and units	
Action taken	Did the adverse event cause the Sponsor's product to be discontinued?	
Relationship to Sponsor's Product	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. **The following components are to be used to assess the relationship between the Sponsor's product and the AE**; 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):	
	Exposure	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?
	Time Course	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)?
	Likely Cause	Is the AE not reasonably explained by another etiology such as underlying disease, other drug(s)/vaccine(s), or other host or environmental factors

Relationship to Sponsor's Product (continued)	**The following components are to be used to assess the relationship between the test drug and the AE: (continued)**	
	Dechallenge	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.)
	Rechallenge	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.
	Consistency with Trial Treatment Profile	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.		
Record one of the following	**Use the following scale of criteria as guidance (not all criteria must be present to be indicative of a Sponsor's product relationship).**	
Yes, there is a reasonable possibility of Sponsor's product relationship.	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.	
No, there is not a reasonable possibility of Sponsor's product relationship	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 Scientific Advisory Committee

This trial was developed in collaboration with a Scientific Advisory Committee (SAC). The SAC comprises both Sponsor and non-Sponsor scientific experts who provide input with respect to trial design, interpretation of trial results and subsequent peer-reviewed scientific publications.

7.3.2 Executive Oversight Committee

The Executive Oversight Committee (EOC) comprises members of Sponsor Senior Management. The EOC will receive and decide upon any recommendations made by the external DMC regarding the trial.

7.3.3 Data Monitoring Committee

To supplement the routine trial monitoring outlined in this protocol, an external Data Monitoring Committee (DMC) will monitor the interim data from this trial. The voting members of the committee are external to the Sponsor. The members of the DMC must not be involved with the trial in any other way (e.g., they cannot be trial investigators) and must have no competing interests that could affect their roles with respect to the trial.

The DMC will make recommendations to the EOC regarding steps to ensure both subject safety and the continued ethical integrity of the trial. Also, the DMC will review interim trial results, consider the overall risk and benefit to trial participants (see Section 8.7 - Interim Analyses) and recommend to the EOC if the trial should continue in accordance with the protocol.

Specific details regarding composition, responsibilities, and governance, including the roles and responsibilities of the various members and the Sponsor protocol team; meeting facilitation; the trial governance structure; and requirements for and proper documentation of DMC reports, minutes, and recommendations will be described in a separate charter that is reviewed and approved by the DMC. The DMC will monitor the trial at an appropriate frequency, as described in the detailed DMC charter. The DMC will also make recommendations to the Sponsor protocol team regarding steps to ensure both subject safety and the continued ethical integrity of the trial.

8.0 STATISTICAL ANALYSIS PLAN

This section outlines the statistical analysis strategy and procedures for the study. If, after the study has begun, changes are made to primary and/or key secondary hypotheses, or the statistical methods related to those hypotheses, then the protocol will be amended (consistent with ICH Guideline E-9). Changes to exploratory or other non-confirmatory analyses made

after the protocol has been finalized, but prior to the conduct of analysis, will be documented in a supplemental statistical analysis plan (sSAP) and referenced in the Clinical Study Report (CSR) for the study. A separate PK analysis and biomarker analysis plan may be provided. Post hoc exploratory analyses will be clearly identified in the CSR. The Patient Reported Outcomes (PRO) analysis plan will also be included in the sSAP.

8.1 Statistical Analysis Plan Summary

Key elements of the statistical analysis plan (SAP) are summarized below. The comprehensive plan is provided in Sections 8.2 – Responsibility for Analyses/In-House Blinding through 8.12 – Extent of Exposure.

Study Design Overview	A Phase III, Randomized, Double-blind Study to Evaluate Pembrolizumab plus Chemotherapy vs Placebo plus Chemotherapy as Neoadjuvant Therapy and Pembrolizumab vs Placebo as Adjuvant Therapy for Triple Negative Breast Cancer (TNBC)
Treatment Assignment	Approximately 1150 subjects will be randomized (double-blind) in a 2:1 ratio between 2 treatment arms: 1. Pembrolizumab plus chemotherapy as neoadjuvant therapy and pembrolizumab as adjuvant therapy, or 2. Placebo plus chemotherapy as neoadjuvant therapy and placebo as adjuvant therapy. Stratification factors are as follows: 1. Nodal status (Positive vs. Negative) 2. Tumor size (T1/T2 vs. T3/T4) 3. Choice of Carboplatin (Cb): Q3W vs. Weekly
Analysis Populations	Efficacy: Intention-to-Treat Population (ITT) Safety: All Subjects as Treated (ASaT)
Primary Endpoint(s)	1. Pathological complete response (pCR) rate (ypT0/Tis ypN0) 2. Event-free survival (EFS)
Key Secondary Endpoint(s)	Overall survival (OS)
Statistical Methods for Key Efficacy Analyses	• Treatment comparisons of the pCR rate (ypT0/Tis ypN0) will be performed using the stratified Miettinen and Nurminen method. • Treatment comparisons for time-to-event endpoints such as EFS and OS will be evaluated using a stratified log-rank test. The HR will be estimated using a stratified Cox model.
Statistical Methods for Key Safety Analyses	The analysis of safety will follow a tiered approach. There are no Tier 1 events for this study. Point estimates and 95% confidence intervals (CIs) for between-treatment comparisons via the Miettinen and Nurminen method will be provided for Tier 2 safety endpoints; only point estimates by treatment group will be provided for Tier 3 safety endpoints.

Interim Analyses	Seven efficacy interim analyses (IAs) are planned. Results will be reviewed by an external DMC. Details are provided in Section 8.7 – Interim Analyses. Efficacy Interim Analyses • IA 1 (IA1): at least 500 subjects have or would have completed surgery after ~6 months neoadjuvant treatment and enrollment is completed. It is estimated ~18 months after the first subject is randomized. o Primary purpose: interim pCR(ypT0/Tis ypN0) analysis. • IA 2 (IA2): ~24 months after the first subject is randomized (The timing of IA is calendar driven). It is estimated that ~93 EFS events will have been observed and ~1000 subjects have or would have completed surgery after ~6 months neoadjuvant treatment. o Primary purpose: interim EFS analysis and final pCR(ypT0/Tis ypN0) analysis. • IA 3 (IA3): ~36 months after the first subject is randomized (The timing of IA is calendar driven). It is estimated that ~154 EFS events will have been observed. o Primary purpose: interim EFS analysis. • IA 4 (IA4): ~48 months after the first subject is randomized (The timing of IA is calendar driven). It is estimated that ~201 EFS events will have been observed. o Primary purpose: interim EFS analysis. • IA 5 (IA5): ~60 months after the first subject is randomized (The timing of IA is calendar driven). It is estimated that ~239 EFS events will have been observed. o Primary purpose: interim EFS analysis. • IA 6 (IA6): ~72 months after the first subject is randomized (The timing of IA is calendar driven). It is estimated that ~270 EFS events will have been observed. o Primary purpose: interim EFS analysis. • IA 7 (IA7): ~84 months after the first subject is randomized (The timing of IA is calendar driven). It is estimated that ~294 EFS events will have been observed. o Primary purpose: interim EFS analysis. Final analysis (FA): ~327 EFS events have been observed (event driven). It is expected to occur at ~102 months after the first subject is randomized. o Primary purpose: final EFS analysis. OS will be tested only when the null hypothesis for EFS is rejected.
Multiplicity	The overall type-I error rate over the 2 primary endpoints will be strongly controlled at 2.5% (one-sided) with 0.5% allocated to the pCR (ypT0/Tis ypN0) and 2.0% allocated to the EFS hypotheses. The graphical approach of Maurer and Bretz [68] will be applied to re-allocate alpha among hypotheses for pCR(ypT0/Tis ypN0), EFS, and OS in subjects with locally advanced TNBC. Group sequential methods will be used to allocate alpha between the interim and final analyses for pCR(ypT0/Tis ypN0), EFS and OS in subjects with locally advanced TNBC.
Sample Size and Power	The FA of the study is EFS event-driven and will be conducted after approximately 327 EFS events have been observed. It may occur at ~102 months after the first subject randomized. The planned sample size is approximately **1150** subjects. (1) pCR (ypT0/Tis ypN0): the trial has an overall ~95% power to detect a true pCR rate difference of 15 percentage points (pembrolizumab + chemotherapy vs. placebo + chemotherapy) at alpha = 0.5% (one-sided) with ~1000 subjects who have or would have completed surgery after ~6 months neoadjuvant treatment at IA2. (2) EFS: the trial has an overall ~80% power at a one-sided 2.0% alpha level, if the true HR is 0.71. (3) OS: the trial has an overall ~79.7% power at a one-sided 2.0% alpha level, if the true HR is 0.70.

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.

The Sponsor will generate the randomized allocation schedule(s) for study treatment assignment for this protocol, and the randomization will be implemented in IVRS.

This study will be conducted as a double-blind trial under in-house blinding procedures. The official, final database will not be unblinded until medical/scientific review has been performed, protocol deviations have been identified, and data have been declared final and complete. In addition, the site radiologist(s) will perform the imaging review without knowledge of treatment group assignment.

All pathologists reviewing and interpreting surgical specimens for assessment of pCR are required to be blinded to treatment assignment.

Planned efficacy IAs are described in Section 8.7 – Interim Analyses. Blinding to treatment assignment will be maintained at all investigational sites.

Treatment-level results of the efficacy IAs will be provided by an external unblinded statistician to the external DMC.

The external DMC will serve as the primary reviewer of the results of the IAs and will make recommendations for discontinuation of the study or modification to an EOC of the Sponsor. Depending on the recommendation of the external DMC, the Sponsor may prepare a regulatory submission. Subject-level unblinding to support regulatory filing will be restricted to a designate team in the Sponsor, who will have no other responsibilities associated with the study.

If the external DMC recommends modifications to the design of the protocol or discontinuation of the study, this EOC may be unblinded to study results at the treatment level in order to act on these recommendations or facilitate regulatory filing. Limited additional Sponsor personnel may also be unblinded to the treatment level results of the IA(s), if required, in order to act on the recommendations of the external DMC or facilitate regulatory filing. The extent to which individuals are unblinded with respect to results of IAs will be documented. Additional logistical details, revisions to the above plan and data monitoring guidance will be provided in the external DMC Charter. Key aspects of the IAs are described in Section 8.7 – Interim Analyses.

Prior to final study unblinding, the external unblinded statistician will not be involved in any discussions regarding modifications to the protocol, statistical methods, identification of protocol deviations, or data validation efforts after the IAs.

8.3 Hypotheses/Estimation

Objectives and hypotheses of the study are stated in Section 3.0 – Objective(s) & Hypothesis(es).

8.4 Analysis Endpoints

Efficacy and safety endpoints that will be evaluated are listed below.

8.4.1 Efficacy Endpoints

Primary Endpoints

Pathological Complete Response (pCR) Rate (ypT0/Tis ypN0)

pCR rate (ypT0/Tis ypN0) is defined as the proportion of subjects without 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 per current AJCC staging criteria assessed by the local pathologist at the time of definitive surgery.

Subjects who don't receive any study medication and subjects who are discontinued from the study treatment and continue neoadjuvant treatment with drug categories not specified by the study prior to definitive surgery will be classified as not having a pCR (non-responders) in the efficacy analyses, regardless of the results obtained from the surgery. Subjects who are discontinued from study treatment due to the reasons that preclude definitive surgery (including the development of distant metastatic disease) are considered non-responders. Subjects without pCR data due to any reason will be counted as non-responders.

Event-Free Survival (EFS)

EFS is defined as the time from randomization to the first occurrence of any of the following events: progression of disease that precludes definitive surgery, local or distant recurrence, second primary malignancy or death due to any cause. Progression of disease, local or distant recurrence, and second primary malignancy are based on investigator determination. See Section 8.6.1 – Statistical Methods for Efficacy Analyses for the definition of censoring.

Subjects who had locoregional PD (as assessed radiologically) during the neoadjuvant treatment phase, but went to definitive surgery and had clear margins, will not be classified as having an EFS event. If the subject had pCR, then the PD will be considered pseudoprogression. Subjects who had locoregional PD (as assessed radiologically) during the neoadjuvant treatment phase, but went to surgery and ended up with positive margins at their last surgery, will be classified as having an EFS event at the time of diagnosis of locoregional PD. Subjects who had distant PD (metastasis, confirmed by biopsy or 2 imaging studies at least 4 weeks apart, if a biopsy is not feasible) during the neoadjuvant treatment phase had an EFS event at the time of diagnosis of distant PD, even if the subjects had palliative breast surgery. Subjects who did not have PD during the neoadjuvant treatment phase, but had positive margins at their last surgery, will be classified as having an EFS event at surgery. Subjects who had cytological, histological, and/or radiological evidence of local or distant recurrence during the adjuvant phase had an EFS event at the time recurrence was diagnosed.

In terms of second primary malignancy**,** any confirmed diagnosis of a second primary cancer other than basal or squamous cell carcinoma of the skin, carcinoma in situ of the cervix, or second primary breast will be considered an event in the analysis of the EFS. Lobular

carcinoma in situ of the breast (LCIS), ductal carcinoma in situ of the breast (DCIS) and myelodysplastic syndrome are not considered an event.

Secondary Endpoints

Pathological Complete Response (pCR) Rate (ypT0 ypN0)

pCR rate (ypT0 ypN0) is defined as the proportion of subjects without 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 per current AJCC staging criteria assessed by the local pathologist at the time of definitive surgery.

Pathological Complete Response (pCR) Rate (ypT0/Tis)

pCR rate (ypT0/Tis) is defined as the proportion of subjects without invasive cancer in the breast irrespective of ductal carcinoma in situ or nodal involvement following completion of neoadjuvant systemic therapy per current AJCC staging criteria assessed by the local pathologist at the time of definitive surgery.

Overall Survival (OS)

OS is defined as the time from randomization 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.

Exploratory Efficacy Endpoints

- ORR based on RECIST 1.1: the percentage of subjects who have achieved CR or PR according to RECIST 1.1 by central radiology review. Subjects with missing outcome for objective response will be considered non-responders. This will be applied to individuals who choose to participate in the breast MRI.
- Distant recurrence-free survival (DRFS): the time from definitive surgery to distance recurrence event as assessed by investigator.
- ORR based on MRI FTV: the percentage of subjects who have achieved CR or PR using MRI FTV as assessed by central radiology review.
- Residual Cancer Burden (RCB): residual disease in either the breast or lymph node at the time of definitive surgery as assessed by the local pathologist.
- The rate of pCR and EFS in subjects with different levels of TILs at baseline.

8.4.2 Safety Endpoints

Safety measurements are described in Section 4.2.3 – Rationale for Endpoints and Section 7.0 – Trial Procedures.

8.4.3 PRO Endpoints

- Health-related QoL assessments using the EORTC QLQ-C30 and EORTC QLQ-BR23
- Assessments using EQ-5D™

8.4.4 Other Exploratory Endpoints

- The rate of BCS at the time of definitive surgery
- Relationship between molecular (genomic, metabolic and/or proteomic) biomarkers and clinical response/resistance, safety, pharmacodynamic activity, and/or the mechanism of action of pembrolizumab and other treatments

8.5 Analysis Populations

8.5.1 Efficacy Analysis Populations

The ITT population will serve as the population for primary efficacy analyses. All randomized subjects will be included in this population. Subjects will be included in the treatment group to which they are randomized.

Details on the approach to handling missing data are provided in Section 8.6 – Statistical Methods.

8.5.2 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 randomized subjects who received at least one study treatment. Subjects will be included in the treatment group corresponding to the study treatment they actually received for the analysis of safety data using the ASaT population. For most subjects this will be the treatment group to which they are randomized. Subjects who take incorrect study treatment for the entire treatment period will be included in the treatment group corresponding to the study treatment actually received. Any subject who receives the incorrect study treatment for one cycle, but receives the correct treatment for all other cycles, will be analyzed according to the randomized treatment group and a narrative will be provided for any events that occur during the cycle for which the subject is incorrectly dosed.

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.

8.5.3 PRO Analysis Population

PRO analyses are based on the PRO Full Analysis Set (FAS) population, defined as subjects who have at least one PRO assessment available and have received at least one dose of study treatment.

8.6 Statistical Methods

8.6.1 Statistical Methods for Efficacy Analyses

This section describes the statistical methods that address the primary and secondary objectives. Methods related to the secondary objectives addressing PROs, as well as exploratory objectives, will be described in the sSAP(s).

Efficacy results that will be deemed to be statistically significant after consideration of the Type I error control strategy are described in Section 8.8 – Multiplicity. Nominal p-values will be computed for other efficacy analyses, but should be interpreted with caution due to potential issues of multiplicity.

8.6.1.1 Pathological Complete Response (pCR) Rate

The stratified Miettinen and Nurminen's method will be used for the comparison of pCR rates using 3 definitions between 2 treatment arms (pembrolizumab + chemotherapy vs. placebo + chemotherapy). The difference in pCR rate and its 95% CI from the stratified Miettinen and Nurminen's method with strata weighting by sample size will be reported for subjects with locally advanced TNBC and for individuals with PD-L1 (+) tumors. The stratification factors used for randomization (see Section 5.4 – Stratification) will be applied to the analysis.

The primary hypothesis of the pCR rate (ypT0/Tis ypN0) in subjects with locally advanced TNBC will be tested according to the hypotheses testing plan as described in Section 8.8 – Multiplicity.

Sensitivity analyses will be performed for pCR rates using Cochran-Mantel-Haenszel test. Associated odds ratios and 95% CIs will be calculated. Additional supportive unstratified analyses may also be provided. Further details of sensitivity and supportive analyses will be described in the sSAP as needed.

8.6.1.2 Event-Free Survival (EFS)

The non-parametric Kaplan-Meier method will be used to estimate the EFS curve in each treatment group. The treatment difference in EFS will be assessed by the stratified log-rank test for subjects with locally advanced TNBC and for individuals with PD-L1 (+) tumors. A stratified Cox proportional hazard model with Efron's method of tie handling will be used to assess the magnitude of the treatment difference (ie, HR) between the treatment arms. The HR and its 95% CI from the stratified Cox model with Efron's method of tie handling and with a single treatment covariate will be reported. Kaplan-Meier estimates and the corresponding 95% CIs at two-year, three-year and five-year will be provided for EFS. The stratification factors used for randomization (see Section 5.4 – Stratification) will be applied to both the stratified log-rank test and the stratified Cox model.

The primary hypothesis of EFS in subjects with locally advanced TNBC will be tested according to the hypotheses testing plan as described in Section 8.8 – Multiplicity.

For the primary analysis, the true date of event will be approximated by the date of the first assessment at which event is objectively documented. Subjects who do not experience an event at the time of data analysis will be censored at the date they were last known to be alive and event free.

In order to evaluate the robustness of the EFS endpoint, sensitivity analyses with a different set of censoring rules may be performed. The details of censoring rules will be specified in the sSAP.

The proportional hazards assumption on EFS will be examined using both graphical and analytical methods if warranted. The log[-log] of the survival function vs time for EFS may be plotted for the comparison between pembrolizumab and placebo arms. If the curves are not parallel, indicating that hazards are not proportional, supportive analyses may be conducted to account for the possible non-proportional hazards effect associated with immunotherapies using, for example, Restricted Mean Survival Time (RMST) method [69] or a parametric method [70].

One assumption for stratified Cox proportional hazard model is that the treatment HR is constant across the strata. If strong departures from this assumption are observed (which can result in a notably biased and/or less powerful analysis), a sensitivity analysis may be performed based on a two-step weighted Cox model approach by Mehrotra et al., 2012 [71], in which the treatment effect is first estimated for each stratum, and then the stratum specific estimates are combined for overall inference using sample size weights.

Additional supportive unstratified analyses may also be provided. Further details of sensitivity analyses will be described in the sSAP.

8.6.1.3 Overall Survival

The non-parametric Kaplan-Meier method will be used to estimate the survival curves. The treatment difference in survival will be assessed by the stratified log-rank test. A stratified Cox proportional hazard model with Efron's method of tie handling will be used to assess the magnitude of the treatment difference (ie, the HR) for subjects with locally advanced TNBC and for individuals with PD-L1 (+) tumors. The HR and its 95% CI from the stratified Cox model with a single treatment covariate will be reported. The stratification factors used for randomization (see Section 5.4 – Stratification) will be applied, as stratification factors used for analysis, to both the stratified log-rank test and the stratified Cox model. Kaplan-Meier estimates and the corresponding 95% CIs at 2-years, 3-years and 5-years will be provided for OS.

The secondary hypothesis of OS in subjects with locally advanced TNBC will be tested according to the hypotheses testing plan as described in Section 8.8 – Multiplicity.

Subjects in the combination of placebo and chemotherapy arm are expected to discontinue treatment earlier compared to subjects in the combination of pembrolizumab and chemotherapy arm and are not allowed to crossover to the combination of pembrolizumab and chemotherapy arm; however, they may be treated with another anti–PD-1 drug. As an exploratory analysis, adjustment for the effect of crossover on OS may be performed using

recognized methods (eg, the Rank Preserving Structural Failure Time (RPSFT) model proposed by Robins and Tsiatis [72], two-stage model), based on an examination of the appropriateness of the data to the assumptions required by the methods.

Additional supportive unstratified analyses may also be provided. Further details of sensitivity analyses will be described in the sSAP as needed.

8.6.1.4 Summary of Statistical Methods for Efficacy

Table 10 summarizes the primary analysis approach for primary and secondary efficacy endpoints. Sensitivity analysis methods are described above for each endpoint as applicable.

The strategy to address multiplicity issues with regard to multiple efficacy endpoints, multiple populations, and IAs is described in Section 8.7 – Interim Analyses and in Section 8.8 – Multiplicity.

Table 10 Analysis Strategy for Key Efficacy Endpoints

Endpoint/Variable (Description, Time Point)	Statistical Method†	Analysis Population	Missing Data Approach
Primary Hypothesis 1			
pCR(ypT0/Tis ypN0)	Stratified M & N method‡	ITT	Subjects with relevant data missing are considered non-responders
Primary Hypothesis 2			
EFS	Test: Stratified log-rank test Estimation: Stratified Cox model with Efron's tie handling method	ITT	Censored at last known alive and event free date
Secondary Hypothesis 1			
OS	Test: Stratified log-rank test Estimation: Stratified Cox model with Efron's tie handling method	ITT	Censored at last known alive date

† Statistical models are described in further details in the text. For stratified analyses, the stratification factors used for randomization will be used as stratification factors for analysis.
‡ Miettinen and Nurminen method with strata weighting by sample size.

8.6.2 Statistical Methods for Safety Analyses

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

The analysis of safety results will follow a tiered approach as shown in Table 11. The tiers differ with respect to the analyses that will be performed. Based on toxicity data across the pembrolizumab program, the combination of chemotherapy with pembrolizumab does not seem to produce toxicity beyond what is expected for these therapies alone. For these reasons, there are no events of interest that warrant inferential testing. Therefore, there are no Tier 1 events in this study. Tier 2 parameters will be assessed via point estimates with 95% CIs provided for

between-group comparisons; only point estimates by treatment group will be provided for Tier 3 safety parameters.

AEs (specific terms as well as system organ class terms) and predefined limits of change will be classified as belonging to "Tier 2" or "Tier 3", based on the percent of subjects with events observed. Specific AEs occurring in ≥ 5% of subjects or specific serious AEs occurring in ≥ 1% of subjects or specific Grade 3-5 AEs occurring in ≥ 1% of subjects will be considered Tier 2 endpoints. All other adverse experiences and predefined limits of change will belong to Tier 3.

The threshold of at least 5% of subjects with events in one or more treatment groups was chosen for specific AEs as Tier 2 endpoints because this incidence rate would allow meaningful statistical assessments for AEs in general. Serious and Grade 3-5 AEs are expected to occur less frequently but important for the overall safety assessment, as such the threshold to classify these AEs as Tier 2 endpoints are lower than that for general specific AEs. Because many 95% CIs may be provided without adjustment for multiplicity, the CIs should be regarded as a helpful descriptive measure to be used in review, not a formal method for assessing the statistical significance of the between-group differences in adverse experiences and predefined limits of change.

Continuous measures such as changes from baseline in laboratory, ECGs, and vital signs will be considered Tier 3 safety parameters. Summary statistics for baseline, on-treatment, and change from baseline values will be provided by treatment group.

The broad clinical and laboratory AE categories consisting of the percentage of subjects with any AE, any drug-related AE, any Grade 3-5 AE, any SAE, any AE which is both drug-related and Grade 3-5, any AE which is both serious and drug-related, dose modification due to AE, and who discontinued due to an AE, and death will be considered Tier 2 endpoints. For Tier 2 endpoints, point estimates and 95% CIs will be provided for between-treatment differences in the percentage of subjects with events; these analyses will be performed using the Miettinen and Nurminen method.

Table 11 Analysis Strategy for Safety Parameters

Safety Tier	Safety Endpoint	95% CI for Treatment Comparison	Descriptive Statistics
Tier 2	Any AE	X	X
	Any Serious AE	X	X
	Any Grade 3-5 AE	X	X
	Any Drug-Related AE	X	X
	Any Serious and Drug-Related AE	X	X
	Any Grade 3-5 and Drug-Related AE	X	X
	Dose Modification due to AE	X	X
	Discontinuation due to AE	X	X
	Death	X	X
	Specific AEs, SOCs (incidence ≥5% of subjects in one of the treatment groups)	X	X
	Specific Serious AEs, SOCs (incidence ≥1% of subjects in one of the treatment groups)	X	X
	Specific Grade 3-5 AEs, SOCs (incidence ≥1% of subjects in one of the treatment groups)	X	X
Tier 3	Specific AEs, SOCs (incidence <5% in both treatment groups) or PDLCs		X
	Specific Serious AEs, SOCs (incidence <1% of subjects in both treatment groups)		X
	Specific Grade 3-5 AEs, SOCs(incidence <1% of subjects in both treatment groups)		X
	Change from Baseline Results (Labs, ECGs, Vital Signs)		X
Note: SOC=System Organ Class; PDLC=Pre-Defined Limit of Change; X = results will be provided.			

8.6.3 Summaries of Demographic and Baseline Characteristics

The comparability of the treatment groups for each relevant characteristic will be assessed by the use of tables and/or graphs. No statistical hypothesis testing will be performed on these characteristics. The number and percentage of subjects screened, randomized, the primary reasons for screening failure, and the primary reasons for discontinuation will be displayed. Demographic variables (eg, age) and baseline characteristics will be summarized by treatment either by descriptive statistics or categorical tables.

8.7 Interim Analyses

8.7.1 Safety Interim Analyses

The external DMC will conduct regular safety monitoring. The timing of the safety monitoring will be specified in the DMC charter.

8.7.2 Efficacy Interim Analyses

Two IAs are planned for the rate of pCR (ypT0/Tis ypN0) and should be at least 3 months apart. The timing of IAs for EFS is calendar-based and the IAs are planned to be conducted

annually after 2 years. In addition, the FA for EFS needs to be at least 1 year apart from the last IA. Currently, seven efficacy IAs are planned in addition to the FA for this study. Results of the efficacy IAs will be reviewed by an external DMC. If the EFS null hypotheses are rejected prior to the FA, the external DMC may recommend stopping the study early for efficacy. This study is not planned to be stopped for futility. Therefore, no futility bound is provided. Details on how the above planned analyses are incorporated into establishing statistical significance and the boundaries with regard to efficacy are discussed further in Section 8.8, Multiplicity.

Interim Analysis 1 (Interim pCR (ypT0/Tis ypN0) Analysis)

The primary purpose of efficacy IA 1 (IA1) is to evaluate superiority of pembrolizumab + chemotherapy compared to placebo + chemotherapy with respect to the rate of pCR (ypT0/Tis ypN0). IA1 will be performed after: (1) enrollment is completed, and (2) at least 500 subjects have or would have completed surgery after ~6 months neoadjuvant treatment. It may occur ~18 months after the first subject is randomized.

A supportive analysis to summarize the EFS data will be performed at IA1 and no hypothesis testing will be performed.

Interim Analysis 2 (Interim EFS Analysis and Final pCR (ypT0/Tis ypN0) Analysis)

The primary purpose of efficacy IA 2 (IA2) is to evaluate superiority of pembrolizumab compared to placebo with respect to EFS. The timing of IA2 is calendar driven and IA2 will be performed at ~24 months after the first subject is randomized. It is estimated that approximately 93 EFS events will have been observed among subjects with locally advanced TNBC.

Another purpose of efficacy IA 2 (IA2) is to evaluate superiority of pembrolizumab + chemotherapy compared to placebo + chemotherapy with respect to the rate of pCR (ypT0/Tis ypN0). It is estimated that approximately 1000 subjects have or would have completed surgery after ~6 months neoadjuvant treatment. If more than 1000 subjects have or would have surgery data in IA2, the pCR results from additional subjects may be included in the analyses.

Interim Analysis 3 (Interim EFS Analysis)

The primary purpose of efficacy IA 3 (IA3) is to evaluate superiority of pembrolizumab compared to placebo with respect to EFS. The timing of IA3 is calendar driven and IA3 will be performed at ~36 months after the first subject is randomized. It is estimated that approximately 154 EFS events will have been observed among subjects with locally advanced TNBC.

A supportive pCR analysis to summarize the data for all subjects who have or would have completed surgery after ~6 months neoadjuvant treatment will be performed at IA3 and no hypothesis testing will be performed.

Interim Analysis 4 (Interim EFS Analysis)

The primary purpose of efficacy IA 4 (IA4) is to evaluate superiority of pembrolizumab compared to placebo with respect to EFS. The timing of IA4 is calendar driven and the analysis may be performed at ~48 months after the first subject is randomized. It is estimated that approximately 201 EFS events will have been observed among subjects with locally advanced TNBC in IA4.

Interim Analysis 5 (Interim EFS Analysis)

The primary purpose of efficacy IA 5 (IA5) is to evaluate superiority of pembrolizumab compared to placebo with respect to EFS. The timing of IA5 is calendar driven and the analysis may be performed at ~ 60 months after the first subject randomized. It is estimated that approximately 239 EFS events will have been observed among subjects with locally advanced TNBC in IA5.

Interim Analysis 6 (Interim EFS Analysis)

The primary purpose of efficacy IA 6 (IA6) is to evaluate superiority of pembrolizumab compared to placebo with respect to EFS. The timing of IA6 is calendar driven and the analysis may be performed at ~ 72 months after the first subject randomized. It is estimated that approximately 270 EFS events will have been observed among subjects with locally advanced TNBC in IA6.

Interim Analysis 7 (Interim EFS Analysis)

The primary purpose of efficacy IA 7 (IA7) is to evaluate superiority of pembrolizumab compared to placebo with respect to EFS. The timing of IA7 is calendar driven and the analysis may be performed at ~ 84 months after the first subject randomized. It is estimated that approximately 294 EFS events will have been observed among subjects with locally advanced TNBC in IA7.

Final Analysis (Final EFS Analysis)

The FA of the study is event-driven and will be conducted after approximately 327 EFS events have been observed. It may occur at ~102 months after the first subject is randomized. If 327 EFS events are observed before 102 months after the first subject is randomized, the FA will be conducted at the time when approximately 327 EFS events have been observed. The final significance boundary will be adjusted for the EFS events seen at the interim analyses performed and the number of EFS events that have occurred by the FA. OS will be tested only after when the null hypothesis for EFS is rejected.

The analyses planned, endpoints evaluated, drivers of the timing, and primary purpose of analyses are summarized in Table 12 Any changes to the timing of the analyses, along with its rational, will be documented in a memo to the study file before the database lock.

Table 12 Analyses Planned, Endpoints Evaluated, and Drivers of Timing

Analysis	Criteria for Conduct of Analysis	Endpoint	Estimated Time after First Subject Randomized	Primary Purpose of Analysis
IA1: Interim pCR Analysis	(1) enrollment is completed, and (2) at least 500 subjects have or would have completed surgery after ~6 months neoadjuvant treatment	pCR (ypT0/Tis ypN0)	~18 months	pCR IA
IA2: Interim EFS Analysis and Final pCR Analysis	~24 months after first subject randomized.	EFS	~24 months	EFS IA
		pCR (ypT0/Tis ypN0)		pCR FA
IA3: Interim EFS Analysis	~36 months after first subject randomized.	EFS	~36 months	EFS IA
IA4: Interim EFS Analysis	~48 months after the first subject is randomized.	EFS	~48 months	EFS IA
IA5: Interim EFS Analysis	~60 months after the first subject is randomized.	EFS	~60 months	EFS IA
IA6: Interim EFS Analysis	~72 months after the first subject is randomized.	EFS	~72 months	EFS IA
IA7: Interim EFS Analysis	~84 months after the first subject is randomized.	EFS	~84 months	EFS IA
FA: Final EFS Analysis	~327 EFS events have been observed.	EFS	~102 months	EFS FA

8.8 Multiplicity

The multiplicity strategy specified in this section will be applied to the dual primary hypotheses and the secondary hypothesis. The dual primary hypotheses are testing superiority of pembrolizumab compared to placebo in pCR (ypT0/Tis ypN0) or EFS in subjects with locally advanced TNBC. The secondary hypothesis is testing superiority in OS in subjects with locally advanced TNBC. The overall Type-I error among multiple endpoints is strongly controlled at 2.5% (one-sided), with 0.5% initially allocated to the pCR (ypT0/Tis ypN0) hypothesis and 2.0% initially allocated to the EFS hypothesis. The study will be

considered a success if pCR (ypT0/Tis ypN0) or EFS is demonstrated to be statistically significant at either an IA or the FA under multiplicity control.

The study uses the graphical method of Maurer and Bretz [68] to control multiplicity for multiple hypotheses as well as IAs. According to this approach, study hypotheses may be tested more than once, and when a particular null hypothesis is rejected, the α allocated to that hypothesis can be reallocated to other hypothesis tests. Figure 3 shows the initial one-sided α allocation for each hypothesis in the ellipse representing the hypothesis. The weights for reallocation from each hypothesis to the others are represented in the boxes on the lines connecting hypotheses.

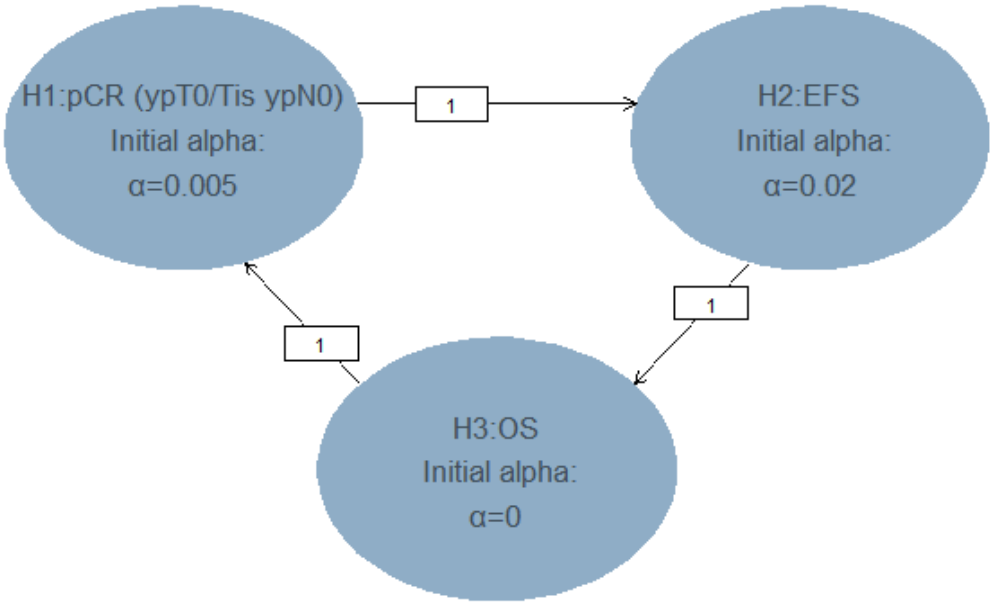


Figure 3 Multiplicity Graph for Type I Error Control of Study Hypotheses

8.8.1 pCR (ypT0/Tis ypN0)

The trial initially allocates α=0.005, one-sided to test pCR (ypT0/Tis ypN0). Table 13 shows the boundary properties for the IAs, which were derived using a Hwang-Shih-DeCani α-spending function with gamma parameter (0). Note that the final row indicates the total power to reject the null hypothesis for pCR. If the actual number of subjects at the pCR analysis differs from those specified in the table, the bounds will be adjusted using the Hwang-Shih-DeCani α-spending function accordingly. If the test of pCR (ypT0/Tis ypN0) hypothesis does not achieve statistical significance at either IA1 or IA2, the p-value from IA2 (ie, no new data is added after IA2) can be compared to an updated α-level based on group sequential design with α=0.025 if the null hypotheses for both EFS and OS are rejected at a later time. It gives >99% power to detect a true pCR rate difference of 15 percentage points (pembrolizumab + chemotherapy vs. placebo + chemotherapy) at α=0.025 (one-sided) and the observed difference in pCR between the treatment groups needs to be approximately 6.8 percentage points for the analysis to be considered positive.

Table 13 Boundary Properties for Planned Analyses of pCR (ypT0/Tis ypN0) Superiority Hypotheses Based on α=0.005

Analysis	Value	α=0.005
IA 1: 50%*	Z	2.8070
N: 500	p (1-sided) [§]	0.0025
	delta at bound[%]	0.1379
	P(Cross) if delta=0[†]	0.0025
	P(Cross) if delta=0.15[#]	0.5971
IA 2	Z	2.7403
N: 1000	p (1-sided) [§]	0.0031
	delta at bound[%]	0.0952
	P(Cross) if delta=0[†]	0.0050
	P(Cross) if delta=0.15[#]	0.9460

*Percentage of expected number of subjects at final analysis required at IA
[§]p (1-sided) is the nominal α for testing.
[%]delta at bound is the approximate delta required to reach an efficacy bound.
[†]P(Cross if delta=0) is the probability of crossing a bound under the null hypothesis, with an underlying pCR rate of 50%.
[#]P(Cross if delta=0.15) is the probability of crossing a bound under the alternative hypothesis.
Abbreviations: IA = interim analysis; pCR = pathological complete response.

8.8.2 Event-free Survival

The trial initially allocates α=0.02, one-sided to test EFS. If the null hypothesis for pCR (ypT0/Tis ypN0) is rejected, Figure 3 shows that its α=0.005 is fully reallocated to EFS hypothesis testing. Thus, the EFS null hypothesis may be tested at α=0.02, or α=0.025. Table 14 shows the boundary properties calculated based on the estimated number of events for each of these α-levels for the IAs and FA, which were derived using a cure rate model and Lan-DeMets O'Brien-Fleming spending function. Note that the final row indicates the total power to reject the null hypothesis for EFS at each α-level. If the actual number of events at the EFS analyses differ from those specified in the table, the bounds will be adjusted using the actual observed numbers of events and the Lan-DeMets O'Brien-Fleming spending function accordingly.

Of note, the efficacy interim analysis 2 (IA 2) occurred prior to Amendment 04 and as such the efficacy boundaries for EFS in IA 2 were calculated based on the estimated number of events.

Table 14 Efficacy Boundaries and Properties for EFS Analyses

Analysis	Value	α=0.02	α=0.025
IA 2: 28%*	Z	4.225	4.059
N: 1149	p (1-sided) [§]	0.00001	0.00002
Events: 93	HR at bound[%]	0.3934	0.4116
Month: 24	P(Cross) if HR=1[†]	<0.0001	<0.0001
	P(Cross) if HR=0.71[#]	0.0039	0.0063
IA 3: 47%*	Z	3.201	3.071
N: 1149	p (1-sided) [§]	0.0007	0.0011
Events: 154	HR at bound[%]	0.5782	0.5942
Month: 36	P(Cross) if HR=1[†]	0.0007	0.0011
	P(Cross) if HR=0.71[#]	0.1191	0.1470
IA 4: 61%*	Z	2.773	2.660
N: 1149	p (1-sided) [§]	0.0028	0.0039
Events: 201	HR at bound[%]	0.6603	0.6741
Month: 48	P(Cross) if HR=1[†]	0.0030	0.0042
	P(Cross) if HR=0.71[#]	0.3269	0.3691
IA 5: 73%*	Z	2.541	2.439
N: 1149	p (1-sided) [§]	0.0055	0.0074
Events: 239	HR at bound[%]	0.7054	0.7177
Month: 60	P(Cross) if HR=1[†]	0.0065	0.0087
	P(Cross) if HR=0.71[#]	0.5037	0.5455
IA 6: 82%*	Z	2.399	2.303
N: 1149	p (1-sided) [§]	0.0082	0.0106
Events: 270	HR at bound[%]	0.7333	0.7446
Month: 72	P(Cross) if HR=1[†]	0.0103	0.0135
	P(Cross) if HR=0.71[#]	0.6277	0.6646
IA 7: 90%*	Z	2.304	2.213
N: 1149	p (1-sided) [§]	0.0106	0.0135
Events: 294	HR at bound[%]	0.7519	0.7625
Month: 84	P(Cross) if HR=1[†]	0.0141	0.0181
	P(Cross) if HR=0.71[#]	0.7111	0.7427

Analysis	Value	α=0.02	α=0.025
Final	Z	2.168	2.082
N: 1149	p (1-sided) [§]	0.0151	0.0187
Events: 327	HR at bound[%]	0.7754	0.7851
Month: 102	P(Cross) if HR=1[†]	0.0200	0.0250
	P(Cross) if HR=0.71[#]	0.8005	0.8248

*Percentage of expected number of events at final analysis required at IA

[§]p (1-sided) is the nominal α for testing.

[%]HR at bound is the approximate HR required to reach an efficacy bound

[†]P(Cross if HR=1) is the probability of crossing a bound under the null hypothesis

[#]P(Cross if HR=0.71) is the probability of crossing a bound under the alternative hypothesis
A Haybittle-Peto type adjustment with p<0.0001 may be applied for EFS summary in IA1.

Abbreviations: EFS = event-free survival; HR = hazard ratio; IA = interim analysis.

8.8.3 CCI [redacted]

CCI [redacted]

CCI [redacted]

CCI

[redacted]

8.8.4 Safety Analyses

The external DMC has responsibility for assessment of overall risk: benefit. When prompted by safety concerns, the external DMC can request corresponding efficacy data. External DMC review of efficacy data to assess the overall risk:benefit to trial subjects will not require a multiplicity adjustment typically associated with a planned efficacy IA; however, to account for any multiplicity concerns raised by the external DMC review of unplanned efficacy data prompted by safety concerns, a sensitivity analysis for efficacy endpoints adopting a conservative multiplicity adjustment will be pre-specified in the sSAP. This analysis will be performed if requested by the external DMC.

8.9 Sample Size and Power Calculations

The study will randomize approximately 1150 subjects in a 2:1 ratio between pembrolizumab plus chemotherapy as neoadjuvant therapy and pembrolizumab as adjuvant therapy (Arm 1) and placebo plus chemotherapy as neoadjuvant therapy and placebo as adjuvant therapy (Arm 2). The sample size was driven by EFS.

Randomization will be implemented centrally using IVRS and will be monitored on a regular basis. When IVRS alerts study is approaching the desired enrollment, screening should be stopped in time. However, subjects already in screening phase may be enrolled even after the maximum sample size has been reached.

pCR (ypT0/Tis ypN0) Rate

The first primary endpoint is pCR (ypT0/Tis ypN0) rate. The final pCR analysis will be performed after enrollment is completed, and ~1000 subjects have or would have completed surgery after ~6 months neoadjuvant treatment.

A sample size of ~1000 gives ~95 % power to detect a true pCR rate difference of 15 percentage points (pembrolizumab + chemotherapy vs. placebo + chemotherapy) at $\alpha = 0.5\%$ (one-sided). The sample size calculation is based on the following assumptions: 1) the α of 0.5% is allocated to the pCR hypothesis; 2) the underlying pCR is 50% in the placebo + chemotherapy arm, and there is 15 percentage points increase in pCR in the pembrolizumab + chemotherapy arm (pCR of 65%) in subjects with locally advanced TNBC; and 3) a drop-out rate of ~10%. In addition, a Hwang-Shih-DeCani alpha-spending function with gamma parameter (0) and are constructed to implement group sequential boundaries that control the Type-I error. The power for the pCR endpoint at different true pCRs for subjects with locally advanced TNBC is summarized in Table 16.

Table 16 Power for pCR

pCR Difference Between the 2 Treatment Arms	Subjects with Locally Advanced TNBC (N = 1000, α = 0.005)
12 percentage points	77%
15 percentage points	95%
17 percentage points	99%
All calculations assume pCR is 50% in the placebo + chemotherapy arm.	

The assumptions for a pCR rate of 50% in the placebo + chemotherapy arm are based on the estimates from Sikov et al., 2015 [2], and von Minckwitz et al., 2014 [1].

EFS

The other dual-primary endpoint is EFS. The final analysis of the study is EFS event-driven and will be conducted after approximately 327 EFS events have been observed, unless the study is terminated early. It may occur at ~ 102 months after first subject randomized (depending on enrollment rate and event accumulation rate).

With the α of 2% (one-sided) and sample size of ~1150, the trial has an overall ~80% power for EFS in subjects with locally advanced TNBC, assuming the true HR (pembrolizumab vs. placebo) is 0.71. According to published meta-analysis on this population that suggests ~50% of subjects may be disease-free long-term [14], a cure rate model is applied to account for the failure rates decreasing over time [73]. These calculations are based on the following assumptions: (1) EFS follows a Poisson mixture model (cure rate model with decreasing failure rate) distribution with ~78% EFS rate at 36 months and ~50% cure rate in the placebo arm, (2) an enrollment period of 18 months and at least 84 months follow-up, and (3) A yearly drop-out rate of 2% and additional ~3% to ~5% drop-out rate after surgery. The EFS control rate of 78% was estimated from an updated report from CALGB40603, presented at SABCS 2015 [74]. In addition, a Lan-DeMets O'Brien-Fleming approximation α-spending function is constructed to implement group sequential boundaries that control the Type-I error. Details on the Poisson mixture model are provided in Appendix 12.6.

OS

The key secondary endpoint is OS. If the null hypothesis for EFS is rejected at an interim analysis, the final OS analysis is event-driven and will be conducted after approximately 297 OS events would have been observed, unless the study is terminated early. It may occur at ~102 months after first subject randomized (depending on enrollment rate and event accumulation rate). If after 102 months after the first subject randomized the estimated number of OS events still haven't been observed, then the final OS analysis may be conducted at that time.

With the α of 2% (one-sided) and sample size of ~1150, the trial has an overall ~79.7% power for OS in subjects with locally advanced TNBC, assuming the true HR (pembrolizumab vs. placebo) is 0.70. According to published meta-analysis on this

population that suggests ~50% of subjects may be disease-free long-term [14], a cure rate model is applied to account for the failure rates decreasing over time [73]. These calculations are based on the following assumptions: (1) OS follows a Poisson mixture model (cure rate model with decreasing failure rate) distribution with ~81% OS rate at 36 months [74] and ~50% cure rate in the placebo arm, (2) an enrollment period of 18 months and at least 84 months follow-up, and (3) A yearly drop-out rate of 3%. In addition, a Lan-DeMets O'Brien-Fleming approximation α-spending function is constructed to implement group sequential boundaries that control the Type-I error.

The sample size and power calculations were performed in the software R (package "gsDesign").

8.10 Subgroup Analyses and Effect of Baseline Factors

To determine whether the treatment effect is consistent across various subgroups, the estimate of the between-group treatment effect (with a nominal 95% CI) for the primary endpoints will be estimated and plotted within each category of the following classification variables in subjects with locally advanced TNBC and in individuals with PD-L1 (+) tumors (CPS ≥1):

- Nodal status: Positive vs. Negative
- Tumor size: T1/T2 vs. T3/T4
- Choice of Carboplatin (Cb): Q3W vs. Weekly
- Tumor PD-L1 status (applies to all subjects with locally advanced TNBC): CPS ≥1 vs. CPS <1; CPS ≥10 vs. CPS <10; CPS ≥20 vs. CPS <20
- Menopausal status (for females only): pre- vs. post-menopausal
- Age: <65 years vs. ≥65 years
- Geographic region: Europe/Israel/North America/Australia vs. Asia vs. Rest of World
- Ethnic origin: Hispanic vs. Non-Hispanic
- ECOG performance status: 0 vs. 1
- HER2 status: IHC 2+ (but FISH-) vs. IHC 0-1+
- LDH: >upper limit of normal [ULN] vs. ≤ULN

8.11 Compliance (Medication Adherence)

Drug accountability data for study treatment will be collected during the study. Any deviation from protocol-directed administration will be reported.

8.12 Extent of Exposure

The extent of exposure will be summarized as duration of treatment in number of cycles or administrations as appropriate.

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 17.

Table 17 Product Descriptions

Product Name & Potency	Dosage Form	Source/Additional Information
Pembrolizumab (MK-3475), 25 mg/mL	Sterile solution for IV infusion	Provided centrally by the Sponsor
Paclitaxel (potency may vary by study country)	Solution for infusion (may vary by study country)	Provided centrally by the Sponsor or locally by the trial site, subsidiary, or designee
Carboplatin (potency may vary by study country)	Solution for Infusion (may vary by study country)	Provided centrally by the Sponsor or locally by the trial site, subsidiary, or designee
Doxorubicin (potency may vary by study country)	Solution for Infusion (may vary by study country)	Provided centrally by the Sponsor or locally by the trial site, subsidiary, or designee
Epirubicin (potency may vary by study country)	Solution for Injection (may vary by study country)	Provided centrally by the Sponsor or locally by the trial site, subsidiary, or designee
Cyclophosphamide (potency may vary by study country)	Powder for solution for injection or infusion (may vary by study country)	Provided centrally by the Sponsor or locally by the trial site, subsidiary, or designee

All supplies indicated in Table 17 will be provided per the "Source/Additional Information" column depending on local country operational requirements.

Any commercially available product not included in Table 17 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.

9.3 Clinical Supplies Disclosure

The emergency unblinding call center will use the treatment/randomization schedule for the trial to unblind subjects and to unmask treatment identity. The emergency unblinding call center should only be used in cases of emergency (see Section 7.1.4.2). In the event that the emergency unblinding call center is not available for a given site in this trial, the central electronic treatment allocation/randomization system (IVRS/IWRS) should be used in order to unblind subjects and to unmask treatment/vaccine identity. The Sponsor will not provide random code/disclosure envelopes or lists with the clinical supplies.

See Section 7.1.4.2, Blinding/Unblinding, for a description of the method of unblinding a subject during the trial, should such action be warranted.

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 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 MSD, is provided in Section 12.1 - 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, MSD, 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 Protocol/CSR 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 or other local registries. MSD, as Sponsor of this trial, will review this protocol and submit the information necessary to fulfill these requirements. MSD 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. MSD will post a synopsis of trial results for approved products on 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 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 Code of Conduct for Clinical Trials

Merck Sharp & Dohme LLC, Rahway, NJ, USA (MSD)

Code of Conduct for Interventional Clinical Trials

I. Introduction

A. Purpose

MSD, 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 participants in clinical trials is the overriding concern in the design and conduct of clinical trials. In all cases, MSD clinical trials will be conducted in compliance with local and/or national regulations (including all applicable data protection laws and regulations), and International Council for Harmonisation Good Clinical Practice (ICH-GCP), and also in accordance with the ethical principles that have their origin in the Declaration of Helsinki.

B. Scope

Highest ethical and scientific standards shall be endorsed for all clinical interventional investigations sponsored by MSD 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 that are observational in nature, or which are retrospective. Further, this Code does not apply to investigator-initiated trials, which are not under the full control of MSD.

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 MSD or comparator products. Alternatively, MSD may conduct outcomes research trials, trials to assess or validate various endpoint measures, or trials to determine patient preferences, etc.

The design (i.e., participant population, duration, statistical power) must be adequate to address the specific purpose of the trial and shall respect the data protection rights of all participants, trial site staff and, where applicable, third parties. All trial protocols are and will be assessed for the need and capability to enroll underrepresented groups. Participants must meet protocol entry criteria to be enrolled in the trial.

2. Site Selection

MSD's clinical trials are conducted globally in many different countries and in diverse populations, including people of varying age, race, ethnicity, gender, and accounting for other potential disease related factors. MSD selects investigative sites based on medical expertise, access to appropriate participants, adequacy of facilities and staff, previous performance in clinical trials, as well as budgetary considerations. Prior to trial initiation, sites are evaluated by MSD personnel (or individuals acting on behalf of MSD) to assess the ability to successfully conduct the trial.

Where appropriate, and in accordance with regulatory authority guidance, MSD will make concerted efforts to raise awareness of clinical trial opportunities in various communities. MSD will seek to engage underrepresented groups and those disproportionately impacted by the disease under study. MSD will support clinical trial investigators to enroll underrepresented groups and expand access to those who will ultimately use the products under investigation.

3. Site Monitoring/Scientific Integrity

Investigative trial sites are monitored to assess compliance with the trial protocol and Good Clinical Practice (GCP). MSD reviews clinical data for accuracy, completeness, and consistency. Data are verified versus source documentation according to standard operating procedures. Per MSD policies and procedures, if potential fraud, scientific/research misconduct, privacy incidents/breaches or Clinical Trial-related Significant Quality Issues are reported, such matters are investigated. When necessary, appropriate corrective and/or preventative actions are defined and regulatory authorities and/or ethics review committees are notified.

B. Publication and Authorship

Regardless of trial outcome, MSD commits to publish the primary and secondary results of its registered trials of marketed products in which treatment is assigned, according to the pre-specified plans for data analysis. To the extent scientifically appropriate, MSD seeks to publish the results of other analyses it conducts that are important to patients, physicians, and payers. 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 such as multiplicity.

MSD's policy on authorship is consistent with the recommendations published by the International Committee of Medical Journal Editors (ICMJE). 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. MSD funding of a trial will be acknowledged in publications.

III. Participant Protection

A. Regulatory Authority and Ethics Committee Review (Institutional Review Board [IRB]/Independent Ethics Committee [IEC])

All protocols and protocol amendments will be submitted by MSD for regulatory authority acceptance/authorization prior to implementation of the trial or amendment, in compliance with local and/or national regulations.

The protocol, protocol amendment(s), informed consent form, investigator's brochure, and other relevant trial documents must be reviewed and approved by an IRB/IEC before being implemented at each site, in compliance with local and/or national regulations. Changes to the protocol that are required urgently to eliminate an immediate hazard and to protect participant safety may be enacted in anticipation of ethics committee approval. MSD will inform regulatory authorities of such new measures to protect participant safety, in compliance with local and/or national regulations.

B. Safety

The guiding principle in decision-making in clinical trials is that participant welfare is of primary importance. Potential participants 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.

All participation in MSD clinical trials is voluntary. Participants enter the trial only after informed consent is obtained. Participants may withdraw from an MSD 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

MSD is committed to safeguarding participant confidentiality, to the greatest extent possible, as well as all applicable data protection rights. Unless required by law, only the investigator, Sponsor (or individuals acting on behalf of MSD), ethics committee, and/or regulatory authorities will have access to confidential medical records that might identify the participant by name.

D. Genomic Research

Genomic research will only be conducted in accordance with a protocol and informed consent authorized by an ethics committee.

IV. Financial Considerations

A. Payments to Investigators

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

MSD does not pay for participant referrals. However, MSD may compensate referring physicians for time spent on chart review and medical evaluation to identify potentially eligible participants.

B. Clinical Research Funding

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

V. Investigator Commitment

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

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.[1]

b. Pharmacogenomics: The investigation of variations of DNA and RNA characteristics as related to drug/vaccine response.[2]

c. Pharmacogenetics: A subset of pharmacogenomics, pharmacogenetics is the influence of variations in DNA sequence on drug/vaccine response.[2]

d. DNA: Deoxyribonucleic acid.

e. RNA: Ribonucleic acid.

2. Scope of Future Biomedical Research

The specimens consented and/or collected in this trial as outlined in Section 7.1.3.8 – Future Biomedical Research Samples will be used in various experiments to understand:

- The biology of how drugs/vaccines work
- Biomarkers responsible for how a drug/vaccine enters and is removed by the body
- Other pathways drugs/vaccines may interact with
- The biology 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 Future Biomedical Research.

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 the visit designated in the trial flow chart. If delayed, present consent at next possible Subject Visit. 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.

c. eCRF Documentation for Future Biomedical Research Specimens

Documentation of subject 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(s)

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. This 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 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 Sponsor 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 ask that their biospecimens not be used for Future Biomedical Research. 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@MSD.com). Subsequently, the subject's specimens will be flagged in the biorepository and restricted to main study use only. If specimens were collected from study participants specifically for Future Biomedical Research, these specimens will be removed from the biorepository and destroyed. Documentation will be sent to the investigator confirming withdrawal and/or destruction, if applicable. It is the responsibility of the investigator to inform the subject of completion of the withdrawal and/or destruction, if applicable. Any analyses in progress at the time of request for withdrawal/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 withdrawal of consent and/or destruction cannot 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 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 important research findings are discovered, the Sponsor may publish results, present results in national meetings, and make results accessible on a public website in order to rapidly report this information to doctors and subjects. 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 (ie, 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@MSD.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
3. Industry Pharmacogenomics Working Group. Understanding the Intent, Scope and Public Health Benefits of Exploratory Biomarker Research: A Guide for IRBs/IECs and Investigational Site Staff. Available at http://i-pwg.org/
4. Industry Pharmacogenomics Working Group. Pharmacogenomics Informational Brochure for IRBs/IECs and Investigational Site Staff. Available at http://i-pwg.org/

12.3 ECOG Performance Status Scale

Grade	Description
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, eg, 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. *Am J Clin Oncol.* 1982;5:649-655. http://ecog-acrin.org/resources/ecog-performance-status	

12.4 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).

12.5 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.

*As published in the European Journal of Cancer: New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, Dancey J, Arbuck S, Gwyther S, Mooney M, Rubinstein L, Shankar L, Dodd L, Kaplan R, Lacombe D, Verweij J. New response evaluation criteria in solid tumors: Revised RECIST guideline (version 1.1). *Eur J Cancer*. 2009 Jan;45(2):228-247.

12.6 Technical Note for the Poisson Mixture Model

The Poisson mixture model is applied to account for the failure rates decreasing over time in the trial, which is a mixture of patients suffering disease recurrence and others who have excellent long-term results. The survival function [1] as a function of time t for a control group (c) is:

$$S(t) = \exp(-\theta(1 - \exp(-\lambda t))),$$

where $\theta = -\log(Cure\_Rate)$, λ is a constant hazard rate, and $t \geq 0$.

For the neoadjuvant/adjuvant setting, according to the published literature [2] and [3], Investigator's feedback and study assumption, ~50% subjects will get cured in a long-term (ie, *Cure_Rate* = 0.5) and it is more likely after 3-4 years of study initiation, there will be minimum event-free survival (EFS) events accumulation.

According to the published literature [3], we assume EFS follows a Poisson mixture model distribution with ~78% EFS rate at 36 months in the combination of placebo and chemotherapy arm. Figure 4 shows the EFS curves using the Poisson mixture model and exponential model. The curve from the Poisson mixture model looks similar to the curve in in the published literature [3].

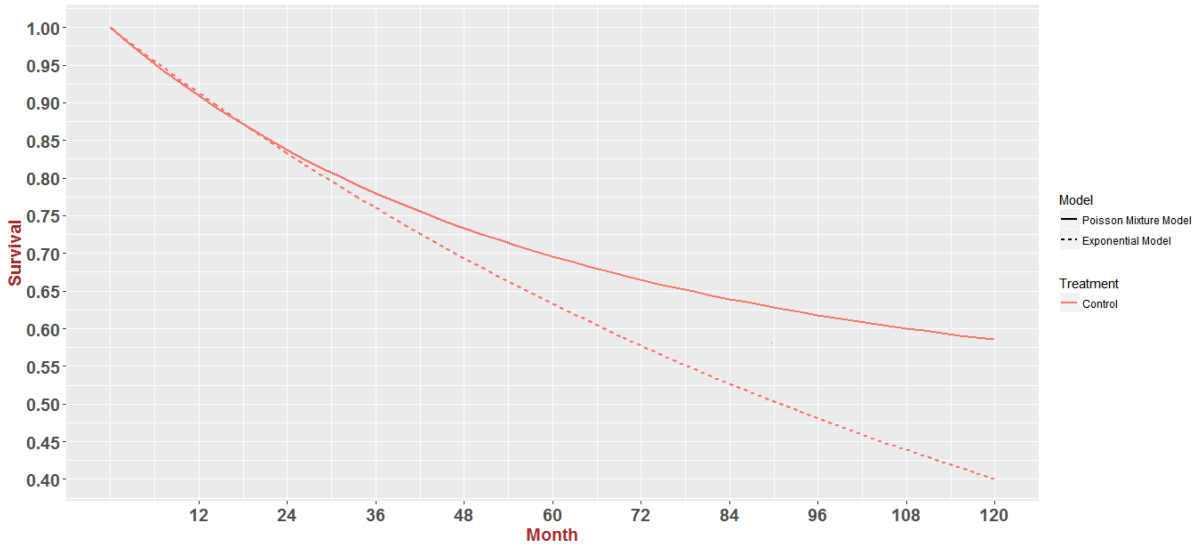

Figure 4 EFS Curves Using the Poisson Mixture Model and Exponential Model

References:

[1] Mário de Castro, Vicente G. Cancho and Josemar Rodrigues. A hands-on approach for fitting long-term survival models under the GAMLSS framework. Computer Methods and Programs in Biomedicine. 2010:97:168–177.

[2] Cortazar P, Zhang L, Untch M, Mehta K, Costantino JP, Wolmark N, et al. Pathological complete response and long-term clinical benefit in breast cancer: the CTNeoBC pooled analysis. Lancet. 2014;384:164-172.

[3] William S, Donald B, Charles P, Balijit S, Constance C, Sara T, et al. Event-free and overall survival following neoadjuvant weekly paclitaxel and dose-dense AC +/- carboplatin and/or bevacizumab in triple-negative breast cancer: outcomes from CALGB 40603 (Alliance): San Antonio Breast Cancer Symposium, December 8-12, 2015

12.7 Abbreviations

Abbreviation/ Term	Definition
AC	Doxorubicin + Cyclophosphamide
ADA	Anti-Drug Antibodies
AE	Adverse Event
AJCC	American Joint Committee on Cancer
ALT	Alanine Aminotransferase
ASaT	All Subjects as Treated
ASCO	American Society of Clinical Oncology
AST	Aspartate Aminotransferase
aPTT	Activated partial thromboplastin time
AUC	Area under the curve
β-hCG	β-human Chorionic Gonadotropin
BCS	Breast Conservation Surgery
BRCA	Breast Cancer 1
CAP	College of American Pathologists
Cb	Carboplatin
CbK	Carboplatin + Pembrolizumab
CBC	Complete Blood Count
CbP	Carboplatin + Placebo
CD8+	Cluster of Differentiation 8 positive
CHF	Congestive Heart Failure
CI	Confidence Interval
cN+	Palpable and/or sonographically suspicious lymph nodes
cN0	Node-negative disease;
CPS	Combined positive score
CR	Complete Response
CRF	Case Report Form
CSR	Clinical Study Report
CT	Computed Tomography
CTCs	Circulating Tumor Cells
CTCAE	Common Toxicity Criteria for Adverse Events
ctDNA	circulating tumor DNA
CTLA-4	Cytotoxic T-lymphocyte-associated antigen-4
CTL	Circulating T Lymphocytes
DIC	Disseminated intravascular coagulation
DMC	Data Monitoring Committee
DNA	Deoxyribonucleic acid
EC	Epirubicin + cyclophosphamide
ECG	Electrocardiogram
ECHO	Echocardiogram
ECI	Events of Clinical Interest
ECOG	Eastern Cooperative Oncology Group
EDC	Electronic Data Capture
eCRF	Electronic Case Report Form
EOC	Executive Oversight Committee
EFS	Event-free Survival
EGFR	Epidermal Growth Factor Receptor
EORTC	European Organisation for Research and Treatment of Cancer
EORTC QLQ-BR23	European Organisation for Research and Treatment of Cancer Breast Cancer–Specific Quality of Life Questionnaire
EORTC QLQ-C30	European Organisation for Research and Treatment of Cancer

Abbreviation/ Term	Definition
	Quality of Life Questionnaire Core 30
ePRO	Electronic Patient Reported Outcomes
EQ-5D™	EuroQol-5 Dimension Questionnaire
ER	Estrogen Receptor
ERC	Ethics Review Committee
FA	Final Analysis
FBR	Future Biomedical Research
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act
FFPE	Formalin-fixed Paraffin Embedded
FTV	Functional Tumor Volume
GCP	Good Clinical Practice
G-CSF	Granulocyte-colony Stimulating Factor
HBsAg	Hepatitis B surface Antigen
HCV	Hepatitis C Virus
HER2	Human Epidermal Growth Factor Receptor 2
HIV	Human Immunodeficiency Virus
HNSCC	Head and neck squamous cell cancer
HR	Hazard Ratio
IA	Interim Analysis
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IgG	Immunoglobulin
IHC	Immunohistochemistry
INR	International Normalized Ratio
irAEs	Immune-related Adverse Events
IRB	Institutional Review Board
ITIM	Immunoreceptor tyrosine-based inhibition motif
ITSM	Immunoreceptor tyrosine-based switch motif
IV	Intravenous
IVRS	Interactive Voice Response System
IWRS	Integrated Web Response System
K	Pembrolizumab
KAC	Pembrolizumab + doxorubicin + cyclophosphamide
KCb	Pembrolizumab + carboplatin
KEC	Pembrolizumab + epirubicin + cyclophosphamide
KN	KEYNOTE
KX	Pembrolizumab + paclitaxel
LMP	Last Menstrual Period
LVEF	Left ventricular ejection fraction
M0	non-metastatic
mAb	Monoclonal antibody
MAH	Marketing Authorisation Holder
miRNA	microRNA
MRI	Magnetic Resonance Imaging
mRNA	Messenger Ribonucleic Acid
mTNBC	Metastatic Triple-negative Breast Cancer
MUGA	Multigated Acquisition
N	Node
NACT	Neoadjuvant chemotherapy
NCI	National Cancer Institute

Abbreviation/ Term	Definition
NKC	Natural Killer Cell
NMR	Nuclear Magnetic Resonance
NSCLC	Non-Small Cell Lung Cancer
NYHA	New York Heart Association
ORR	Objective Response Rate
OS	Overall Survival
OTC	Over-the-counter
P	Placebo
PAC	Placebo + doxorubicin + cyclophosphamide
PCb	Placebo + carboplatin
PEC	Placebo + epirubicin + cyclophosphamide
pCR	Pathological Complete Response
PD	Progressive Disease
PD-1	Programmed cell death protein 1
PD-L1	Programmed Death - Ligand 1
PD-L2	Programmed Death - Ligand 2
PIN	Personal Identification Number
PK	Pharmacokinetic
PR	Partial Response
PT	Prothrombin Time
PTT	Partial thromboplastin time
PTEN	Phosphatase and Tensin Homolog
PX	Placebo + paclitaxel
Q2W	Every 2 Weeks
Q3W	Every 3 Weeks
QoL	Quality of Life
RCB	Residual Cancer Burden
RECIST	Response Evaluation Criteria in Solid Tumors
RNA	Ribonucleic Acid
SAC	Scientific Advisory Committee
SAE	Serious Adverse Events
SAP	Statistical Analysis Plan
SC	Subcutaneous(ly)
SD	Stable Disease
SHP	Src homology phosphatase
SOP	Standard Operating Procedures
sSAP	Supplemental statistical analysis plan
SmPC	Summary of Product Characteristics
T	Tumor
T3	Total triiodothyronine
T4	Free thyroxine
TCR	T Cell Receptor
TILs	Tumor-Infiltrating T Lymphocytes
TNBC	Triple-negative Breast Cancer
TSH	Thyroid Stimulating Hormone
ULN	Upper Limit of Normal
WBC	White Blood Cell
X	Paclitaxel
yCN0	Node-negative disease after chemotherapy

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 – TRIAL PROCEDURES (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	

THIS PROTOCOL AMENDMENT AND ALL OF THE INFORMATION RELATING TO IT ARE CONFIDENTIAL AND PROPRIETARY PROPERTY OF MERCK SHARP & DOHME LLC, RAHWAY, NJ, USA (MSD).

SPONSOR:
Merck Sharp & Dohme LLC
(hereafter referred to as the Sponsor or MSD)
126 East Lincoln Avenue
P.O. Box 2000
Rahway, NJ 07065 USA

Protocol-specific Sponsor Contact information can be found in the Investigator Trial File Binder (or equivalent).

TITLE:

A Phase III, Randomized, Double-blind Study to Evaluate Pembrolizumab plus Chemotherapy vs Placebo plus Chemotherapy as Neoadjuvant Therapy and Pembrolizumab vs Placebo as Adjuvant Therapy for Triple Negative Breast Cancer (TNBC)

IND NUMBER: 124,442
EudraCT NUMBER: 2016-004740-11

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 Scientific Advisory Committee

This trial was developed in collaboration with a Scientific Advisory Committee (SAC). The SAC comprises both Sponsor and non-Sponsor scientific experts who provide input with respect to trial design, interpretation of trial results and subsequent peer-reviewed scientific publications.

7.3.2 Executive Oversight Committee

The Executive Oversight Committee (EOC) comprises members of Sponsor Senior Management. The EOC will receive and decide upon any recommendations made by the external DMC regarding the trial.

7.3.3 Data Monitoring Committee

To supplement the routine trial monitoring outlined in this protocol, an external Data Monitoring Committee (DMC) will monitor the interim data from this trial. The voting members of the committee are external to the Sponsor. The members of the DMC must not be involved with the trial in any other way (e.g., they cannot be trial investigators) and must have no competing interests that could affect their roles with respect to the trial.

The DMC will make recommendations to the EOC regarding steps to ensure both subject safety and the continued ethical integrity of the trial. Also, the DMC will review interim trial results, consider the overall risk and benefit to trial participants (see Section 8.7 - Interim Analyses) and recommend to the EOC if the trial should continue in accordance with the protocol.

Specific details regarding composition, responsibilities, and governance, including the roles and responsibilities of the various members and the Sponsor protocol team; meeting facilitation; the trial governance structure; and requirements for and proper documentation of DMC reports, minutes, and recommendations will be described in a separate charter that is reviewed and approved by the DMC. The DMC will monitor the trial at an appropriate frequency, as described in the detailed DMC charter. The DMC will also make recommendations to the Sponsor protocol team regarding steps to ensure both subject safety and the continued ethical integrity of the trial.

8.0 STATISTICAL ANALYSIS PLAN

This section outlines the statistical analysis strategy and procedures for the study. If, after the study has begun, changes are made to primary and/or key secondary hypotheses, or the statistical methods related to those hypotheses, then the protocol will be amended (consistent with ICH Guideline E-9). Changes to exploratory or other non-confirmatory analyses made

after the protocol has been finalized, but prior to the conduct of analysis, will be documented in a supplemental statistical analysis plan (sSAP) and referenced in the Clinical Study Report (CSR) for the study. A separate PK analysis and biomarker analysis plan may be provided. Post hoc exploratory analyses will be clearly identified in the CSR. The Patient Reported Outcomes (PRO) analysis plan will also be included in the sSAP.

8.1 Statistical Analysis Plan Summary

Key elements of the statistical analysis plan (SAP) are summarized below. The comprehensive plan is provided in Sections 8.2 – Responsibility for Analyses/In-House Blinding through 8.12 – Extent of Exposure.

Study Design Overview	A Phase III, Randomized, Double-blind Study to Evaluate Pembrolizumab plus Chemotherapy vs Placebo plus Chemotherapy as Neoadjuvant Therapy and Pembrolizumab vs Placebo as Adjuvant Therapy for Triple Negative Breast Cancer (TNBC)
Treatment Assignment	Approximately 1150 subjects will be randomized (double-blind) in a 2:1 ratio between 2 treatment arms: 1. Pembrolizumab plus chemotherapy as neoadjuvant therapy and pembrolizumab as adjuvant therapy, or 2. Placebo plus chemotherapy as neoadjuvant therapy and placebo as adjuvant therapy. Stratification factors are as follows: 1. Nodal status (Positive vs. Negative) 2. Tumor size (T1/T2 vs. T3/T4) 3. Choice of Carboplatin (Cb): Q3W vs. Weekly
Analysis Populations	Efficacy: Intention-to-Treat Population (ITT) Safety: All Subjects as Treated (ASaT)
Primary Endpoint(s)	1. Pathological complete response (pCR) rate (ypT0/Tis ypN0) 2. Event-free survival (EFS)
Key Secondary Endpoint(s)	Overall survival (OS)
Statistical Methods for Key Efficacy Analyses	• Treatment comparisons of the pCR rate (ypT0/Tis ypN0) will be performed using the stratified Miettinen and Nurminen method. • Treatment comparisons for time-to-event endpoints such as EFS and OS will be evaluated using a stratified log-rank test. The HR will be estimated using a stratified Cox model.
Statistical Methods for Key Safety Analyses	The analysis of safety will follow a tiered approach. There are no Tier 1 events for this study. Point estimates and 95% confidence intervals (CIs) for between-treatment comparisons via the Miettinen and Nurminen method will be provided for Tier 2 safety endpoints; only point estimates by treatment group will be provided for Tier 3 safety endpoints.

Interim Analyses	Seven efficacy interim analyses (IAs) are planned. Results will be reviewed by an external DMC. Details are provided in Section 8.7 – Interim Analyses. Efficacy Interim Analyses • IA 1 (IA1): at least 500 subjects have or would have completed surgery after ~6 months neoadjuvant treatment and enrollment is completed. It is estimated ~18 months after the first subject is randomized. o Primary purpose: interim pCR(ypT0/Tis ypN0) analysis. • IA 2 (IA2): ~24 months after the first subject is randomized (The timing of IA is calendar driven). It is estimated that ~93 EFS events will have been observed and ~1000 subjects have or would have completed surgery after ~6 months neoadjuvant treatment. o Primary purpose: interim EFS analysis and final pCR(ypT0/Tis ypN0) analysis. • IA 3 (IA3): ~36 months after the first subject is randomized (The timing of IA is calendar driven). It is estimated that ~154 EFS events will have been observed. o Primary purpose: interim EFS analysis. • IA 4 (IA4): ~48 months after the first subject is randomized (The timing of IA is calendar driven). It is estimated that ~201 EFS events will have been observed. o Primary purpose: interim EFS analysis. • IA 5 (IA5): ~60 months after the first subject is randomized (The timing of IA is calendar driven). It is estimated that ~239 EFS events will have been observed. o Primary purpose: interim EFS analysis. • IA 6 (IA6): ~72 months after the first subject is randomized (The timing of IA is calendar driven). It is estimated that ~270 EFS events will have been observed. o Primary purpose: interim EFS analysis. • IA 7 (IA7): ~84 months after the first subject is randomized (The timing of IA is calendar driven). It is estimated that ~294 EFS events will have been observed. o Primary purpose: interim EFS analysis. Final analysis (FA): ~327 EFS events have been observed (event driven). It is expected to occur at ~102 months after the first subject is randomized. o Primary purpose: final EFS analysis. OS will be tested only when the null hypothesis for EFS is rejected.
Multiplicity	The overall type-I error rate over the 2 primary endpoints will be strongly controlled at 2.5% (one-sided) with 0.5% allocated to the pCR (ypT0/Tis ypN0) and 2.0% allocated to the EFS hypotheses. The graphical approach of Maurer and Bretz [68] will be applied to re-allocate alpha among hypotheses for pCR(ypT0/Tis ypN0), EFS, and OS in subjects with locally advanced TNBC. Group sequential methods will be used to allocate alpha between the interim and final analyses for pCR(ypT0/Tis ypN0), EFS and OS in subjects with locally advanced TNBC.
Sample Size and Power	The FA of the study is EFS event-driven and will be conducted after approximately 327 EFS events have been observed. It may occur at ~102 months after the first subject randomized. The planned sample size is approximately **1150** subjects. (1) pCR (ypT0/Tis ypN0): the trial has an overall ~95% power to detect a true pCR rate difference of 15 percentage points (pembrolizumab + chemotherapy vs. placebo + chemotherapy) at alpha = 0.5% (one-sided) with ~1000 subjects who have or would have completed surgery after ~6 months neoadjuvant treatment at IA2. (2) EFS: the trial has an overall ~80% power at a one-sided 2.0% alpha level, if the true HR is 0.71. (3) OS: the trial has an overall ~79.7% power at a one-sided 2.0% alpha level, if the true HR is 0.70.

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.

The Sponsor will generate the randomized allocation schedule(s) for study treatment assignment for this protocol, and the randomization will be implemented in IVRS.

This study will be conducted as a double-blind trial under in-house blinding procedures. The official, final database will not be unblinded until medical/scientific review has been performed, protocol deviations have been identified, and data have been declared final and complete. In addition, the site radiologist(s) will perform the imaging review without knowledge of treatment group assignment.

All pathologists reviewing and interpreting surgical specimens for assessment of pCR are required to be blinded to treatment assignment.

Planned efficacy IAs are described in Section 8.7 – Interim Analyses. Blinding to treatment assignment will be maintained at all investigational sites.

Treatment-level results of the efficacy IAs will be provided by an external unblinded statistician to the external DMC.

The external DMC will serve as the primary reviewer of the results of the IAs and will make recommendations for discontinuation of the study or modification to an EOC of the Sponsor. Depending on the recommendation of the external DMC, the Sponsor may prepare a regulatory submission. Subject-level unblinding to support regulatory filing will be restricted to a designate team in the Sponsor, who will have no other responsibilities associated with the study.

If the external DMC recommends modifications to the design of the protocol or discontinuation of the study, this EOC may be unblinded to study results at the treatment level in order to act on these recommendations or facilitate regulatory filing. Limited additional Sponsor personnel may also be unblinded to the treatment level results of the IA(s), if required, in order to act on the recommendations of the external DMC or facilitate regulatory filing. The extent to which individuals are unblinded with respect to results of IAs will be documented. Additional logistical details, revisions to the above plan and data monitoring guidance will be provided in the external DMC Charter. Key aspects of the IAs are described in Section 8.7 – Interim Analyses.

Prior to final study unblinding, the external unblinded statistician will not be involved in any discussions regarding modifications to the protocol, statistical methods, identification of protocol deviations, or data validation efforts after the IAs.

8.3 Hypotheses/Estimation

Objectives and hypotheses of the study are stated in Section 3.0 – Objective(s) & Hypothesis(es).

8.4 Analysis Endpoints

Efficacy and safety endpoints that will be evaluated are listed below.

8.4.1 Efficacy Endpoints

Primary Endpoints

Pathological Complete Response (pCR) Rate (ypT0/Tis ypN0)

pCR rate (ypT0/Tis ypN0) is defined as the proportion of subjects without 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 per current AJCC staging criteria assessed by the local pathologist at the time of definitive surgery.

Subjects who don't receive any study medication and subjects who are discontinued from the study treatment and continue neoadjuvant treatment with drug categories not specified by the study prior to definitive surgery will be classified as not having a pCR (non-responders) in the efficacy analyses, regardless of the results obtained from the surgery. Subjects who are discontinued from study treatment due to the reasons that preclude definitive surgery (including the development of distant metastatic disease) are considered non-responders. Subjects without pCR data due to any reason will be counted as non-responders.

Event-Free Survival (EFS)

EFS is defined as the time from randomization to the first occurrence of any of the following events: progression of disease that precludes definitive surgery, local or distant recurrence, second primary malignancy or death due to any cause. Progression of disease, local or distant recurrence, and second primary malignancy are based on investigator determination. See Section 8.6.1 – Statistical Methods for Efficacy Analyses for the definition of censoring.

Subjects who had locoregional PD (as assessed radiologically) during the neoadjuvant treatment phase, but went to definitive surgery and had clear margins, will not be classified as having an EFS event. If the subject had pCR, then the PD will be considered pseudoprogression. Subjects who had locoregional PD (as assessed radiologically) during the neoadjuvant treatment phase, but went to surgery and ended up with positive margins at their last surgery, will be classified as having an EFS event at the time of diagnosis of locoregional PD. Subjects who had distant PD (metastasis, confirmed by biopsy or 2 imaging studies at least 4 weeks apart, if a biopsy is not feasible) during the neoadjuvant treatment phase had an EFS event at the time of diagnosis of distant PD, even if the subjects had palliative breast surgery. Subjects who did not have PD during the neoadjuvant treatment phase, but had positive margins at their last surgery, will be classified as having an EFS event at surgery. Subjects who had cytological, histological, and/or radiological evidence of local or distant recurrence during the adjuvant phase had an EFS event at the time recurrence was diagnosed.

In terms of second primary malignancy**,** any confirmed diagnosis of a second primary cancer other than basal or squamous cell carcinoma of the skin, carcinoma in situ of the cervix, or second primary breast will be considered an event in the analysis of the EFS. Lobular

carcinoma in situ of the breast (LCIS), ductal carcinoma in situ of the breast (DCIS) and myelodysplastic syndrome are not considered an event.

Secondary Endpoints

Pathological Complete Response (pCR) Rate (ypT0 ypN0)

pCR rate (ypT0 ypN0) is defined as the proportion of subjects without 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 per current AJCC staging criteria assessed by the local pathologist at the time of definitive surgery.

Pathological Complete Response (pCR) Rate (ypT0/Tis)

pCR rate (ypT0/Tis) is defined as the proportion of subjects without invasive cancer in the breast irrespective of ductal carcinoma in situ or nodal involvement following completion of neoadjuvant systemic therapy per current AJCC staging criteria assessed by the local pathologist at the time of definitive surgery.

Overall Survival (OS)

OS is defined as the time from randomization 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.

Exploratory Efficacy Endpoints

- ORR based on RECIST 1.1: the percentage of subjects who have achieved CR or PR according to RECIST 1.1 by central radiology review. Subjects with missing outcome for objective response will be considered non-responders. This will be applied to individuals who choose to participate in the breast MRI.
- Distant recurrence-free survival (DRFS): the time from definitive surgery to distance recurrence event as assessed by investigator.
- ORR based on MRI FTV: the percentage of subjects who have achieved CR or PR using MRI FTV as assessed by central radiology review.
- Residual Cancer Burden (RCB): residual disease in either the breast or lymph node at the time of definitive surgery as assessed by the local pathologist.
- The rate of pCR and EFS in subjects with different levels of TILs at baseline.

8.4.2 Safety Endpoints

Safety measurements are described in Section 4.2.3 – Rationale for Endpoints and Section 7.0 – Trial Procedures.

8.4.3 PRO Endpoints

- Health-related QoL assessments using the EORTC QLQ-C30 and EORTC QLQ-BR23
- Assessments using EQ-5D™

8.4.4 Other Exploratory Endpoints

- The rate of BCS at the time of definitive surgery
- Relationship between molecular (genomic, metabolic and/or proteomic) biomarkers and clinical response/resistance, safety, pharmacodynamic activity, and/or the mechanism of action of pembrolizumab and other treatments

8.5 Analysis Populations

8.5.1 Efficacy Analysis Populations

The ITT population will serve as the population for primary efficacy analyses. All randomized subjects will be included in this population. Subjects will be included in the treatment group to which they are randomized.

Details on the approach to handling missing data are provided in Section 8.6 – Statistical Methods.

8.5.2 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 randomized subjects who received at least one study treatment. Subjects will be included in the treatment group corresponding to the study treatment they actually received for the analysis of safety data using the ASaT population. For most subjects this will be the treatment group to which they are randomized. Subjects who take incorrect study treatment for the entire treatment period will be included in the treatment group corresponding to the study treatment actually received. Any subject who receives the incorrect study treatment for one cycle, but receives the correct treatment for all other cycles, will be analyzed according to the randomized treatment group and a narrative will be provided for any events that occur during the cycle for which the subject is incorrectly dosed.

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.

8.5.3 PRO Analysis Population

PRO analyses are based on the PRO Full Analysis Set (FAS) population, defined as subjects who have at least one PRO assessment available and have received at least one dose of study treatment.

8.6 Statistical Methods

8.6.1 Statistical Methods for Efficacy Analyses

This section describes the statistical methods that address the primary and secondary objectives. Methods related to the secondary objectives addressing PROs, as well as exploratory objectives, will be described in the sSAP(s).

Efficacy results that will be deemed to be statistically significant after consideration of the Type I error control strategy are described in Section 8.8 – Multiplicity. Nominal p-values will be computed for other efficacy analyses, but should be interpreted with caution due to potential issues of multiplicity.

8.6.1.1 Pathological Complete Response (pCR) Rate

The stratified Miettinen and Nurminen's method will be used for the comparison of pCR rates using 3 definitions between 2 treatment arms (pembrolizumab + chemotherapy vs. placebo + chemotherapy). The difference in pCR rate and its 95% CI from the stratified Miettinen and Nurminen's method with strata weighting by sample size will be reported for subjects with locally advanced TNBC and for individuals with PD-L1 (+) tumors. The stratification factors used for randomization (see Section 5.4 – Stratification) will be applied to the analysis.

The primary hypothesis of the pCR rate (ypT0/Tis ypN0) in subjects with locally advanced TNBC will be tested according to the hypotheses testing plan as described in Section 8.8 – Multiplicity.

Sensitivity analyses will be performed for pCR rates using Cochran-Mantel-Haenszel test. Associated odds ratios and 95% CIs will be calculated. Additional supportive unstratified analyses may also be provided. Further details of sensitivity and supportive analyses will be described in the sSAP as needed.

8.6.1.2 Event-Free Survival (EFS)

The non-parametric Kaplan-Meier method will be used to estimate the EFS curve in each treatment group. The treatment difference in EFS will be assessed by the stratified log-rank test for subjects with locally advanced TNBC and for individuals with PD-L1 (+) tumors. A stratified Cox proportional hazard model with Efron's method of tie handling will be used to assess the magnitude of the treatment difference (ie, HR) between the treatment arms. The HR and its 95% CI from the stratified Cox model with Efron's method of tie handling and with a single treatment covariate will be reported. Kaplan-Meier estimates and the corresponding 95% CIs at two-year, three-year and five-year will be provided for EFS. The stratification factors used for randomization (see Section 5.4 – Stratification) will be applied to both the stratified log-rank test and the stratified Cox model.

The primary hypothesis of EFS in subjects with locally advanced TNBC will be tested according to the hypotheses testing plan as described in Section 8.8 – Multiplicity.

For the primary analysis, the true date of event will be approximated by the date of the first assessment at which event is objectively documented. Subjects who do not experience an event at the time of data analysis will be censored at the date they were last known to be alive and event free.

In order to evaluate the robustness of the EFS endpoint, sensitivity analyses with a different set of censoring rules may be performed. The details of censoring rules will be specified in the sSAP.

The proportional hazards assumption on EFS will be examined using both graphical and analytical methods if warranted. The log[-log] of the survival function vs time for EFS may be plotted for the comparison between pembrolizumab and placebo arms. If the curves are not parallel, indicating that hazards are not proportional, supportive analyses may be conducted to account for the possible non-proportional hazards effect associated with immunotherapies using, for example, Restricted Mean Survival Time (RMST) method [69] or a parametric method [70].

One assumption for stratified Cox proportional hazard model is that the treatment HR is constant across the strata. If strong departures from this assumption are observed (which can result in a notably biased and/or less powerful analysis), a sensitivity analysis may be performed based on a two-step weighted Cox model approach by Mehrotra et al., 2012 [71], in which the treatment effect is first estimated for each stratum, and then the stratum specific estimates are combined for overall inference using sample size weights.

Additional supportive unstratified analyses may also be provided. Further details of sensitivity analyses will be described in the sSAP.

8.6.1.3 Overall Survival

The non-parametric Kaplan-Meier method will be used to estimate the survival curves. The treatment difference in survival will be assessed by the stratified log-rank test. A stratified Cox proportional hazard model with Efron's method of tie handling will be used to assess the magnitude of the treatment difference (ie, the HR) for subjects with locally advanced TNBC and for individuals with PD-L1 (+) tumors. The HR and its 95% CI from the stratified Cox model with a single treatment covariate will be reported. The stratification factors used for randomization (see Section 5.4 – Stratification) will be applied, as stratification factors used for analysis, to both the stratified log-rank test and the stratified Cox model. Kaplan-Meier estimates and the corresponding 95% CIs at 2-years, 3-years and 5-years will be provided for OS.

The secondary hypothesis of OS in subjects with locally advanced TNBC will be tested according to the hypotheses testing plan as described in Section 8.8 – Multiplicity.

Subjects in the combination of placebo and chemotherapy arm are expected to discontinue treatment earlier compared to subjects in the combination of pembrolizumab and chemotherapy arm and are not allowed to crossover to the combination of pembrolizumab and chemotherapy arm; however, they may be treated with another anti–PD-1 drug. As an exploratory analysis, adjustment for the effect of crossover on OS may be performed using

recognized methods (eg, the Rank Preserving Structural Failure Time (RPSFT) model proposed by Robins and Tsiatis [72], two-stage model), based on an examination of the appropriateness of the data to the assumptions required by the methods.

Additional supportive unstratified analyses may also be provided. Further details of sensitivity analyses will be described in the sSAP as needed.

8.6.1.4 Summary of Statistical Methods for Efficacy

Table 10 summarizes the primary analysis approach for primary and secondary efficacy endpoints. Sensitivity analysis methods are described above for each endpoint as applicable.

The strategy to address multiplicity issues with regard to multiple efficacy endpoints, multiple populations, and IAs is described in Section 8.7 – Interim Analyses and in Section 8.8 – Multiplicity.

Table 10 Analysis Strategy for Key Efficacy Endpoints

Endpoint/Variable (Description, Time Point)	Statistical Method†	Analysis Population	Missing Data Approach
Primary Hypothesis 1			
pCR(ypT0/Tis ypN0)	Stratified M & N method‡	ITT	Subjects with relevant data missing are considered non-responders
Primary Hypothesis 2			
EFS	Test: Stratified log-rank test Estimation: Stratified Cox model with Efron's tie handling method	ITT	Censored at last known alive and event free date
Secondary Hypothesis 1			
OS	Test: Stratified log-rank test Estimation: Stratified Cox model with Efron's tie handling method	ITT	Censored at last known alive date

† Statistical models are described in further details in the text. For stratified analyses, the stratification factors used for randomization will be used as stratification factors for analysis.
‡ Miettinen and Nurminen method with strata weighting by sample size.

8.6.2 Statistical Methods for Safety Analyses

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

The analysis of safety results will follow a tiered approach as shown in Table 11. The tiers differ with respect to the analyses that will be performed. Based on toxicity data across the pembrolizumab program, the combination of chemotherapy with pembrolizumab does not seem to produce toxicity beyond what is expected for these therapies alone. For these reasons, there are no events of interest that warrant inferential testing. Therefore, there are no Tier 1 events in this study. Tier 2 parameters will be assessed via point estimates with 95% CIs provided for

between-group comparisons; only point estimates by treatment group will be provided for Tier 3 safety parameters.

AEs (specific terms as well as system organ class terms) and predefined limits of change will be classified as belonging to "Tier 2" or "Tier 3", based on the percent of subjects with events observed. Specific AEs occurring in ≥ 5% of subjects or specific serious AEs occurring in ≥ 1% of subjects or specific Grade 3-5 AEs occurring in ≥ 1% of subjects will be considered Tier 2 endpoints. All other adverse experiences and predefined limits of change will belong to Tier 3.

The threshold of at least 5% of subjects with events in one or more treatment groups was chosen for specific AEs as Tier 2 endpoints because this incidence rate would allow meaningful statistical assessments for AEs in general. Serious and Grade 3-5 AEs are expected to occur less frequently but important for the overall safety assessment, as such the threshold to classify these AEs as Tier 2 endpoints are lower than that for general specific AEs. Because many 95% CIs may be provided without adjustment for multiplicity, the CIs should be regarded as a helpful descriptive measure to be used in review, not a formal method for assessing the statistical significance of the between-group differences in adverse experiences and predefined limits of change.

Continuous measures such as changes from baseline in laboratory, ECGs, and vital signs will be considered Tier 3 safety parameters. Summary statistics for baseline, on-treatment, and change from baseline values will be provided by treatment group.

The broad clinical and laboratory AE categories consisting of the percentage of subjects with any AE, any drug-related AE, any Grade 3-5 AE, any SAE, any AE which is both drug-related and Grade 3-5, any AE which is both serious and drug-related, dose modification due to AE, and who discontinued due to an AE, and death will be considered Tier 2 endpoints. For Tier 2 endpoints, point estimates and 95% CIs will be provided for between-treatment differences in the percentage of subjects with events; these analyses will be performed using the Miettinen and Nurminen method.

Table 11 Analysis Strategy for Safety Parameters

Safety Tier	Safety Endpoint	95% CI for Treatment Comparison	Descriptive Statistics
Tier 2	Any AE	X	X
	Any Serious AE	X	X
	Any Grade 3-5 AE	X	X
	Any Drug-Related AE	X	X
	Any Serious and Drug-Related AE	X	X
	Any Grade 3-5 and Drug-Related AE	X	X
	Dose Modification due to AE	X	X
	Discontinuation due to AE	X	X
	Death	X	X
	Specific AEs, SOCs (incidence ≥5% of subjects in one of the treatment groups)	X	X
	Specific Serious AEs, SOCs (incidence ≥1% of subjects in one of the treatment groups)	X	X
	Specific Grade 3-5 AEs, SOCs (incidence ≥1% of subjects in one of the treatment groups)	X	X
Tier 3	Specific AEs, SOCs (incidence <5% in both treatment groups) or PDLCs		X
	Specific Serious AEs, SOCs (incidence <1% of subjects in both treatment groups)		X
	Specific Grade 3-5 AEs, SOCs(incidence <1% of subjects in both treatment groups)		X
	Change from Baseline Results (Labs, ECGs, Vital Signs)		X
Note: SOC=System Organ Class; PDLC=Pre-Defined Limit of Change; X = results will be provided.			

8.6.3 Summaries of Demographic and Baseline Characteristics

The comparability of the treatment groups for each relevant characteristic will be assessed by the use of tables and/or graphs. No statistical hypothesis testing will be performed on these characteristics. The number and percentage of subjects screened, randomized, the primary reasons for screening failure, and the primary reasons for discontinuation will be displayed. Demographic variables (eg, age) and baseline characteristics will be summarized by treatment either by descriptive statistics or categorical tables.

8.7 Interim Analyses

8.7.1 Safety Interim Analyses

The external DMC will conduct regular safety monitoring. The timing of the safety monitoring will be specified in the DMC charter.

8.7.2 Efficacy Interim Analyses

Two IAs are planned for the rate of pCR (ypT0/Tis ypN0) and should be at least 3 months apart. The timing of IAs for EFS is calendar-based and the IAs are planned to be conducted

annually after 2 years. In addition, the FA for EFS needs to be at least 1 year apart from the last IA. Currently, seven efficacy IAs are planned in addition to the FA for this study. Results of the efficacy IAs will be reviewed by an external DMC. If the EFS null hypotheses are rejected prior to the FA, the external DMC may recommend stopping the study early for efficacy. This study is not planned to be stopped for futility. Therefore, no futility bound is provided. Details on how the above planned analyses are incorporated into establishing statistical significance and the boundaries with regard to efficacy are discussed further in Section 8.8, Multiplicity.

Interim Analysis 1 (Interim pCR (ypT0/Tis ypN0) Analysis)

The primary purpose of efficacy IA 1 (IA1) is to evaluate superiority of pembrolizumab + chemotherapy compared to placebo + chemotherapy with respect to the rate of pCR (ypT0/Tis ypN0). IA1 will be performed after: (1) enrollment is completed, and (2) at least 500 subjects have or would have completed surgery after ~6 months neoadjuvant treatment. It may occur ~18 months after the first subject is randomized.

A supportive analysis to summarize the EFS data will be performed at IA1 and no hypothesis testing will be performed.

Interim Analysis 2 (Interim EFS Analysis and Final pCR (ypT0/Tis ypN0) Analysis)

The primary purpose of efficacy IA 2 (IA2) is to evaluate superiority of pembrolizumab compared to placebo with respect to EFS. The timing of IA2 is calendar driven and IA2 will be performed at ~24 months after the first subject is randomized. It is estimated that approximately 93 EFS events will have been observed among subjects with locally advanced TNBC.

Another purpose of efficacy IA 2 (IA2) is to evaluate superiority of pembrolizumab + chemotherapy compared to placebo + chemotherapy with respect to the rate of pCR (ypT0/Tis ypN0). It is estimated that approximately 1000 subjects have or would have completed surgery after ~6 months neoadjuvant treatment. If more than 1000 subjects have or would have surgery data in IA2, the pCR results from additional subjects may be included in the analyses.

Interim Analysis 3 (Interim EFS Analysis)

The primary purpose of efficacy IA 3 (IA3) is to evaluate superiority of pembrolizumab compared to placebo with respect to EFS. The timing of IA3 is calendar driven and IA3 will be performed at ~36 months after the first subject is randomized. It is estimated that approximately 154 EFS events will have been observed among subjects with locally advanced TNBC.

A supportive pCR analysis to summarize the data for all subjects who have or would have completed surgery after ~6 months neoadjuvant treatment will be performed at IA3 and no hypothesis testing will be performed.

Interim Analysis 4 (Interim EFS Analysis)

The primary purpose of efficacy IA 4 (IA4) is to evaluate superiority of pembrolizumab compared to placebo with respect to EFS. The timing of IA4 is calendar driven and the analysis may be performed at ~48 months after the first subject is randomized. It is estimated that approximately 201 EFS events will have been observed among subjects with locally advanced TNBC in IA4.

Interim Analysis 5 (Interim EFS Analysis)

The primary purpose of efficacy IA 5 (IA5) is to evaluate superiority of pembrolizumab compared to placebo with respect to EFS. The timing of IA5 is calendar driven and the analysis may be performed at ~ 60 months after the first subject randomized. It is estimated that approximately 239 EFS events will have been observed among subjects with locally advanced TNBC in IA5.

Interim Analysis 6 (Interim EFS Analysis)

The primary purpose of efficacy IA 6 (IA6) is to evaluate superiority of pembrolizumab compared to placebo with respect to EFS. The timing of IA6 is calendar driven and the analysis may be performed at ~ 72 months after the first subject randomized. It is estimated that approximately 270 EFS events will have been observed among subjects with locally advanced TNBC in IA6.

Interim Analysis 7 (Interim EFS Analysis)

The primary purpose of efficacy IA 7 (IA7) is to evaluate superiority of pembrolizumab compared to placebo with respect to EFS. The timing of IA7 is calendar driven and the analysis may be performed at ~ 84 months after the first subject randomized. It is estimated that approximately 294 EFS events will have been observed among subjects with locally advanced TNBC in IA7.

Final Analysis (Final EFS Analysis)

The FA of the study is event-driven and will be conducted after approximately 327 EFS events have been observed. It may occur at ~102 months after the first subject is randomized. If 327 EFS events are observed before 102 months after the first subject is randomized, the FA will be conducted at the time when approximately 327 EFS events have been observed. The final significance boundary will be adjusted for the EFS events seen at the interim analyses performed and the number of EFS events that have occurred by the FA. OS will be tested only after when the null hypothesis for EFS is rejected.

The analyses planned, endpoints evaluated, drivers of the timing, and primary purpose of analyses are summarized in Table 12 Any changes to the timing of the analyses, along with its rational, will be documented in a memo to the study file before the database lock.

Table 12 Analyses Planned, Endpoints Evaluated, and Drivers of Timing

Analysis	Criteria for Conduct of Analysis	Endpoint	Estimated Time after First Subject Randomized	Primary Purpose of Analysis
IA1: Interim pCR Analysis	(1) enrollment is completed, and (2) at least 500 subjects have or would have completed surgery after ~6 months neoadjuvant treatment	pCR (ypT0/Tis ypN0)	~18 months	pCR IA
IA2: Interim EFS Analysis and Final pCR Analysis	~24 months after first subject randomized.	EFS	~24 months	EFS IA
		pCR (ypT0/Tis ypN0)		pCR FA
IA3: Interim EFS Analysis	~36 months after first subject randomized.	EFS	~36 months	EFS IA
IA4: Interim EFS Analysis	~48 months after the first subject is randomized.	EFS	~48 months	EFS IA
IA5: Interim EFS Analysis	~60 months after the first subject is randomized.	EFS	~60 months	EFS IA
IA6: Interim EFS Analysis	~72 months after the first subject is randomized.	EFS	~72 months	EFS IA
IA7: Interim EFS Analysis	~84 months after the first subject is randomized.	EFS	~84 months	EFS IA
FA: Final EFS Analysis	~327 EFS events have been observed.	EFS	~102 months	EFS FA

8.8 Multiplicity

The multiplicity strategy specified in this section will be applied to the dual primary hypotheses and the secondary hypothesis. The dual primary hypotheses are testing superiority of pembrolizumab compared to placebo in pCR (ypT0/Tis ypN0) or EFS in subjects with locally advanced TNBC. The secondary hypothesis is testing superiority in OS in subjects with locally advanced TNBC. The overall Type-I error among multiple endpoints is strongly controlled at 2.5% (one-sided), with 0.5% initially allocated to the pCR (ypT0/Tis ypN0) hypothesis and 2.0% initially allocated to the EFS hypothesis. The study will be

considered a success if pCR (ypT0/Tis ypN0) or EFS is demonstrated to be statistically significant at either an IA or the FA under multiplicity control.

The study uses the graphical method of Maurer and Bretz [68] to control multiplicity for multiple hypotheses as well as IAs. According to this approach, study hypotheses may be tested more than once, and when a particular null hypothesis is rejected, the α allocated to that hypothesis can be reallocated to other hypothesis tests. Figure 3 shows the initial one-sided α allocation for each hypothesis in the ellipse representing the hypothesis. The weights for reallocation from each hypothesis to the others are represented in the boxes on the lines connecting hypotheses.

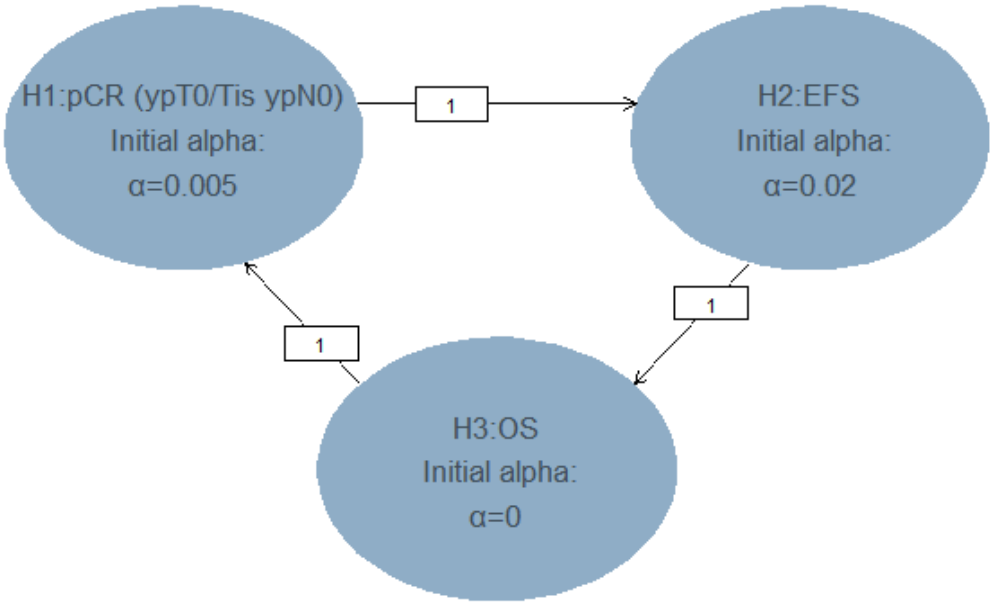

Figure 3 Multiplicity Graph for Type I Error Control of Study Hypotheses

8.8.1 pCR (ypT0/Tis ypN0)

The trial initially allocates α=0.005, one-sided to test pCR (ypT0/Tis ypN0). Table 13 shows the boundary properties for the IAs, which were derived using a Hwang-Shih-DeCani α-spending function with gamma parameter (0). Note that the final row indicates the total power to reject the null hypothesis for pCR. If the actual number of subjects at the pCR analysis differs from those specified in the table, the bounds will be adjusted using the Hwang-Shih-DeCani α-spending function accordingly. If the test of pCR (ypT0/Tis ypN0) hypothesis does not achieve statistical significance at either IA1 or IA2, the p-value from IA2 (ie, no new data is added after IA2) can be compared to an updated α-level based on group sequential design with α=0.025 if the null hypotheses for both EFS and OS are rejected at a later time. It gives >99% power to detect a true pCR rate difference of 15 percentage points (pembrolizumab + chemotherapy vs. placebo + chemotherapy) at α=0.025 (one-sided) and the observed difference in pCR between the treatment groups needs to be approximately 6.8 percentage points for the analysis to be considered positive.

Table 13 Boundary Properties for Planned Analyses of pCR (ypT0/Tis ypN0) Superiority Hypotheses Based on α=0.005

Analysis	Value	α=0.005
IA 1: 50%*	Z	2.8070
N: 500	p (1-sided) [§]	0.0025
	delta at bound[%]	0.1379
	P(Cross) if delta=0[†]	0.0025
	P(Cross) if delta=0.15[#]	0.5971
IA 2	Z	2.7403
N: 1000	p (1-sided) [§]	0.0031
	delta at bound[%]	0.0952
	P(Cross) if delta=0[†]	0.0050
	P(Cross) if delta=0.15[#]	0.9460

*Percentage of expected number of subjects at final analysis required at IA
[§]p (1-sided) is the nominal α for testing.
[%]delta at bound is the approximate delta required to reach an efficacy bound.
[†]P(Cross if delta=0) is the probability of crossing a bound under the null hypothesis, with an underlying pCR rate of 50%.
[#]P(Cross if delta=0.15) is the probability of crossing a bound under the alternative hypothesis.
Abbreviations: IA = interim analysis; pCR = pathological complete response.

8.8.2 Event-free Survival

The trial initially allocates α=0.02, one-sided to test EFS. If the null hypothesis for pCR (ypT0/Tis ypN0) is rejected, Figure 3 shows that its α=0.005 is fully reallocated to EFS hypothesis testing. Thus, the EFS null hypothesis may be tested at α=0.02, or α=0.025. Table 14 shows the boundary properties calculated based on the estimated number of events for each of these α-levels for the IAs and FA, which were derived using a cure rate model and Lan-DeMets O'Brien-Fleming spending function. Note that the final row indicates the total power to reject the null hypothesis for EFS at each α-level. If the actual number of events at the EFS analyses differ from those specified in the table, the bounds will be adjusted using the actual observed numbers of events and the Lan-DeMets O'Brien-Fleming spending function accordingly.

Of note, the efficacy interim analysis 2 (IA 2) occurred prior to Amendment 04 and as such the efficacy boundaries for EFS in IA 2 were calculated based on the estimated number of events.

Table 14 Efficacy Boundaries and Properties for EFS Analyses

Analysis	Value	α=0.02	α=0.025
IA 2: 28%*	Z	4.225	4.059
N: 1149	p (1-sided) §	0.00001	0.00002
Events: 93	HR at bound%	0.3934	0.4116
Month: 24	P(Cross) if HR=1†	<0.0001	<0.0001
	P(Cross) if HR=0.71#	0.0039	0.0063
IA 3: 47%*	Z	3.201	3.071
N: 1149	p (1-sided) §	0.0007	0.0011
Events: 154	HR at bound%	0.5782	0.5942
Month: 36	P(Cross) if HR=1†	0.0007	0.0011
	P(Cross) if HR=0.71#	0.1191	0.1470
IA 4: 61%*	Z	2.773	2.660
N: 1149	p (1-sided) §	0.0028	0.0039
Events: 201	HR at bound%	0.6603	0.6741
Month: 48	P(Cross) if HR=1†	0.0030	0.0042
	P(Cross) if HR=0.71#	0.3269	0.3691
IA 5: 73%*	Z	2.541	2.439
N: 1149	p (1-sided) §	0.0055	0.0074
Events: 239	HR at bound%	0.7054	0.7177
Month: 60	P(Cross) if HR=1†	0.0065	0.0087
	P(Cross) if HR=0.71#	0.5037	0.5455
IA 6: 82%*	Z	2.399	2.303
N: 1149	p (1-sided) §	0.0082	0.0106
Events: 270	HR at bound%	0.7333	0.7446
Month: 72	P(Cross) if HR=1†	0.0103	0.0135
	P(Cross) if HR=0.71#	0.6277	0.6646
IA 7: 90%*	Z	2.304	2.213
N: 1149	p (1-sided) §	0.0106	0.0135
Events: 294	HR at bound%	0.7519	0.7625
Month: 84	P(Cross) if HR=1†	0.0141	0.0181
	P(Cross) if HR=0.71#	0.7111	0.7427

Analysis	Value	α=0.02	α=0.025
Final	Z	2.168	2.082
N: 1149	p (1-sided) [§]	0.0151	0.0187
Events: 327	HR at bound[%]	0.7754	0.7851
Month: 102	P(Cross) if HR=1[†]	0.0200	0.0250
	P(Cross) if HR=0.71[#]	0.8005	0.8248

*Percentage of expected number of events at final analysis required at IA

[§]p (1-sided) is the nominal α for testing.

[%]HR at bound is the approximate HR required to reach an efficacy bound

[†]P(Cross if HR=1) is the probability of crossing a bound under the null hypothesis

[#]P(Cross if HR=0.71) is the probability of crossing a bound under the alternative hypothesis
A Haybittle-Peto type adjustment with p<0.0001 may be applied for EFS summary in IA1.

Abbreviations: EFS = event-free survival; HR = hazard ratio; IA = interim analysis.

8.8.3 Overall Survival

The study initially allocates α=0, one-sided to test OS and OS is tested only when the null hypothesis for EFS is rejected. Thus, the OS null hypothesis may be tested at α=0.02 (if the EFS null hypothesis is rejected but not the pCR [ypT0/Tis ypN0] null hypothesis) or α=0.025 (if both of pCR [ypT0/Tis ypN0] and EFS null hypotheses are rejected). Table 15 shows the boundary properties calculated based on the estimated number of events for each of these α-levels for the IA and FA, which were derived using a cure model and Lan-DeMets O'Brien-Fleming spending function. Note that the final row indicates the total power to reject the null hypothesis for OS at each α-level. If the actual number of events at the OS analyses differs from those specified in the table, the bounds will be adjusted using the actual observed numbers of events and the Lan-DeMets O'Brien-Fleming spending function accordingly. If EFS is found to be positive at an interim, but not OS, OS may continue to be followed.

Table 15 Efficacy Boundaries and Properties for OS Analyses

Analysis	Value	α=0.02	α=0.025
IA 2: 26%*	Z	4.428	4.255
N: 1149	p (1-sided) [§]	<0.00001	0.00001
Events: 77	HR at bound[%]	0.3421	0.3614
Month: 24	P(Cross) if HR=1[†]	<0.0001	<0.0001
	P(Cross) if HR=0.70[#]	0.0017	0.0029
IA 3: 44%*	Z	3.309	3.176
N: 1149	p (1-sided) [§]	0.0005	0.0007
Events: 132	HR at bound[%]	0.5418	0.5595
Month: 36	P(Cross) if HR=1[†]	0.0005	0.0008
	P(Cross) if HR=0.70[#]	0.0872	0.1104

Analysis	Value	α=0.02	α=0.025
IA 4: 59%*	Z	2.827	2.712
N: 1149	p (1-sided) [§]	0.0023	0.0033
Events: 176	HR at bound[%]	0.6360	0.6514
Month: 48	P(Cross) if HR=1[†]	0.0025	0.0036
	P(Cross) if HR=0.70[#]	0.2880	0.3289
IA 5: 71%*	Z	2.566	2.463
N: 1149	p (1-sided) [§]	0.0051	0.0069
Events: 213	HR at bound[%]	0.6881	0.7017
Month: 60	P(Cross) if HR=1[†]	0.0059	0.0080
	P(Cross) if HR=0.70[#]	0.4770	0.5193
IA 6: 82%*	Z	2.405	2.309
N: 1149	p (1-sided) [§]	0.0081	0.0105
Events: 243	HR at bound[%]	0.7204	0.7328
Month: 72	P(Cross) if HR=1[†]	0.0100	0.0131
	P(Cross) if HR=0.70[#]	0.6144	0.6519
IA 7: 90%*	Z	2.297	2.206
N: 1149	p (1-sided) [§]	0.0108	0.0137
Events: 267	HR at bound[%]	0.7421	0.7537
Month: 84	P(Cross) if HR=1[†]	0.0142	0.0181
	P(Cross) if HR=0.70[#]	0.7079	0.7397
Final	Z	2.168	2.082
N: 1149	p (1-sided) [§]	0.0151	0.0187
Events: 297	HR at bound[%]	0.7656	0.7763
Month: 102	P(Cross) if HR=1[†]	0.0200	0.0250
	P(Cross) if HR=0.70[#]	0.7965	0.8211

*Percentage of expected number of events at final analysis required at IA

[§]p (1-sided) is the nominal α for testing.

[%]HR at bound is the approximate HR required to reach an efficacy bound

[†]P(Cross if HR=1) is the probability of crossing a bound under the null hypothesis

[#]P(Cross if HR=0.70) is the probability of crossing a bound under the alternative hypothesis
A Haybittle-Peto type adjustment with p<0.0001 may be applied for OS summary at IA.

Abbreviations: HR = hazard ratio; IA = interim analysis; OS = overall survival.

8.8.4 Safety Analyses

The external DMC has responsibility for assessment of overall risk: benefit. When prompted by safety concerns, the external DMC can request corresponding efficacy data. External DMC review of efficacy data to assess the overall risk:benefit to trial subjects will not require a multiplicity adjustment typically associated with a planned efficacy IA; however, to account for any multiplicity concerns raised by the external DMC review of unplanned efficacy data prompted by safety concerns, a sensitivity analysis for efficacy endpoints adopting a conservative multiplicity adjustment will be pre-specified in the sSAP. This analysis will be performed if requested by the external DMC.

8.9 Sample Size and Power Calculations

The study will randomize approximately 1150 subjects in a 2:1 ratio between pembrolizumab plus chemotherapy as neoadjuvant therapy and pembrolizumab as adjuvant therapy (Arm 1) and placebo plus chemotherapy as neoadjuvant therapy and placebo as adjuvant therapy (Arm 2). The sample size was driven by EFS.

Randomization will be implemented centrally using IVRS and will be monitored on a regular basis. When IVRS alerts study is approaching the desired enrollment, screening should be stopped in time. However, subjects already in screening phase may be enrolled even after the maximum sample size has been reached.

pCR (ypT0/Tis ypN0) Rate

The first primary endpoint is pCR (ypT0/Tis ypN0) rate. The final pCR analysis will be performed after enrollment is completed, and ~1000 subjects have or would have completed surgery after ~6 months neoadjuvant treatment.

A sample size of ~1000 gives ~95 % power to detect a true pCR rate difference of 15 percentage points (pembrolizumab + chemotherapy vs. placebo + chemotherapy) at $\alpha = 0.5\%$ (one-sided). The sample size calculation is based on the following assumptions: 1) the α of 0.5% is allocated to the pCR hypothesis; 2) the underlying pCR is 50% in the placebo + chemotherapy arm, and there is 15 percentage points increase in pCR in the pembrolizumab + chemotherapy arm (pCR of 65%) in subjects with locally advanced TNBC; and 3) a drop-out rate of ~10%. In addition, a Hwang-Shih-DeCani alpha-spending function with gamma parameter (0) and are constructed to implement group sequential boundaries that control the Type-I error. The power for the pCR endpoint at different true pCRs for subjects with locally advanced TNBC is summarized in Table 16.

Table 16 Power for pCR

pCR Difference Between the 2 Treatment Arms	Subjects with Locally Advanced TNBC (N = 1000, α = 0.005)
12 percentage points	77%
15 percentage points	95%
17 percentage points	99%
All calculations assume pCR is 50% in the placebo + chemotherapy arm.	

The assumptions for a pCR rate of 50% in the placebo + chemotherapy arm are based on the estimates from Sikov et al., 2015 [2], and von Minckwitz et al., 2014 [1].

EFS

The other dual-primary endpoint is EFS. The final analysis of the study is EFS event-driven and will be conducted after approximately 327 EFS events have been observed, unless the study is terminated early. It may occur at ~ 102 months after first subject randomized (depending on enrollment rate and event accumulation rate).

With the α of 2% (one-sided) and sample size of ~1150, the trial has an overall ~80% power for EFS in subjects with locally advanced TNBC, assuming the true HR (pembrolizumab vs. placebo) is 0.71. According to published meta-analysis on this population that suggests ~50% of subjects may be disease-free long-term [14], a cure rate model is applied to account for the failure rates decreasing over time [73]. These calculations are based on the following assumptions: (1) EFS follows a Poisson mixture model (cure rate model with decreasing failure rate) distribution with ~78% EFS rate at 36 months and ~50% cure rate in the placebo arm, (2) an enrollment period of 18 months and at least 84 months follow-up, and (3) A yearly drop-out rate of 2% and additional ~3% to ~5% drop-out rate after surgery. The EFS control rate of 78% was estimated from an updated report from CALGB40603, presented at SABCS 2015 [74]. In addition, a Lan-DeMets O'Brien-Fleming approximation α-spending function is constructed to implement group sequential boundaries that control the Type-I error. Details on the Poisson mixture model are provided in Appendix 12.6.

OS

The key secondary endpoint is OS. If the null hypothesis for EFS is rejected at an interim analysis, the final OS analysis is event-driven and will be conducted after approximately 297 OS events would have been observed, unless the study is terminated early. It may occur at ~102 months after first subject randomized (depending on enrollment rate and event accumulation rate). If after 102 months after the first subject randomized the estimated number of OS events still haven't been observed, then the final OS analysis may be conducted at that time.

With the α of 2% (one-sided) and sample size of ~1150, the trial has an overall ~79.7% power for OS in subjects with locally advanced TNBC, assuming the true HR (pembrolizumab vs. placebo) is 0.70. According to published meta-analysis on this

population that suggests ~50% of subjects may be disease-free long-term [14], a cure rate model is applied to account for the failure rates decreasing over time [73]. These calculations are based on the following assumptions: (1) OS follows a Poisson mixture model (cure rate model with decreasing failure rate) distribution with ~81% OS rate at 36 months [74] and ~50% cure rate in the placebo arm, (2) an enrollment period of 18 months and at least 84 months follow-up, and (3) A yearly drop-out rate of 3%. In addition, a Lan-DeMets O'Brien-Fleming approximation α-spending function is constructed to implement group sequential boundaries that control the Type-I error.

The sample size and power calculations were performed in the software R (package "gsDesign").

8.10 Subgroup Analyses and Effect of Baseline Factors

To determine whether the treatment effect is consistent across various subgroups, the estimate of the between-group treatment effect (with a nominal 95% CI) for the primary endpoints will be estimated and plotted within each category of the following classification variables in subjects with locally advanced TNBC and in individuals with PD-L1 (+) tumors (CPS ≥1):

- Nodal status: Positive vs. Negative
- Tumor size: T1/T2 vs. T3/T4
- Choice of Carboplatin (Cb): Q3W vs. Weekly
- Tumor PD-L1 status (applies to all subjects with locally advanced TNBC): CPS ≥1 vs. CPS <1; CPS ≥10 vs. CPS <10; CPS ≥20 vs. CPS <20
- Menopausal status (for females only): pre- vs. post-menopausal
- Age: <65 years vs. ≥65 years
- Geographic region: Europe/Israel/North America/Australia vs. Asia vs. Rest of World
- Ethnic origin: Hispanic vs. Non-Hispanic
- ECOG performance status: 0 vs. 1
- HER2 status: IHC 2+ (but FISH-) vs. IHC 0-1+
- LDH: >upper limit of normal [ULN] vs. ≤ULN

8.11 Compliance (Medication Adherence)

Drug accountability data for study treatment will be collected during the study. Any deviation from protocol-directed administration will be reported.

8.12 Extent of Exposure

The extent of exposure will be summarized as duration of treatment in number of cycles or administrations as appropriate.