Official Protocol Title:	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)
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TITLE:

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)

IND NUMBER:124,442

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DOCUMENT HISTORY

Document	Date of Issue	Overall Rationale
MK-3475-355-07	17-JUN-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.
MK-3475-355-06	01-SEP-2021	To include language pertaining to the KN587 extension trial, as the plan is to transition current subjects over to KN587.
MK-3475-355-05	04-OCT-2019	The objectives, hypotheses, and statistical analysis plan were changed to include subjects with PD-L1 positive tumors with a higher combined positive score (CPS) cutoff of ≥10 (CPS ≥10).
MK-3475-355-04	20-MAR-2019	The timing of the final analysis was changed from overall survival (OS) event driven to both OS event and follow-up time driven to ensure adequate follow-up duration at time of the final analysis.
MK-3475-355-03	31-AUG-2018	Allocation of alpha over the primary endpoints and key secondary endpoints has been adjusted to allocate initial alpha to objective response rate (ORR) hypotheses and will allow testing of ORR hypothesis at interim analysis 1 (IA1) independent of the outcome of the other hypotheses. IA1 timing has been changed from progression-free survival (PFS) event driven to "~ 9 months after 640 Part 2 subjects are randomized". IA1 will now include the analysis of ORR, as well as interim analyses of PFS and OS.

Document	Date of Issue	Overall Rationale
MK-3475-355-02	05-FEB-2018	To align with the most current label and safety information for pembrolizumab, guidelines were added for dose modification in the event of myocarditis and updated guidelines for several other conditions. Additionally, reorganized this information under new headers and tables.
MK-3475-355-01	06-DEC-2016	Updates were made to harmonize the pneumonitis exclusion criterion throughout the pembrolizumab program. This change was not expected to result in a change in the study population.
MK-3475-355-00	21-APR-2016	Original protocol

SUMMARY OF CHANGES

PRIMARY REASON(S) FOR THIS AMENDMENT:

Section Number (s)	Section Title(s)	Description of Change (s)	Rationale
Title Page Section 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.

ADDITIONAL CHANGES FOR THIS AMENDMENT:

No additional changes.

1.0 TRIAL SUMMARY

Abbreviated Title	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)
Sponsor Product Identifiers	MK-3475 Pembrolizumab
Trial Phase	Phase III
Clinical Indication	Locally recurrent inoperable or metastatic triple negative breast cancer (TNBC), which has not been previously treated with chemotherapy
Trial Type	Interventional
Type of control	Part 1: No treatment control Part 2: Placebo-controlled trial on a background of chemotherapy
Route of administration	Intravenous
Trial Blinding	Double-blind
Treatment Groups	Part 1: There are 3 treatment arms (unblinded, open-label): • pembrolizumab + nab-paclitaxel • pembrolizumab + paclitaxel • pembrolizumab + gemcitabine/carboplatin Part 2: There are 2 treatment arms (double-blind): • pembrolizumab + chemotherapy • placebo + chemotherapy Pembrolizumab: 200 mg intravenously (IV) every 3 weeks (Q3W) Placebo: Normal saline IV Q3W Chemotherapy: ➢ Nab-paclitaxel: 100 mg/m^2 IV on Days 1, 8, and 15 every 28 days or ➢ Paclitaxel: 90 mg/m^2 on Days 1, 8, and 15 every 28 days or ➢ Gemcitabine and carboplatin: 1000 mg/m^2 and AUC 2, respectively, on Days 1 and 8 every 21 days
Number of trial subjects	Approximately 30 subjects will be enrolled for Part 1; for Part 2, approximately 828 subjects will be enrolled.
Estimated duration of trial	The Sponsor estimates that the trial will require approximately 65 months from the time the first subject signs the informed consent until the last subject's last study-related phone call or visit.
Duration of Participation	Each subject will participate in the study from the time the subject signs the informed consent form through the final protocol-specified contact. After a screening phase of up to 28 days, eligible subjects will receive assigned treatment. Study treatment will continue until any of the following occurs: disease progression is verified using Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST 1.1) by a central imaging vendor (or progressive disease [PD] is locally confirmed, if subject is further followed by immune-related RECIST [irRECIST]); unacceptable toxicity; intercurrent illness that necessitates discontinuation of study treatment; Investigator's decision to withdraw the subject; pregnancy; non-compliance with study treatment or procedure requirements; withdrawal of consent to treatment; death; end of the study; or other administrative reasons requiring cessation of study treatment.

	After discontinuation of all study treatments, each subject will be followed for 30 days for AE monitoring; serious adverse events (SAEs) will be collected for 90 days after the end of study treatment or until the subject starts a new anti-cancer treatment, but for at least 30 days after the last dose of study treatment, whichever occurs first. Subjects who discontinue all study treatments for reasons other than PD will continue post-treatment imaging studies for disease status follow-up at the same frequency as already used, e.g., every 9 or 12 weeks (±7 days) depending on time elapsed since randomization, until centrally verified disease progression, start of a non–study anti-cancer treatment, withdrawal of consent to study participation, death, or end of the study. All subjects will be followed by telephone every 12 weeks (±7 days), or more often as needed, for overall survival (OS) until death, withdrawal of consent to study participation, or end of the study.

Randomization Ratio	Part 2: 2:1

A list of abbreviations used in this document can be found in Section 12.4 – Abbreviations.

2.0 TRIAL DESIGN

2.1 Trial Design

This is a randomized, placebo-controlled, double-blind, global Phase III study of pembrolizumab + chemotherapy vs. placebo + chemotherapy for subjects with locally recurrent inoperable or metastatic triple negative breast cancer (TNBC), which has not been previously treated with chemotherapy. Prior treatment with chemotherapy in the (neo)adjuvant setting is allowed. For such subjects, the period between completion of treatment with curative intent (e.g., date of primary breast tumor surgery or date of last adjuvant chemotherapy administration, whichever occurred last) and first documented local or distant disease recurrence must be ≥6 months. Subjects who received taxane, gemcitabine, or platinum agents in the (neo)adjuvant setting can be treated with same class anticancer drug (taxane, gemcitabine, or carboplatin, respectively), if ≥12 months have elapsed between completion of treatment with curative intent and the first documented local or distant disease recurrence.

Part 1 will be an unblinded, open-label, safety run-in, in which approximately 30 subjects will be partially randomized with forced randomization depending on prior (neo)adjuvant treatment (as described in Section 5.3 – Randomization or Treatment Allocation), to ensure enrollment of at least 10 subjects to each treatment arm. Subjects will be closely followed for unacceptable toxicities for 21 or 28 days after the first pembrolizumab + gemcitabine/carboplatin or pembrolizumab + taxane administrations, respectively. Since pembrolizumab and chemotherapy have different mechanisms of action and non-overlapping toxicities, safety-compromising interactions between these 2 classes of anticancer regimens are not expected; thus, enrollment to Part 2 will continue while an external Data Monitoring Committee (DMC) reviews the safety data from Part 1 (see Section 7.3.3 – Data Monitoring Committee).

Part 2 will be a Phase III, double-blind, placebo-controlled study on a background of chemotherapy, for which approximately 828 eligible subjects will be randomized 2:1 to receive pembrolizumab + chemotherapy or placebo + chemotherapy, respectively.

Pembrolizumab will be given at 200 mg intravenously (IV) every 3 weeks (Q3W) and normal saline will be used as a placebo. Nab-paclitaxel will be given at 100 mg/m^2 IV on Days 1, 8, and 15 every 28 days; paclitaxel at 90 mg/m^2 IV on Days 1, 8, and 15 of every 28 days; and IV gemcitabine/carboplatin at 1000 mg/m^2 (gemcitabine) and an AUC 2 (carboplatin) on Days 1 and 8 every 21 days. Subject crossover between treatment arms is not permitted. Pembrolizumab/placebo will be prepared in a blinded fashion by an assigned unblinded pharmacist. Subjects, Investigators, other study site staff (except for the unblinded pharmacist), and the Sponsor will be blinded to pembrolizumab/placebo administration but unblinded to chemotherapy administration. Investigators, other study site staff, and subjects will be blinded to subject-level tumor programmed cell death ligand 1 (PD-L1) biomarker results.

Disease status will be followed by imaging studies at Weeks 8 (±7 days), 16 (±7 days), and 24 (–7 days) post randomization (allowing efficacy data to be captured as close to 24 weeks post randomization as possible for a more accurate evaluation of disease control rate [DCR]). Imaging will continue every 9 weeks (±7 days) thereafter during the first year, independent of any treatment delays. Imaging studies will be performed every 12 weeks (±7 days) after the first year. Safety will be monitored according to National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE), version 4.0 (v4.0).

Study treatment will continue until any of the following occurs: disease progression is verified using Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST 1.1) by a central imaging vendor (CIV) (or progressive disease [PD] is locally confirmed if the subject is further followed by immune-related RECIST [irRECIST]) (see Section 7.1.2.9.5 – irRECIST Assessment of Disease); unacceptable toxicity; intercurrent illness that necessitates discontinuation of study treatment; Investigator's decision to withdraw the subject; pregnancy; subject noncompliance with study treatment or procedure requirements; withdrawal of consent to treatment; death; end of the study; or other administrative reasons requiring cessation of study treatment.

See Section 5.8 – Subject Withdrawal/Discontinuation Criteria for information regarding discontinuation of pembrolizumab/placebo in subjects who attain an Investigator-determined confirmed complete response (CR) and in subjects who complete 35 administration of pembrolizumab/placebo. See Section 7.1.5.6 – Second Course Phase (Retreatment Phase) for information regarding criteria for potential retreatment of subjects who stop pembrolizumab with stable disease (SD) or better in the first course treatment of the trial.

After discontinuation of all study treatments, each subject will be followed for 30 days for AE monitoring; serious adverse events (SAEs) will be collected for 90 days after the end of study treatment or until the subject starts a new anti-cancer treatment, but for at least 30 days after the last dose of study treatment, whichever occurs first.

Subjects who discontinue all study treatments for reasons other than PD will continue post-treatment imaging studies for disease status follow-up at the same frequency as already used, e.g., every 9 or 12 weeks (± 7 days) during the first year or second year, respectively, depending on time elapsed since randomization, until centrally verified disease progression, start of a non–study anti-cancer treatment, withdrawal of consent to study participation, death, or end of the study.

All subjects will be followed by telephone every 12 weeks (± 7 days), or more often as needed, for overall survival (OS) until withdrawal of consent to study participation, death, or end of the study.

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

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.

This study will use a DMC to monitor safety and efficacy (see Section 8.1 – Statistical Analysis Plan Summary, Section 8.2 – Responsibility for Analyses/In-House Blinding, and Section 8.7 – Interim Analyses).

With the exception of the Part 1 safety interim analysis (see Section 8.7.1– Part 1: Safety Interim Analysis), safety monitoring will be performed at regular intervals. Information regarding objectives and statistical design and analysis is provided in Section 3.0 – Objective(s) & Hypothesis(es) and Section 8.0 – Statistical Analysis Plan.

2.2 Trial Diagram

The study design for Part 1 is depicted in Figure 1.

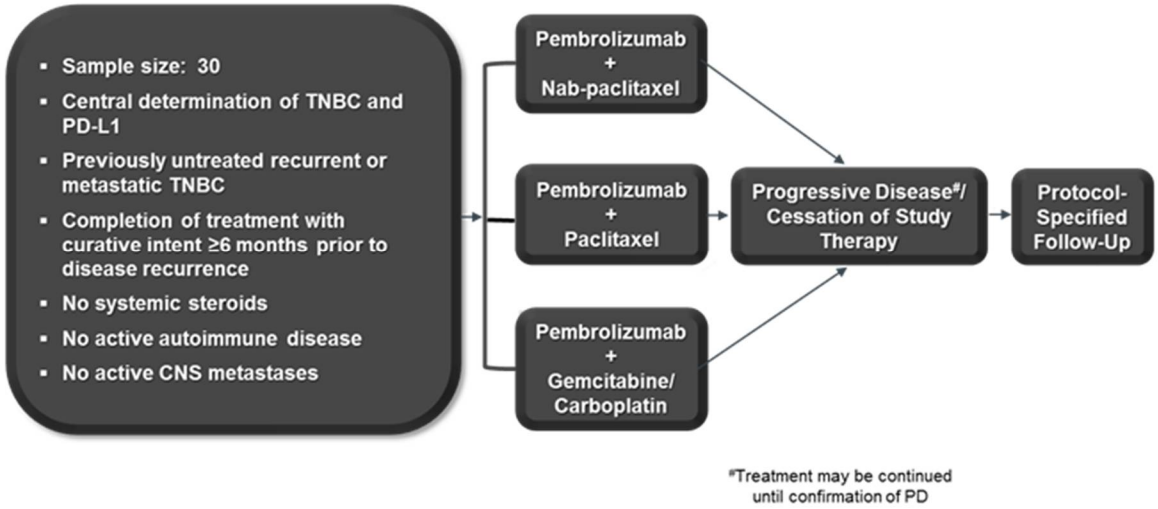


Figure 1 Part 1 Study Design

The study design for Part 2 is depicted in Figure 2.

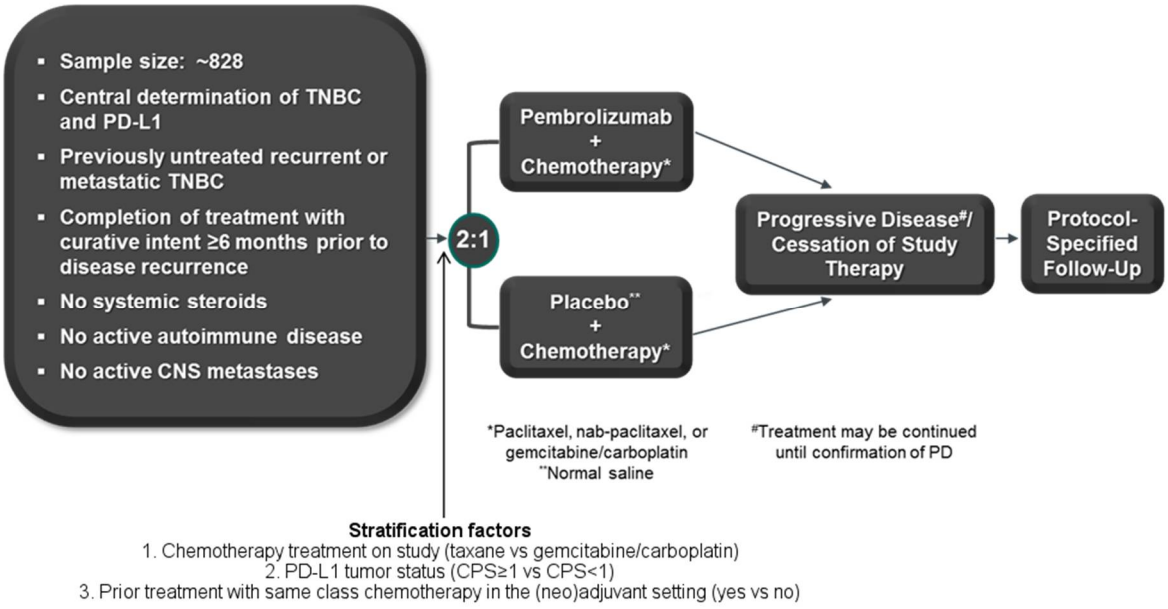


Figure 2 Part 2 (Phase III) Study Design

3.0 OBJECTIVE(S) & HYPOTHESIS(ES)

3.1 Primary Objective(s) & Hypothesis(es)

Part 1 (Safety Run-In):

(1) **Objective:** To evaluate the safety and tolerability of 3 pembrolizumab + chemotherapy combinations, namely, pembrolizumab + paclitaxel, pembrolizumab + nab-paclitaxel, and pembrolizumab + gemcitabine/carboplatin.

Part 2 (Phase III study):

The combination of pembrolizumab and chemotherapy will be compared to placebo and chemotherapy for the treatment of previously untreated locally recurrent inoperable or metastatic centrally confirmed triple negative breast cancer (TNBC):

(1) **Objective:** To compare progression-free survival (PFS) based on Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST 1.1) as assessed by a blinded central imaging vendor (CIV) in all subjects.

Hypothesis: The combination of pembrolizumab and chemotherapy prolongs PFS compared to placebo and chemotherapy in all subjects.

(2) **Objective:** To compare PFS based on RECIST 1.1 as assessed by a blinded CIV in subjects with PD-L1 positive tumors (combined positive score [CPS] ≥1).

Hypothesis: The combination of pembrolizumab and chemotherapy prolongs PFS compared to placebo and chemotherapy in subjects with PD-L1 positive tumors (CPS ≥1).

(3) **Objective:** To compare PFS based on RECIST 1.1 as assessed by a blinded CIV in subjects with PD-L1 positive tumors (CPS ≥10).

Hypothesis: The combination of pembrolizumab and chemotherapy prolongs PFS compared to placebo and chemotherapy in subjects with PD-L1 positive tumors (CPS ≥10).

(4) **Objective:** To compare overall survival (OS) in all subjects.

Hypothesis: The combination of pembrolizumab and chemotherapy prolongs OS compared to placebo and chemotherapy in all subjects.

(5) **Objective:** To compare OS in subjects with PD-L1 positive tumors (CPS ≥1).

Hypothesis: The combination of pembrolizumab and chemotherapy prolongs OS compared to placebo and chemotherapy in subjects with PD-L1 positive tumors (CPS ≥1).

(6) **Objective:** To compare OS in subjects with PD-L1 positive tumors (CPS ≥10).

Hypothesis: The combination of pembrolizumab and chemotherapy prolongs OS compared to placebo and chemotherapy in subjects with PD-L1 positive tumors (CPS ≥10).

The study is considered to have met its primary objective if the combination of pembrolizumab and chemotherapy is superior to placebo and chemotherapy in either PFS or OS in either all subjects or in subjects with PD-L1 positive tumors (CPS ≥1 or CPS ≥10) at either an interim analysis or the final analysis (OS only).

3.2 Secondary Objective(s) & Hypothesis(es)

Part 2 (Phase III study):

For comparisons, the combination of pembrolizumab and chemotherapy will be compared to placebo and chemotherapy for the treatment of previously untreated locally recurrent inoperable or metastatic centrally confirmed TNBC:

(1) **Objective**: To compare objective response rate (ORR) based on RECIST 1.1 as assessed by a blinded CIV in all subjects.

Hypothesis: The combination of pembrolizumab and chemotherapy increases ORR compared to placebo and chemotherapy in all subjects.

(2) **Objective**: To compare ORR based on RECIST 1.1 as assessed by a blinded CIV in subjects with PD-L1 positive tumors (CPS ≥1).

Hypothesis: The combination of pembrolizumab and chemotherapy increases ORR compared to placebo and chemotherapy in subjects with PD-L1 positive tumors (CPS ≥1).

(3) **Objective**: To compare ORR based on RECIST 1.1 as assessed by a blinded CIV in subjects with PD-L1 positive tumors (CPS ≥10).

(4) **Objective**: To evaluate duration of response (DOR) based on RECIST 1.1 as assessed by a blinded CIV in all subjects and in subjects with PD-L1 positive tumors (CPS ≥1 and CPS ≥10).

(5) **Objective**: To compare DCR based on RECIST 1.1 as assessed by a blinded CIV in all subjects and in subjects with PD-L1 positive tumors (CPS ≥1 and CPS ≥10).

(6) **Objective**: To evaluate the safety and tolerability of 3 pembrolizumab + chemotherapy combinations.

(7) **Objective:** To evaluate changes in health-related quality-of-life (QoL) assessments from baseline in all subjects and in subjects with PD-L1 positive tumors (CPS ≥1 and CPS ≥10) using the European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire Core 30 (EORTC QLQ-C30) and EORTC Breast Cancer–Specific Quality of Life Questionnaire (EORTC QLQ-BR23).

3.3 Exploratory Objectives

Part 2 (Phase III study):

For comparisons, the combination of pembrolizumab and chemotherapy will be compared to placebo and chemotherapy for the treatment of previously untreated locally recurrent inoperable or metastatic centrally confirmed TNBC:

(1) **Objective:** To characterize utilities in all subjects and in subjects with PD-L1 positive tumors (CPS ≥1 and CPS ≥10) using EuroQol-5 Dimension Questionnaire (EQ-5D™).

(2) **Objective:** To investigate association(s) between anti-tumor activity of study treatments and efficacy/resistance biomarkers, utilizing tumor and blood specimens obtained before randomization, during treatment, and at disease progression.

(3) **Objective:** To identify molecular (genomic, metabolic, and/or proteomic) determinants of response or resistance to pembrolizumab and other treatments in this study, so as to define novel predictive and pharmacodynamic biomarkers and understand the mechanism of action of pembrolizumab.

4.0 BACKGROUND & RATIONALE

4.1 Background

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

4.1.1 Pharmaceutical and Therapeutic Background

Programmed cell death 1 (PD-1) checkpoint inhibition and cancer treatment. The importance of intact immune surveillance in controlling outgrowth of neoplastic transformation has been known for decades [1]. Accumulating evidence shows a correlation between tumor-infiltrating lymphocytes (TILs) in cancer tissue and prognosis in various

malignancies [2], [3], [4], [5], [6], [7], [8], [9], [10], [11], [12], [13], [14]. In particular, the presence of cluster of differentiation (CD) 8–positive (CD8+) T cells and the ratio of CD8+ effector T cells/FoxP3+ regulatory T cells seem to correlate with improved prognosis and long-term survival in many solid tumors [7], [15], [16], [17], [18], [19], [20], [21].

The PD-1 receptor-ligand interaction is a major pathway hijacked by tumors to suppress immune control [22]. The normal function of PD-1, expressed on the cell surface of activated T cells under healthy conditions, is to down-modulate unwanted or excessive immune responses, including autoimmune reactions. PD-1 (encoded by the gene Pdcd1) is an immunoglobulin (Ig) superfamily member related to CD28 and cytotoxic T-Lymphocyte–associated antigen-4 (CTLA-4), which has been shown to negatively regulate antigen receptor signaling upon engagement of its ligands (PD-L1 and/or programmed cell death ligand 2 [PD-L2]). The structures of murine PD-1 alone [23], and in complex with its ligands, were first resolved [24], [25], 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 [26]. PD-1 and family members are type I transmembrane glycoproteins containing an Ig Variable-type (V-type) domain responsible for ligand binding and a cytoplasmic tail which is responsible for the binding of signaling molecules. The cytoplasmic tail of PD-1 contains 2 tyrosine-based signaling motifs, an immunoreceptor tyrosine-based inhibition motif (ITIM) and an immunoreceptor tyrosine-based switch motif (ITSM). Following T cell stimulation, PD-1 recruits the tyrosine phosphatases Src homology phosphatase (SHP)-1 (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 70kDa (ZAP70), which are involved in the CD3 T cell signaling cascade [27]. The mechanism by which PD-1 down-modulates T cell responses is similar to, but distinct from, that of CTLA-4 [28]. 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) [29]. Expression has also been shown during thymic development on CD4-CD8–double negative T cells [30] as well as subsets of macrophages [31] and dendritic cells [32]. The ligands for PD-1 (PD-L1 and PD-L2) are constitutively expressed or can be induced in a variety of cell types [33]. 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 [33]. 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 [34], [35], which, via its interaction with the PD-1 receptor on tumor-specific T cells, plays a critical role in immune evasion by tumors [36]. As a consequence, the PD-1/PD-L1 pathway is an attractive target for therapeutic intervention in cancer [37].

Information on Disease to be Treated – TNBC. Excluding basal cell and squamous cell skin cancers, breast cancer is the most commonly diagnosed malignancy in women, accounting for 29% of all new cancers. It is also the second leading cause of cancer death (after lung cancer) among women. About 232,670 new cases of breast cancer and 40,000 deaths due to breast cancer are expected in women in the United States (US) in 2014 [38]. TNBC is phenotypically defined by a lack of estrogen receptor and progesterone receptor (EG/PGR) expression and the absence of human epidermal growth factor receptor-2 (HER2) overexpression and/or amplification [39]. TNBC represents 15% to 20% of all breast cancers [40] and is overlapping, but not synonymous, with the basal-like subtype defined by gene expression, as about 70% of TNBCs have basal-like characteristics [41], [42].

TNBC is a molecularly heterogeneous disease and includes tumor subsets with different prognosis. Recent gene expression profiling has identified up to 6 distinct TNBC subtypes (2 basal-like, an immunomodulatory, a mesenchymal, a mesenchymal stem-like, and a luminal androgen receptor [AR] subtype) [43].

TNBC is associated with younger age at diagnosis, premenopausal status, African American race, more advanced disease stage, higher grade, high mitotic indices, family history of breast cancer, breast cancer 1 (*BRCA1*) mutations, and more aggressive behavior than other breast cancer subtypes [40]. As reported in a seminal study on TNBC, 34% of all subjects with TNBC experience distant recurrence with a median distant recurrence-free survival (DRFS) of 2.6 years, compared to a distant recurrence rate of 20% and a median DRFS of 5 years in other breast cancer subtypes; the peak of recurrence for TNBC is within 1 to 3 years after initial diagnosis, and decreases significantly thereafter; subjects with TNBC also have shorter median OS compared to subjects with non-TNBC (4.2 vs 6.0 years) [39]. Finally, subjects with TNBC tend to relapse with distant metastases rather than local recurrences and are more likely to develop visceral metastases, including central nervous system (CNS) involvement [44].

Treatment of TNBC is challenging and represents an area of unmet medical need, as these tumors lack therapeutic targets, such as ER and HER2, and become rapidly resistant to chemotherapy upon local recurrence and/or metastasis (even though they are often sensitive to cytotoxic drugs at initial presentation) [45]. The majority of subjects with metastatic TNBC (mTNBC) have experienced relapse after neoadjuvant or adjuvant therapy for early or locally advanced disease. In a frequently referenced study, the median OS of all (at any line of therapy) subjects with mTNBC was 13.3 months [46].

Immune checkpoint inhibition for the treatment of TNBC. Several studies have demonstrated that presence of TILs is a prognostic factor in TNBC, thus implicating the immune system in the pathophysiology and potentially the treatment of such tumors. Greater lymphocytic infiltration confers better prognosis in TNBC, independent of systemic therapy [47], [48]. In addition, unsupervised gene expression profiling of TNBCs has identified a gene signature enriched for cytotoxic CD8+ T cell genes and NKC activity, which is predictive of good clinical outcome [49]. These findings suggest that inhibition of immune checkpoints has the potential to improve TNBC prognosis by increasing the efficacy of tumor-associated immune response in eliminating breast cancer cells [50].

Targeting the PD-1 immune checkpoint for the treatment of TNBC. The PD-1 ligand, PD-L1, is not detected in normal breast tissue, but has been reported to be expressed in about half of all breast cancers, particularly in hormone receptor–negative and high grade, proliferative tumors [51]. In addition, the presence of regulatory T cells, tumor PD-L1 expression, and PD-1–positive TILs has been associated with high histologic grade, ER negativity, and prominent tumor lymphocytic infiltration [52]. In an independent study, PD-L1 was found expressed in 23% of breast cancer specimens and it was again associated with age, tumor size, American Joint Committee on Cancer (AJCC) primary tumor classification, tumor grade, lymph node status, absence of ER expression, and high Ki-67 expression [53]. A recent publication 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 [54]. Another study mining The Cancer Genome Atlas (TCGA) 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; in the same study, PD-L1 was found expressed in 20% of TNBCs [55]. Finally, in an abstract presented in the 2014 American Society of Clinical Oncology (ASCO) Annual meeting, it was reported that PD-L1 protein levels are positively correlated with expression of other immune regulators, such as CTLA-4 and indoleamine 2,3-dioxygenase 1 (IDO1), and with AR-negative and BRCA1-mutant TNBC [56]. Despite their discordance in the reported absolute PD-L1 levels in breast tumors, the aforementioned studies clearly demonstrate 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 Pre-Clinical and Clinical Studies

PD-1 immune checkpoint inhibition – Preclinical studies. Therapeutic studies in mouse models have shown that administration of antibodies blocking PD-1/PD-L1 interaction enhances infiltration of tumor-specific CD8+ T cells and ultimately leads to tumor rejection, either as a monotherapy or in combination with other treatment modalities [57], [58], [59], [60], [61], [62], [63]. Anti–mouse PD-1 or anti–mouse PD-L1 antibodies have demonstrated anti-tumor responses in models of squamous cell carcinoma, pancreatic carcinoma, melanoma, acute myeloid leukemia and colorectal carcinoma [58], [60], [62], [64], [65]. In such studies, tumor infiltration by CD8+ T cells and increased interferon gamma (IFN-γ), granzyme B and perforin expression were observed, indicating that the mechanism underlying the anti-tumor activity of PD-1 checkpoint inhibition involved local infiltration and activation of effector T cell function in vivo [58]. Experiments have confirmed the in vivo efficacy of anti–mouse PD-1 antibody as a monotherapy, as well as in combination with chemotherapy, in syngeneic mouse tumor models (see the IB).

Pembrolizumab – Clinical studies. Pembrolizumab [Keytruda® (US); previously known as lambrolizumab, MK-3475 and SCH 9000475] is a potent and highly selective humanized monoclonal antibody (mAb) of the IgG4/kappa isotype designed to directly block the interaction between PD-1 and its ligands, PD-L1 and PD-L2. Pembrolizumab was the first anti–PD-1 therapy to receive regulatory approval in the US (September 2014).

Pembrolizumab is approved in the US at a dose of 2 mg/kg administered as an intravenous infusion over 30 minutes Q3W for the treatment of patients with unresectable or metastatic

melanoma with disease progression following ipilimumab and, if BRAF V600 mutation positive, a BRAF inhibitor (see also prescribing information for KEYTRUDA® (pembrolizumab) for injection, for intravenous use) [66]. It is approved in EU for both first-line (1L) and previously treated subjects with unresectable or metastatic melanoma.

Pembrolizumab is also approved in the US (at the same dose as in melanoma) for the treatment of patients with metastatic non-small cell lung cancer (NSCLC) whose tumors express PD-L1 as determined by an FDA-approved test with disease progression on or after platinum-containing chemotherapy. Patients with EGFR or ALK genomic tumor aberrations should have disease progression on FDA-approved therapy for these aberrations prior to receiving pembrolizumab. (See also prescribing information for KEYTRUDA® (pembrolizumab) for injection, for intravenous use.)

KEYNOTE-012 (KN012) – Clinical data supporting pembrolizumab use for the treatment of mTNBC. In the first report of clinical activity of an immune checkpoint inhibitor in TNBC, an MSD-sponsored multi-center, nonrandomized Phase Ib study (KN012) showed that single agent pembrolizumab given at 10 mg/kg every 2 weeks (Q2W) is a well-tolerated and effective treatment with significant anticancer activity in a subset of heavily pre-treated subjects with mTNBC [67].

Methods: PD-L1 expression in ≥1% tumor cells or in stroma (i.e., PD-L1 positive mTNBC) was required for study entry. Tumor PD-L1 status was determined by immunohistochemical analysis of archival tumor specimens using the MSD proprietary 22C3 antibody. Primary objectives of this study were to determine the safety, tolerability, and anti-tumor activity of pembrolizumab in subjects with PD-L1 positive mTNBC. Secondary objectives included assessments of PFS, OS, and DOR. Adverse events reported in any subject receiving at least 1 dose of study treatment were monitored and graded using NCI CTCAE v4.0. Radiographic imaging was obtained every 8 weeks and evaluated by both investigator and an independent radiologist to assess clinical responses as defined by RECIST 1.1.

Results: Of the 111 subjects whose tumor samples were screened for PD-L1 expression, 58% had PD-L1 positive tumors. A total of 32 female subjects with a median age of 50.5 years (range 29 to 72 years) and PD-L1 positive 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. Overall, 56% of subjects experienced one or more treatment-related toxicities, including 16% who experienced one or more Grade 3-5 events. The most common treatment-related AEs of any grade included arthralgia (18.8%), fatigue (18.8%), myalgia (18.8%), and nausea (15.6%). As of the data cutoff date of 23-Mar-2015, 5 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 with rapidly progressing metastatic disease experienced Grade 5 disseminated intravascular coagulation (DIC) with thrombocytopenia and decreased blood fibrinogen. Of the 27 subjects with centrally confirmed measurable disease, 1 subject (3.7%) had a CR, 4 subjects (14.8%) had a confirmed partial response (PR), 25.9% had SD, and 44.4% had PD, as assessed by central radiology review. The median time to response was 18 weeks (range 7 to 32). 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.

Conclusions: This was the first report of clinical activity of an immune checkpoint inhibitor in TNBC. The preliminary results from this study suggest that single agent pembrolizumab is a well-tolerated and effective treatment with significant anticancer activity in a subset of heavily pre-treated subjects with recurrent/metastatic TNBC.

4.1.3 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 (KN86) and KEYNOTE-119 (KN119).

- KN-086 (NCT02447003): A Phase II Clinical Trial of Pembrolizumab (MK-3475) as Monotherapy for Metastatic Triple Negative Breast Cancer (mTNBC) – (KEYNOTE-086), and
- KN-119 (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)

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.

4.1.4 Information on Other Study-Related Therapy

Taxanes are among the most effective and commonly used therapies for the treatment of breast cancer, particularly in the adjuvant setting. Accordingly, the role of taxanes in the metastatic setting continues to evolve as new strategies to optimize taxane use and clinical outcomes are actively investigated [68].

Paclitaxel is a natural product (obtained via a semi-synthetic process from the Pacific yew tree [*Taxus brevifolia*]) with anti-tumor activity. It promotes the assembly and stabilization of microtubules, while inhibiting their depolymerization, and thus results in inhibition of mitosis and cell death. In the US, paclitaxel is approved for the adjuvant treatment of node-positive breast cancer administered sequentially to standard doxorubicin-containing combination chemotherapy; it is also approved as single agent for the treatment of metastatic breast cancer (mBC) after failure of combination chemotherapy for metastatic disease or relapse within 6 months of adjuvant chemotherapy. Approval was based on a Phase III study of 2 different doses (175 mg/m^2 vs 135 mg/m^2) of Cremofor EL (CrEL)-dissolved paclitaxel given Q3W in subjects with mBC whose disease had progressed on or after previous chemotherapy [69]. Compared to the lower dose, the higher dose was associated with a longer median time to disease progression (TTP) (4.2 vs 3.0 months, respectively; $P = 0.027$) and a longer median OS (11.7 vs 10.5 months, respectively; $P = 0.321$). In the European Union (EU), paclitaxel is approved as monotherapy for late mBC and in combination with bevacizumab as 1L treatment.

Nab-paclitaxel is a combination of albumin and paclitaxel that forms particles of a mean 130 nm in diameter. Unlike previous taxanes, the nab-paclitaxel formulation is solvent-free and does not require premedication to prevent solvent-related hypersensitivity reactions. It

received US Food and Drug Administration (FDA) approval in 2005 for the treatment of breast cancer after failure of combination chemotherapy for metastatic disease or relapse within 6 months of adjuvant chemotherapy (prior therapy should have included an anthracycline, unless clinically contraindicated). Nab-paclitaxel is also approved in the EU as second-line (2L) monotherapy for mBC. These approvals were based on a randomized phase III study, which compared nab-paclitaxel 260 mg/m^2 Q3W to paclitaxel 175 mg/m^2 Q3W with corticosteroid or antihistamine premedication [70]. Treatment with nab-paclitaxel led to a significantly higher ORR compared with paclitaxel based on the intention-to-treat (ITT) population (33% vs 19%, respectively; $P = 0.001$). The ORR was also significantly higher in subjects who received nab-paclitaxel as 1L therapy (42% vs 27%; $P = 0.029$) or 2L and above (2L+) therapy (27% vs 13%; $P = 0.006$). Subjects who received nab-paclitaxel had a 25% lower risk of progression compared with those receiving paclitaxel (hazard ratio [HR] 0.75; $P = 0.006$). The incidence of Grade 4 neutropenia was significantly lower with nab-paclitaxel treatment (9% vs 22%, respectively; $P = 0.001$). Nab-paclitaxel was associated with higher incidence of Grade 3 sensory neuropathy (10% vs 2%; $P = 0.001$), which improved to $\leq$ Grade 2 in about 3 weeks. Nab-paclitaxel demonstrated a statistically significant improvement in OS in subjects who received it as 2L+ therapy (56.4 vs 46.7 weeks; $P = 0.024$), but only a modest, nonsignificant OS difference in the ITT population (65 vs 56 weeks; $P = 0.374$).

Gemcitabine/carboplatin was the first chemotherapy regimen investigated in a randomized, double-blind, Phase III study for the treatment of mTNBC [71]. In this Sanofi-sponsored study, the combination of iniparib and gemcitabine/carboplatin was compared to gemcitabine/carboplatin for the treatment of mTNBC [71]; gemcitabine/carboplatin were used at 1000 mg/m^2 and AUC 2, respectively, on Days 1 and 8 of a 3-week cycle and resulted in a median PFS of 4.6 months and a median OS of 12.6 months as 1L therapy. Although not formally approved for the treatment of metastatic breast cancer, the combination of gemcitabine and carboplatin is included in oncology society guidelines [72], [73] and used as 1L combination treatment for mTNBC worldwide.

4.2 Rationale

4.2.1 Rationale for the Trial and Selected Subject Population

4.2.1.1 Rationale for the Study

Rationale for combining pembrolizumab with chemotherapy. This study will investigate whether the combination of pembrolizumab and chemotherapy (nab-paclitaxel, paclitaxel or gemcitabine/carboplatin) improves the PFS and OS of subjects with previously untreated locally recurrent inoperable or metastatic TNBC compared to placebo and chemotherapy.

The rationale behind combining pembrolizumab with chemotherapy is based on the immunomodulatory effects of the latter [74], which may in turn increase the anti-tumor activity of PD-1 pathway inhibition. Even though cytotoxic drugs, including taxanes and gemcitabine/carboplatin, have historically been considered immunosuppressive, they can also have immunopotentiating roles by **1)** depleting immuno-suppressive cells, such as regulatory T cells and myeloid-derived suppressor cells, to enhance a latent anti-tumor immune response, **2)** inducing an immunogenic cell death, **3)** enhancing tumor antigen

presentation by upregulating the expression of tumor antigens themselves, or of the major histocompatibility complex (MHC) class I molecules to which the antigens bind, **4)** upregulating co-stimulatory molecules (B7-1) or down regulating co-inhibitory molecules (PD-L1/B7-H1 or B7-H4) expressed on the tumor cell surface, thus enhancing the strength of effector T cell activity, and **5)** rendering tumor cells more sensitive to T cell–mediated lysis through fas-, perforin-, and granzyme B–dependent mechanisms [75].

Rationale for chemotherapy choices. No standard of care (SOC) currently exists for the treatment for TNBC in any setting. Similar to any advanced breast cancer, the recommended initial treatment for subjects with locally recurrent inoperable or metastatic TNBC includes anthracyclines and taxanes. For subjects previously treated with an anthracycline, or for whom anthracyclines are contraindicated or not considered the best treatment option, taxanes are most commonly used as 1L treatment, when the time interval between completion of taxane-based (neo)adjuvant therapy and recurrence is at least 12 months [76]. Subjects with earlier (<12 months) local or distant disease recurrence are treated with chemotherapies not previously used in the (neo)adjuvant setting; in the case of aggressive disease and/or visceral crisis, combination, rather than single agent, chemotherapy is indicated and may include **any one** of different regimens, such as gemcitabine/carboplatin, capecitabine/vinorelbine, gemcitabine/cisplatin, etc.

In KEYNOTE-355 (KN355), 3 such combination regimens will be investigated, namely pembrolizumab + nab-paclitaxel, pembrolizumab + paclitaxel, and pembrolizumab + gemcitabine/carboplatin. This design ensures inclusion of the most commonly used single agent chemotherapy class (taxanes) and a combination regimen frequently used as 1L treatment for locally recurrent inoperable or metastatic TNBC.

The rationale for including both nab-paclitaxel and paclitaxel as the taxane options in this multicenter, international study is based on their:

- Differential availability and clinical use worldwide
- Similar efficacies in terms of OS in mBC

Docetaxel was not included as a taxane option in KN355, as it is associated with a more severe toxicity profile than paclitaxel or nab-paclitaxel, as well as a strict requirement for steroid premedication that cannot be tapered during the entire length of its administration.

In regard to efficacy, although in earlier studies nab-paclitaxel showed higher anti-tumor activity than paclitaxel in mBC, results from a recent study indicated that paclitaxel and nab-paclitaxel resulted in similar PFS when given on a weekly basis (in combination with bevacizumab) as 1L treatment for mBC and mTNBC [77]. Comparison of paclitaxel or nab-paclitaxel to gemcitabine/carboplatin also reveals similar efficacies, in terms of PFS and OS, as 1L treatment for mTNBC (Table 1), and further supports use of these 3 regimens as chemotherapy choices in KN355.

Table 1 Efficacy of Chemotherapy as 1L Treatment for mTNBC

Study/Breast Cancer Subtype/Reference	Line	Drug	ORR%/PFS_{mo}/OS_{mo}
Meta-analysis of 3 Phase III trials: E2100, AVADO, RIBBON 1 – MBC TNBC subgroup analysis Miles et al. 2013 [78]	1L	Paclitaxel or docetaxel or capecitabine or (A/EC, FA/EC)	**23/5.4/17.5**
E2100-Phase III – MBC TNBC subgroup analysis Gray et al. 2009 [79]	1L	Paclitaxel	**22/5.3/16.3**
Phase III – TNBC 1L subgroup analysis O'Shaughnessy et al. 2014 [71]	1L	Gemcitabine + carboplatin	NR/**4.6/13.9**
Phase III – MBC TNBC subgroup analysis Rugo et al. 2015 [77]	1L	Paclitaxel + bevacizumab	NR/**6.5**/NR
		Nab-paclitaxel + bevacizumab	NR/**7.4**/NR

1L=first line; MBC=metastatic breast cancer; mTNBC=metastatic triple negative breast cancer; NR=not reached; ORR=objective response rate; OS=overall survival; PFS=progression-free survival; TNBC=triple negative breast cancer.
Note: In all studies included in Table 1, paclitaxel and nab-paclitaxel were both given on Days 1, 8, and 15 every 28 days.

4.2.1.2 Rationale for Selected Subject Population

Adults with locally recurrent inoperable or metastatic TNBC, which has not been previously treated with chemotherapy. As mentioned in Section 4.1.1 – Pharmaceutical and Therapeutic Background, treatment of advanced TNBC is challenging and represents an area of high unmet medical need. Triple negative breast tumors lack therapeutic targets, such as ER and HER2, become rapidly resistant to chemotherapy, and are associated with poor clinical outcomes. Locally recurrent inoperable breast cancer is considered clinically similar to previously untreated metastatic disease [80], and thus the KN355 study population includes subjects with "early" advanced disease, requiring 1L treatment for locally recurrent inoperable or metastatic TNBC.

4.2.2 Rationale for Dose Selection/Regimen/Modification

4.2.2.1 Rationale for Pembrolizumab Dose Selection

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 eight randomized studies demonstrating flat dose- and exposure-efficacy relationships from 2 mg/kg Q3W to 10 mg/kg every two weeks (Q2W)

- Clinical data showing meaningful improvement in benefit-risk including overall survival 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 eight 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 three 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.

4.2.2.2 Rationale for Chemotherapy Dose Selections

Taxanes will be used at the following doses and schedules: paclitaxel 90 mg/m^2 on Days 1, 8, and 15 every 28 days and nab-paclitaxel 100 mg/m^2 on Days 1, 8, and 15 every 28 days. Although approved for metastatic breast cancer on a tri-weekly basis, paclitaxel at 80 mg/m^2 weekly was better tolerated and superior in efficacy compared to 175 mg/m^2 Q3W [81], and in clinical practice both paclitaxel and nab-paclitaxel are most commonly used on a 3-week on (Days 1, 8, and 15)/1-week off schedule every 28 days (Table 1). Furthermore, in data presented at the 2015 San Antonio Breast Cancer Symposium (SABCS), nab-paclitaxel at 100 mg/m^2 on Days 1, 8, 15 every 28 days was overall tolerated, when given in combination with the PD-L1 inhibitor atezolizumab [82], [83].

Gemcitabine/carboplatin will be used at the following doses and schedules: gemcitabine at 1000 mg/m^2 + carboplatin at a dose equivalent to an AUC of 2, on Days 1 and 8 every 21 days [71].

Normal saline infusion Q3W will be used as placebo for pembrolizumab. The use of saline placebo in combination with chemotherapy will ensure the objectivity of investigator- and centrally assessed disease progression.

4.2.2.3 Rationale for Dose Interval and Trial Design

4.2.2.3.1 Rationale for Dose Interval

As explained in Section 4.2.2.1 – Rationale for Pembrolizumab Dose Selection and Section 4.2.2.2 – Rationale for Chemotherapy Dose Selections, pembrolizumab will be given Q3W, paclitaxel and nab-paclitaxel will be given on a 3-week on (Days 1, 8, and 15)/1-week off schedule every 28 days, and gemcitabine/carboplatin will be given on Days 1 and 8 every 21 days, according to most common clinical practice.

4.2.2.3.2 Rationale for Study Design

KN355 is a randomized, double-blind, Phase III clinical study, as this is the gold standard for demonstrating superiority of a therapeutic regimen compared to another.

Rationale for Central Confirmation of TNBC Status. Several studies have reported discordance in evaluation of ER, PGR, and HER2 status between local and central laboratories, due to both technical issues in immunohistochemistry (IHC) testing and interpretation issues in fluorescence in situ hybridization (FISH) testing [84], [85], [86]. It is, thus, recommended that central testing should be performed to determine study eligibility, particularly in large studies involving multiple collaborating institutions in several countries [85].

Rationale for Selection of Stratification Factors.

1. Chemotherapy on study (taxane [i.e., paclitaxel or nab-paclitaxel] vs gemcitabine/carboplatin). The efficacy of pembrolizumab/placebo + taxane may be different from that of pembrolizumab/placebo + gemcitabine/carboplatin combination therapy. Stratification for chemotherapy on study will ensure similar distribution of subjects receiving taxane and gemcitabine/carboplatin in the 2 study arms, which allows efficient subgroup analysis by chemotherapy on study. Taxane options, e.g., nab-paclitaxel and paclitaxel, are grouped in one stratum given that both are used as monotherapy and are microtubule disassembly inhibitors, whereas gemcitabine/carboplatin is a combination of 2 chemotherapies with different mechanisms of action, e.g., antimetabolite (gemcitabine) and DNA damaging agent (carboplatin). Furthermore, given 1) the higher (almost universal) use of taxanes in the (neo)adjuvant setting, 2) the restriction in rechallenge with taxanes to subjects whose disease recurrence occurred ≥12 months since completion of treatment, and 3) the more frequent use of gemcitabine/carboplatin in subjects with more aggressive disease, about equal distribution of subjects to the taxane and gemcitabine/carboplatin strata is expected.
2. Tumor PD-L1 status (positive [i.e., CPS ≥1]; vs negative [CPS <1]). Given that the dual primary objectives of this study are PFS and OS in all subjects and in subjects with PD-L1 positive tumors (CPS ≥1 and CPS ≥10), stratification for tumor PD-L1 status will be applied to ensure similar distribution of subjects with PD-L1 CPS ≥1

and PD-L1 CPS <1 in the 2 study arms. Efficacy will also be analyzed in patients with PD-L1 CPS ≥10.

3. Prior treatment with same class of chemotherapy in the (neo)adjuvant setting (yes vs no). Use of taxane, gemcitabine, and/or platinum agents for initially diagnosed Stage I-III breast cancer may differentially impact tumor responsiveness to the same vs different class of chemotherapy in the metastatic setting. Furthermore, in clinical trials evaluating taxane use for metastatic breast cancer, prior treatment with taxanes is a commonly used stratification factor.

4.2.3 Rationale for Endpoints

4.2.3.1 Efficacy Endpoints

4.2.3.1.1 Primary

OS and PFS were selected as the dual primary endpoints for KN355, because OS has been recognized as the gold standard for demonstration of superiority of a new anti-neoplastic therapy in a randomized Phase III study, whereas PFS based on RECIST 1.1 has been an acceptable endpoint and has been used as a primary efficacy endpoint in a number of randomized Phase III studies in metastatic breast cancer. Drugs approved in the recent years for the treatment of mBC based on PFS data include: 1) pertuzumab in combination with trastuzumab and docetaxel for HER2-positive mBC (2012), 2) everolimus in combination with exemestane for hormone receptor–positive, HER2-negative mBC (2012), 3) lapatinib for HER2-positive mBC (2007), 3) ixabepilone for mBC (2007).

RECIST 1.1 will be used to determine the dates of progression as this methodology is accepted by regulatory authorities. In addition, final determination of radiographic PD will be based on the CIV assessment of progression rather than local site investigator/radiology assessment. Expedited assessment by the CIV in instances of suspected radiologic progression identified at the site (verification of PD) will be communicated to the site study team.

4.2.3.1.2 Secondary

ORR, DOR, and DCR based on RECIST 1.1 and assessed by blinded CIV are commonly used efficacy endpoints in Phase III clinical studies.

4.2.3.1.3 Exploratory

RECIST 1.1 will be adapted to account for the unique tumor response characteristics seen with treatment of pembrolizumab. 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 a clinical response after an initial increase in tumor burden or even the appearance of new lesions. Standard RECIST 1.1 may, thus, not provide an accurate response assessment of immunotherapeutic agents such as pembrolizumab. Based on an analysis of subjects with melanoma enrolled in Keynote-001, 7% of evaluable subjects experienced delayed or early tumor pseudo-progression. Of note,

subjects who had PD by RECIST 1.1, but not by immune-related Response Criteria, had longer OS than subjects with PD by both criteria. Additionally, the data suggest that RECIST 1.1 may underestimate the benefit of pembrolizumab in approximately 15% of subjects. These findings support the need to apply a modification to RECIST 1.1 that takes into account the unique patterns of atypical response in immunotherapy and enable treatment beyond initial radiographic progression.

4.2.3.2 Safety Endpoints

Commonly used safety parameters for evaluating investigational systemic anti-cancer treatments are included as safety endpoints for the study including rate of AE/SAEs and fatal SAEs, causality and outcome of AE/SAEs, rate of treatment discontinuations and reasons, changes in vital signs, laboratory values etc. Grading of AE/SAEs will be based on NCI CTCAE v4.0.

4.2.3.3 Planned Exploratory Biomarker Research

Introduction: Cancer immunotherapies are an important novel class of anti-tumor agents. However, much remains to be learned about how cancer immunotherapies work and 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 AEs in the course of our clinical trials. To that end we seek to define novel predictive/pharmacodynamic biomarkers and the best strategies of combination therapy with immuno-oncology drugs. To fully leverage the clinical data collected in this trial, we will also collect biospecimens (blood components, tumor material, etc.) to support biomarker analyses of cellular components (e.g., protein, deoxyribonucleic acid [DNA], RNA, metabolites) and other blood soluble molecules. A recently or newly obtained core or excisional biopsy from a locally recurrent inoperable or metastatic tumor site should be submitted, unless contraindicated due to site inaccessibility and/or subject safety concerns. An archival tumor specimen obtained before the diagnosis of locally recurrent inoperable or metastatic breast cancer may be submitted after consultation with the Sponsor, if neither a recently nor a newly obtained biopsy from a locally recurrent inoperable or a metastatic site is available.

Investigations may include, but are not limited to, the following:

Germline (blood) for Genetic Analyses (e.g., single nucleotide polymorphism [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 AEs, 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.

Although its prevalence is low and its significance in TNBC has not yet been determined, microsatellite instability (MSI) may be evaluated as this is an important biomarker for response to pembrolizumab in some cancers, such as colorectal carcinoma [87]. Microsatellite instability is a form of genomic instability, through the insertion or deletion of

repeating units during DNA replication and failure of the mismatch repair system to correct DNA replication errors.

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 (i.e., mutations, methylation status, MSI, etc.). Key molecular changes of interest to immune-oncology drug development are 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) is one of the major mechanisms of neo-antigen presentation in the context of a tumor. The increased presence of foreign-like peptides on the cell surface due to somatic mutations in the DNA of the tumor increases the chances that the tumor will be 'visible' to the adaptive immune system through the Class I MHC (MHC-I) antigen presentation mechanism. There are a number of mechanisms by which a tumor can have increased mutational burden, such as defects in key genes related to DNA mismatch repair mechanisms or environmental induced factors such as smoking or ultraviolet (UV) light exposure. Additionally, a DNA tetrapeptide neo-antigen mutational signature can also be obtained by use of bioinformatic prediction tools of human leukocyte antigen–restricted (HLA-restricted) mutated peptide binding to MHC-I and to the T cell. There is a potential that in the hyper-mutated state, the presence of neo-antigen mutational patterns and the detection of increased T cell clonality, both of which can be determined by use of next-generation sequencing methods, may correlate with response to pembrolizumab therapy and/or that the converse, the 'hypomutated' state (the absence of neo-antigens) may correlate with nonresponse. 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. Particular emphasis will be placed on the following biological determinants/pathways: BRCA1/2, PI3K, PTEN, epidermal growth factor receptor (EGFR), MEK, fibroblast growth factor receptor (FGFR), MET, and Notch signaling [88], [89], [90], [91]. Microsatellite instability may also be evaluated in the tumor.

Hereditary and somatic defects in genes that support homologous recombination have been implicated in predisposition to a variety of cancers and in their responsiveness to therapy. TNBC is such a cancer, as *BRCA1/2* mutations and other homologous recombination defects play an important role in the pathophysiology of this tumor type and the degree of homologous recombination defect (HRD) (low vs high HRD score) may predict efficacy of anti-cancer regimens [92]. An HRD assay may be used in this study.

Tumor and blood RNA analyses: Both genome-wide and targeted 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 (e.g., interleukin 10 [IL-10]). MicroRNA profiling may also be pursued.

Proteomics and Immunohistochemistry (IHC) using Blood or Tumor: Tumor and blood samples from this study may undergo proteomic analyses (e.g., PD-L1 IHC). Triple negative tumor status will be assessed according to the most recent ASCO/College of American Pathologists (CAP) guidelines. PD-L1 protein level, as assessed by IHC in tumor sections, has been shown to correlate with response to pembrolizumab in patients with NSCLC, and a PD-L1 IHC diagnostic is marketed for use with pembrolizumab in NSCLC. Preliminary data indicate that this association may also be true in additional cancer types (i.e., TNBC, head and neck squamous cell carcinoma [HNSCC], and gastric). Additional tumor or blood-derived proteins may also correlate with response to pembrolizumab. Therefore, tumor tissue may be subjected to proteomic profiling using a variety of platforms that could include but are not limited to immunoassay, liquid chromatography/mass spectrometry. This approach could identify novel protein biomarkers that could aid in patient selection for pembrolizumab therapy.

Other Biomarkers in Tumor Specimens: TILs have been shown to provide prognostic and potentially predictive value, particularly in TNBC [54], [93], [94], [95] and HER2-overexpressing breast cancer [95], [96], [97]. Hematoxylin and eosin–stained (H&E-stained) breast tumor sections will be evaluated for TILs, according to a recently published standardized methodology [9].

Other blood-derived Biomarkers: In addition to expression on the tumor tissue, PD-L1 and other tumor derived proteins can be shed from tumors and released into the blood. Enzyme-linked immunoassay can measure such proteins in serum and correlate this expression with response to pembrolizumab therapy, as well as levels of PD-L1 IHC or protein in the tumor. Advantages to this method are that blood is an easily accessed compartment from which tumor- derived protein biomarkers may be measured. This research would serve to develop such assays for clinical use.

4.2.3.4 Future Biomedical Research

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

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

4.3 Benefit/Risk

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

Additional potential benefits are addressed in Section 4.1.3 – Ongoing Clinical Studies, which details responses to pembrolizumab in the TNBC cohort of the multi-cohort Phase Ib study, KEYNOTE-012, which enrolled subjects with PD-L1 positive (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 positive 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 CIV. 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 study 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 with locally recurrent inoperable or metastatic TNBC, which has not been previously treated with chemotherapy, and who are at least 18 years of age 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. Have signed informed consent to study participation. The subject may also provide consent for Future Biomedical Research (FBR). However, the subject may participate in the main trial without participating in FBR.
2. Be at least 18 years of age on the day of signing informed consent.
3. Have locally recurrent inoperable breast cancer not previously treated with chemotherapy and which cannot be treated with curative intent.

OR

Have metastatic breast cancer not previously treated with chemotherapy.

Note: Subjects with a history of locally recurrent breast cancer, which was previously treated with curative intent, may be eligible.

4. Have centrally confirmed TNBC, as defined by the most recent ASCO/CAP guidelines.

   Note: Subjects initially diagnosed with hormone receptor–positive and/or HER2-positive breast cancer must have central confirmation of TNBC in a tumor biopsy obtained from a local recurrence or distant metastasis site.

5. Have completed treatment for Stage I-III breast cancer, if indicated, and ≥6 months elapsed between the completion of treatment with curative intent (e.g., date of primary breast tumor surgery or date of last adjuvant chemotherapy administration, whichever occurred last) and first documented local or distant disease recurrence.

   Note: Adjuvant radiation therapy is not considered treatment with curative intent for the purpose of calculating the ≥6 month interval requirement described above.

   Note: First documentation of local or distant disease recurrence must be in the form of a dated biopsy, pathology, or imaging study report. A laboratory report indicating tumor marker elevation cannot be used as documentation of local or distant disease recurrence, unless accompanied by dated biopsy, pathology, or imaging study report.

   Note: Subjects who received taxane, gemcitabine, or platinum agents in the (neo)adjuvant setting can be treated with same class of chemotherapy (taxane or gemcitabine/carboplatin), if ≥12 months have elapsed between the completion of treatment with curative intent (e.g., date of primary breast tumor surgery or date of last adjuvant chemotherapy administration, whichever occurred last) and first documented local or distant disease recurrence.

6. Have been treated with (neo)adjuvant anthracycline, if they received systemic treatment in the (neo)adjuvant setting, unless anthracycline was contraindicated or not considered the best treatment option for the subject in the opinion of the treating physician.

   Note: Subjects presenting with de novo metastatic TNBC are eligible for the study, if anthracycline is contraindicated or not considered the best treatment option for the subject in the opinion of the treating physician.

7. Have measurable disease based on RECIST 1.1 as determined by local radiology review.

   Note: Target lesions situated in a previously irradiated area are considered measurable, only if they have shown unequivocal progression based on RECIST 1.1 after radiation therapy.

   Note: Chest wall recurrence can be used as a target lesion, only if measurable by diagnostic quality imaging modality (digital photography alone is not adequate).

8. Have provided recently or newly obtained core or excisional biopsy from a locally recurrent inoperable or metastatic tumor lesion for central determination of TNBC status and PD-L1 expression, unless contraindicated due to site inaccessibility and/or subject safety concerns.

   Note: Adequacy of biopsy specimen for the above analyses must be confirmed by the central laboratory. Submission of another tumor specimen may be required, if adequate tumor tissue was not provided the first time.

   Note: An archival tumor specimen obtained before the diagnosis of locally recurrent inoperable or metastatic breast cancer may be submitted after consultation with the Sponsor, if neither a recently nor a newly obtained biopsy from a locally recurrent inoperable or a metastatic site is available.

9. Have an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1, as assessed within 10 days prior to the start of study treatment.
10. Have life expectancy ≥12 weeks from randomization.
11. Demonstrate adequate organ function, within 10 days prior to the start of study treatment, as defined in the following table (Table 2).

Table 2 Adequate Organ Function Laboratory Values

System	Laboratory value
Hematological	
Absolute neutrophil count (ANC)	≥1,500/µL
Platelets	≥100,000/µL
Hemoglobin	≥9.0 g/dL or ≥5.6 mmol/L[a]
Renal	
Creatinine **OR** Measured or calculated[b] creatinine clearance (GFR can also be used in place of creatinine or CrCl)	≤1.5 × ULN **OR** ≥30 mL/min for subject with creatinine levels >1.5 × institutional ULN
Hepatic	
Total bilirubin	≤1.5 ×ULN OR Direct bilirubin ≤ULN for subjects with total bilirubin levels >1.5 × ULN
AST (SGOT) and ALT (SGPT)	≤2.5 × ULN (≤5 × ULN for subjects with liver metastases)
Albumin	≥3.0 g/dL

System	Laboratory value
Coagulation	
International Normalized Ratio (INR) or Prothrombin Time (PT)	≤1.5 × ULN unless subject is receiving anticoagulant therapy as long as PT or PTT is within therapeutic range of intended use of anticoagulants
Activated Partial Thromboplastin Time (aPTT)	≤1.5 × ULN unless subject is receiving anticoagulant therapy as long as PT or PTT is within therapeutic range of intended use of anticoagulants

ALT (SGPT) = alanine aminotransferase (serum glutamic pyruvic transaminase); AST (SGOT) = aspartate aminotransferase (serum glutamic oxaloacetic transaminase); GFR = glomerular filtration rate; ULN = upper limit of normal.

[a] Criteria must be met without erythropoietin dependency and without packed red blood cell (pRBC) transfusion within last 2 weeks.

[b] Creatinine clearance (CrCl) should be calculated per institutional standard.

Note: This table includes eligibility-defining laboratory value requirements for treatment; laboratory value requirements should be adapted according to local regulations and guidelines for the administration of specific chemotherapies.

12. This inclusion criterion was removed during amendment 06 as a result of updates to the contraception and pregnancy criteria. The updated information has been added to inclusion criterion #13.
13. A female participant is eligible to participate if she is not pregnant or breastfeeding, and at least one of the following conditions applies:

    • Is not a WOCBP

      OR

    • Is a WOCBP and:

      - Uses a contraceptive method that is highly effective (with a failure rate of <1% per year), with low user dependency, or be abstinent from heterosexual intercourse as their preferred and usual lifestyle (abstinent on a long-term and persistent basis), as described in Appendix 6 during the intervention period and for at least the time needed to eliminate each study intervention after the last dose of study intervention and agrees not to donate eggs (ova, oocytes) to others or freeze/store for her own use for the purpose of reproduction during this period. The length of time required to continue contraception for each study intervention is as follows:

        ◦ pembrolizumab: 120 days

        ◦ chemotherapy: 180 days

      The investigator should evaluate the potential for contraceptive method failure (ie, noncompliance, recently initiated) in relationship to the first dose of study intervention. Contraceptive use by women should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies. If the contraception requirements in the local label for any of the

study interventions is more stringent than the requirements above, the local label requirements are to be followed.

- Has a negative highly-sensitive pregnancy test ([urine or serum] as required by local regulations) within 24 hours (urine) or 72 hours (serum) before the first dose of study intervention. (If a urine test cannot be confirmed as negative [eg, an ambiguous result], a serum pregnancy test is required. In such cases, the participant must be excluded from participation if the serum pregnancy result is positive). Additional requirements for pregnancy testing during and after study intervention are in Appendix 6.
- Has had her medical history, menstrual history, and recent sexual activity reviewed by the investigator to decrease the risk for inclusion of a woman with an early undetected pregnancy.

14. Male participants are eligible to participate if they agree to the following during the intervention period and for at least the time needed to eliminate each study intervention after the last dose of study intervention. The length of time required to continue contraception for each study intervention is as follows:
    - chemotherapy: 95 days

• Refrain from donating sperm

PLUS either:

• Be abstinent from heterosexual intercourse as their preferred and usual lifestyle (abstinent on a long-term and persistent basis) and agree to remain abstinent

OR

• Must agree to use contraception unless confirmed to be azoospermic (vasectomized or secondary to medical cause [Appendix 6]) as detailed below:
    - Agree to use a male condom plus partner use of an additional contraceptive method when having penile-vaginal intercourse with a WOCBP who is not currently pregnant. Note: Men with a pregnant or breastfeeding partner must agree to remain abstinent from penile-vaginal intercourse or use a male condom during each episode of penile-vaginal penetration.
    - Contraceptive use by men should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies. If the contraception requirements in the local label for any of the study interventions is more stringent than the requirements above, the local label requirements are to be followed.

5.1.3 Subject Exclusion Criteria

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

1. Is currently participating in a clinical study and receiving an investigational agent and/or using an investigational device, or has participated in a clinical study and

received an investigational agent and/or used an investigational device within 4 weeks prior to randomization.

Note: Subjects who have entered the follow-up phase of a clinical study may participate as long as 4 weeks have elapsed since the last dose of the investigational agent and/or removal of the device.

Note: Subjects who were treated with radiation therapy may participate as long as at least 2 weeks have elapsed since the last dose of radiation therapy was administered.

2. Has not recovered (e.g., to ≤Grade 1 or to baseline) from AEs due to a previously administered therapy.

   Note: Alopecia of any grade is an exception to this criterion.

   Note: Prior to randomization, the subject must have recovered adequately from any toxicity and/or complications associated with any recent procedure.

3. Has neuropathy ≥Grade 2.

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

5. Has a diagnosis of immunodeficiency or is receiving systemic steroid therapy or any other form of immunosuppressive therapy within 7 days prior to randomization.

6. Has a known additional malignancy that progressed or required active treatment within the last 5 years. Exceptions include basal cell carcinoma of the skin, squamous cell carcinoma of the skin that has undergone potentially curative therapy, and in situ cervical cancer.

7. Has known active CNS metastases and/or carcinomatous meningitis. Subjects with known brain metastases may participate provided that the brain metastases have been previously treated (except with chemotherapy) and are radiographically stable. To demonstrate radiographic stability of previously treated brain metastases, a minimum of 2 post-treatment brain imaging assessments are required: 1) The first brain imaging must be acquired after treatment of brain metastases has been completed 2) The second brain imaging must be obtained during screening (i.e., within 28 days of randomization) and ≥ 4 weeks after the previous post-treatment brain imaging.

   Note: Known brain metastases are considered active, if any of the following criteria are applicable:

   a. Brain imaging during screening demonstrates progression of existing metastases and/or appearance of new lesions compared to brain imaging performed at least 4 weeks earlier.

      Radiographic stability of previously treated brain metastases is based on local radiology/investigator review, but dated reports of 2 imaging studies (the most recent performed during screening) documenting stability of brain metastasis(es) over ≥4 weeks must be submitted to the Sponsor.

Such brain imaging studies should be available at the site for submission to CIV, if later needed.

b. Neurological symptoms attributed to brain metastases have not returned to baseline

c. Steroids were used for management of symptoms related to brain metastases within 28 days of randomization

8. Has history of (non-infectious) pneumonitis that required steroids or current pneumonitis
9. Has active, or a history of, interstitial lung disease.
10. Has a known history of active TB (Bacillus Tuberculosis)
11. Has an active infection requiring systemic therapy.
12. Has a history of class II-IV congestive heart failure or myocardial infarction within 6 months of randomization.
13. Has a history or current evidence of any condition, therapy, or laboratory abnormality that might confound the results of the study, interfere with subject participation for the full duration of the study, or render study participation not compatible with the subject's best interest, in the opinion of the treating Investigator.
14. Has a known psychiatric or substance abuse disorders that would interfere with cooperation with the requirements of the study.
15. Is pregnant or breastfeeding, or expecting to conceive or father children within the projected duration of the study, starting with the screening visit through 120 days (or longer as specified by local institutional guidelines) after the last dose of study treatment.
16. 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 (such as CTLA-4, OX-40, CD137) or has previously participated in MSD pembrolizumab (MK-3475) clinical studies.
17. Has a known history of human immunodeficiency virus (HIV) (HIV 1/2 antibodies).
18. Has known active hepatitis B (e.g., hepatitis B surface antigen [HBsAg] reactive) or hepatitis C (e.g., HCV RNA [qualitative] is detected).
19. Has received a live vaccine within 30 days prior to randomization.
20. Has a known history of hypersensitivity or allergy to pembrolizumab and any of its components and/or to any of the study chemotherapies (e.g., nab-paclitaxel, paclitaxel, gemcitabine, or carboplatin) and any of their components.
21. Is receiving any medication prohibited in combination with study chemotherapies as described in the respective product labels, unless medication was stopped within 7 days prior to randomization.

5.2 Trial Treatment(s)

The treatments to be used in this trial are outlined below in Table 3. If a particular taxane is not approved in a participating country, this agent cannot be used and selected via the Interactive Voice Response System (IVRS)/Integrated Web Response System (IWRS) during randomization.

Table 3 Study Treatments

Drug	Dose/ Potency	Dose Frequency	Route of Administration	Treatment Period	Use
Pembrolizumab	200 mg	Day 1	IV infusion	Every 21 days	Experimental
Nab-paclitaxel	100 mg/m^2	Days 1, 8, and 15	IV infusion	Every 28 days	Chemotherapy background treatment
Paclitaxel	90 mg/m^2	Days 1, 8, and 15	IV infusion	Every 28 days	
Gemcitabine Carboplatin	1000 mg/m^2 AUC 2	Days 1 and 8	IV infusion	Every 21 days	
Placebo (Normal Saline)	NA	Day 1	IV infusion	Every 21 days	Placebo for Pembrolizumab

Study treatment should begin on the day of randomization or within 3 days after the randomization date.

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

For any commercially available product that is provided by the trial site, subsidiary or designee every attempt will be made to source these supplies from a single lot/batch number. The trial site 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)

The rationale for selection of doses to be used in this study is provided in Section 4.2.2 – Rationale for Dose Selection/Regimen/Modification.

The dose amount required to prepare the pembrolizumab infusion solution will be based on a fixed dose of 200 mg. Details on dose calculation, preparation, and administration of pembrolizumab are provided in the Pharmacy Manual.

Taxanes will be prepared and administered per local guidelines and practices at the doses indicated below:

- nab-paclitaxel: 100 mg/m^2
- paclitaxel: 90 mg/m^2

Gemcitabine will be prepared and administered per local guidelines and practices at 1000 mg/m^2.

Carboplatin will be prepared and administered per local guidelines and practices at AUC 2.

5.2.1.2 Dose Modification

The NCI CTCAE v4.0 must be used to grade the severity of AEs. If appropriate, the Investigator may attribute each toxicity event to an immunologic etiology and/or chemotherapy. If the dose of one drug in the regimen is delayed, treatment with the other drug(s) may continue as scheduled. Missed doses in chemotherapy treatment periods should be skipped, if not given within the allowed window of ±3 days.

Dose modifications for individual study treatment(s) must be based on the maximum toxicity experienced during the previous treatment period with this(these) drug(s) and must be performed in a stepwise manner, as described in Table 4 and Table 5. Toxicity (except for alopecia) needs to resolve to ≤Grade 1 or baseline prior to resuming treatment with the same drug(s). For subjects requiring a study treatment dose modification, the next treatment period with this(these) drug(s) may be delayed, if the scheduled off-drug periods are not adequate to allow for recovery to ≤Grade 1 or the baseline status of the subject.

Pembrolizumab dose reductions are not permitted. Pembrolizumab/placebo treatment may be interrupted or discontinued due to an adverse event. If a dose reduction for toxicity occurs with chemotherapy, the dose(s) may not be re-escalated. Subjects may have a maximum of 2 dose modifications per chemotherapy (if applicable) for toxicities throughout the course of the study. If a subject experiences several toxicities and there are conflicting recommendations, the most conservative dose adjustment recommended should be followed (dose reduction appropriate to the most severe toxicity).

If the toxicity may be attributed to both an immunologic etiology (pembrolizumab/placebo-related) and chemotherapy, pembrolizumab/placebo should be interrupted or discontinued and chemotherapy should be reduced (if applicable), interrupted, or discontinued, according to local guidelines and practices. Subjects may have chemotherapy discontinued and continue on pembrolizumab/placebo. Any requests for unblinding will be considered on an individual subject basis and only after consultation with the Sponsor. Should an Investigator discontinue treatment with chemotherapy and continue the subject on treatment with pembrolizumab/placebo the subject does not need to come to the clinic on dates when only the chemotherapy would have been administered. Similarly, subjects may discontinue pembrolizumab/placebo and continue on chemotherapy alone, if appropriate.

Chemotherapy administration may be interrupted due to AEs for a maximum of 4 weeks; pembrolizumab/placebo may be interrupted due to AEs for a maximum of 12 weeks.

Note: Pembrolizumab/placebo and chemotherapy dosing interruptions are permitted in the case of medical/surgical events or logistical reasons not related to study therapy

(e.g., elective surgery, unrelated medical events, subject vacation, and/or holidays). Subjects should be placed back on study treatment within 3 weeks of the scheduled interruption, unless otherwise discussed with the Sponsor. The reason for interruption should be documented in the subject's study record.

Suggested dose modifications for chemotherapy are detailed in Table 4 (local guidelines and practices should be followed, if different than below recommendations).

Table 4 Suggested Dose Modifications for Study Chemotherapies

	Dose level 0	**Dose level -1**	**Dose level -2**	**Dose level -3**
Nab-paclitaxel	100 mg/m^2	~ 20% reduction	~ 20% reduction	Discontinue
Paclitaxel	90 mg/m^2	~ 20% reduction	~ 20% reduction	Discontinue
Gemcitabine	1000 mg/m^2	~ 20% reduction	~ 20% reduction	Discontinue
Carboplatin	AUC 2	AUC 1.5	AUC 1	Discontinue

5.2.1.2.1 Dose Modification and Toxicity Management Guidelines for Pembrolizumab

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

AEs (both serious and non-serious) associated with pembrolizumab exposure may represent an immunologic etiology. These immune-related AEs (irAEs) may occur shortly after the first dose or several months after the last dose of pembrolizumab treatment and may affect more than one body system simultaneously. Therefore, early recognition and initiation of treatment is critical to reduce complications. Based on existing clinical trial data, most irAEs were reversible and could be managed with interruptions of pembrolizumab, administration of corticosteroids and/or other supportive care. For suspected irAEs, ensure adequate evaluation to confirm etiology or exclude other causes. Additional procedures or tests such as bronchoscopy, endoscopy, skin biopsy may be included as part of the evaluation. Based on the severity of irAEs, withhold or permanently discontinue pembrolizumab/placebo and administer corticosteroids. Dose modification and toxicity management guidelines for irAEs associated with pembrolizumab are provided in Table 5.

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

General instructions:

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

Immune-related AEs	**Toxicity grade or conditions (CTCAEv4.0)**	**Action taken to pembrolizumab**	**irAE management with corticosteroid and/or other therapies**	**Monitor and follow-up**
Pneumonitis	Grade 2	Withhold	• Administer corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper	• 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	Permanently discontinue		

Immune-related AEs	Toxicity grade or conditions (CTCAEv4.0)	Action taken to pembrolizumab	irAE management with corticosteroid and/or other therapies	Monitor and follow-up
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 (e.g., 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 (e.g., levothyroxine or liothyronine) per standard of care	• Monitor for signs and symptoms of thyroid disorders.
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		

Immune-related AEs	Toxicity grade or conditions (CTCAEv4.0)	Action taken to pembrolizumab	irAE management with corticosteroid and/or other therapies	Monitor and follow-up
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 immune-related AEs	Intolerable/ persistent Grade 2	Withhold	• Based on type and severity of AE administer corticosteroids	• Ensure adequate evaluation to confirm etiology and/or exclude other causes
	Grade 3	Withhold or discontinue based on the type of event. Events that require discontinuation include and not limited to: Guillain-Barre Syndrome, encephalitis		
	Grade 4 or recurrent Grade 3	Permanently discontinue		

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

NOTE:
For 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).

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

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

Table 6 Pembrolizumab Infusion Reaction Dose Modification and Treatment Guidelines

NCI CTCAE Grade	Treatment	Premedication at Subsequent Dosing
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 (e.g., 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 (e.g., from 100 mL/hr to 50 mL/hr). Otherwise dosing will be held until symptoms resolve and the subject should be premedicated for the next scheduled dose. Subjects who develop Grade 2 toxicity despite adequate premedication should be permanently discontinued from further study drug treatment	Subject may be premedicated 1.5h (± 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 (i.e., not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae (e.g., renal impairment, pulmonary infiltrates) Grade 4: Life-threatening; pressor or ventilatory support indicated	**Stop Infusion.** Additional appropriate medical therapy may include but is not limited to: 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
Appropriate resuscitation equipment should be available at the bedside and a physician readily available during the period of drug administration. For further information, please refer to the Common Terminology Criteria for Adverse Events v4.0 (CTCAE) at http://ctep.cancer.gov		

5.2.1.2.2 Nab-Paclitaxel

Dose modifications for nab-paclitaxel will be implemented according to local guidelines and practices.

5.2.1.2.3 Paclitaxel

Dose modifications for paclitaxel will be implemented according to local guidelines and practices.

5.2.1.2.4 Gemcitabine/Carboplatin

Dose modifications for gemcitabine and/or carboplatin will be implemented according to local guidelines and practices.

5.2.2 Timing of Dose Administration

Study treatment will be administered on an outpatient basis after all procedures/assessments have been completed, and in the following order: pembrolizumab or saline placebo infusion will be administered first, followed by premedication for the assigned chemotherapy (if applicable; see Section 5.6.2 – Supportive Care Guidelines for Chemotherapy-related Adverse Events) and then administration of chemotherapy, according to local guidelines and practices.

5.2.2.1 Pembrolizumab/Saline Placebo

Pembrolizumab or saline placebo will be administered as a 30-minute IV infusion Q3W. Sites should make every effort to target infusion timing to be as close to 30 minutes as possible. A window of –5 minutes/+10 minutes is permitted. The reason for any delay in infusion outside of the protocol specified window should be documented in the subject's chart and recorded on the electronic Case Report Forms (eCRFs).

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

5.2.2.2 Nab-Paclitaxel

Nab-paclitaxel will be administered as IV infusion on Days 1, 8, and 15 every 28 days according to local guidelines and practices.

5.2.2.3 Paclitaxel

Paclitaxel will be administered as IV infusion on Days 1, 8, and 15 every 28 days according to local guidelines and practices.

5.2.2.4 Gemcitabine/Carboplatin

Gemcitabine and carboplatin will be administered as IV infusions on Days 1 and 8 every 21 days according to local guidelines and practices.

5.2.3 Trial Blinding

Part 1 (Safety Run-In): Both pembrolizumab and chemotherapy administration will be open-label.

Part 2 (Phase III Study): Chemotherapy administration will be open-label. Because this is a double-blind study for pembrolizumab, the Sponsor, investigators, other study site staff (except for the unblinded pharmacist), and subjects will be blinded to pembrolizumab vs saline placebo administration. The study site's unblinded pharmacist will obtain each subject's study identification number and study drug assignment from the IVRS/IWRS and prepare study treatment solutions for infusion. The unblinded pharmacist will provide the blinded study site staff with ready-to-use blinded identically packaged pembrolizumab/saline infusion solutions for administration at scheduled infusion visits. In addition to emergent unblinding for severe or life-threatening AEs with potential immunologic etiology, non-emergent unblinding to pembrolizumab versus placebo administration may occur on an individual subject basis and only after consultation with the Sponsor at the time of (1) centrally verified disease progression and subject has discontinued all study treatments or, (2) when the subject has discontinued all study treatments and a new anti-cancer treatment is going to be started. Non-emergent unblinding only after consultation and approval from the Sponsor is implemented through IRT by following the instructions in the IRT site user manual. Investigators, other study site staff, and subjects will be blinded to subject-level tumor PD-L1 biomarker results.

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 main treatment arms. Subjects will be assigned randomly in a 2:1 ratio to pembrolizumab + chemotherapy or placebo + chemotherapy, respectively, in Part 2 (Phase III study), after stratification as described in Section 5.4 – Stratification. The chemotherapy that each subject is eligible for will be determined according to Inclusion Criterion #5 in Section 5.1.2 – Subject Inclusion Criteria. If chemotherapy options include more than one regimen, choice of study chemotherapy will be at physician's discretion. The distribution of the subjects among the 3 chemotherapy options (paclitaxel, nab-paclitaxel, or gemcitabine/carboplatin) will be monitored closely.

For Part 1 (Safety Run-In), there are 3 treatment arms: pembrolizumab + paclitaxel, pembrolizumab + nab-paclitaxel, or pembrolizumab + gemcitabine/carboplatin. Enrollment in Part 1 will stop once ≥10 subjects are enrolled in each arm. To ensure approximately synchronous enrollment to all 3 treatment arms in Part 1, subject randomization/allocation will be performed as summarized in Table 7. Forced randomization will be applied to stop enrollment into a specific treatment once ≥10 subjects are enrolled in that treatment. Approximately 30 subjects are expected to enroll in total in Part 1.

Table 7 Subject Randomization/Allocation for Part 1

Group	Subject Breast Cancer History	Subject Randomization/Allocation
1	• No prior (neo)adjuvant chemotherapy treatment (including subjects with de novo mTNBC), *or* • Local or distant disease recurrence ≥12 months after completion of treatment with curative intent (e.g., date of primary breast tumor surgery or date of last adjuvant chemotherapy administration, whichever occurred last), *or* • Interval between completion of treatment with curative intent and disease recurrence of 6 to 12 months, and no prior treatment with either platinum or gemcitabine or taxane in the (neo)adjuvant setting.	Subjects will be randomized in a 1:1:1 ratio among • pembrolizumab + nab-paclitaxel • pembrolizumab + paclitaxel • pembrolizumab + gemcitabine/carboplatin
2	Interval between completion of treatment with curative intent and disease recurrence of 6 to 12 months, and prior platinum or gemcitabine treatment in the (neo)adjuvant setting, and no prior taxane treatment in the (neo)adjuvant setting.	Subjects will be randomized in a 1:1 ratio between • pembrolizumab + nab-paclitaxel • pembrolizumab + paclitaxel
3	Interval between completion of treatment with curative intent and disease recurrence of 6 to 12 months, and prior taxane treatment in the (neo)adjuvant setting, and no prior platinum or gemcitabine treatment in the (neo)adjuvant setting.	Subjects will be allocated to • pembrolizumab + gemcitabine/carboplatin

5.4 Stratification

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

Part 1 (Safety Run-In):

There is no stratification factor for Part 1.

Part 2 (Phase III Study):

1. Chemotherapy on study (taxane [i.e., paclitaxel or nab-paclitaxel] vs gemcitabine/carboplatin).
2. Tumor PD-L1 status (CPS ≥1 vs CPS <1).
3. Prior treatment with same class of chemotherapy in the (neo)adjuvant setting (yes vs no).

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 medications will be recorded on the eCRF, including all prescription, over-the-counter (OTC), and IV medications and fluids. If changes occur during the study period, documentation of drug dosage, frequency, route, and date should also be included on the eCRF.

All concomitant medications received within 30 days before randomization, while on study treatment, and up to 30 days after the last dose of study treatment should be recorded. Concomitant medications administered beyond 30 days after the last dose of study treatment should be recorded when prescribed for SAEs (see Section 7.2 – Assessing and Recording Adverse Events).

5.5.2 Prohibited Concomitant Medications

Subjects are prohibited from receiving the following therapies during the Screening, Treatment, and Retreatment Phase of this study:

- Antineoplastic systemic chemotherapy or biological therapy
  - Immunotherapy not specified in this protocol
  - Chemotherapy not specified in this protocol

- Investigational agents other than pembrolizumab
- Radiation therapy
  - Radiation therapy is prohibited within 2 weeks prior to randomization

  Note: Radiation therapy to a symptomatic solitary lesion or to the brain may be allowed after consultation with Sponsor (except during screening).

- Herbal supplements
- Live vaccines within 30 days prior to randomization and while participating in the study. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, varicella, herpes zoster, yellow fever, rabies, Bacillus Calmette–Guérin (BCG), and typhoid (oral) vaccines. Seasonal influenza vaccines for injection are generally killed virus vaccines and are allowed. However, intranasal influenza vaccines (e.g., Flu - Mist®) are live attenuated vaccines, and are not allowed.
- Glucocorticoids for any purpose other than the following:
  - To modulate symptoms from an AE of suspected immunologic etiology.
  - Inhaled steroids for management of asthma.
  - Physiologic doses of prednisone 10 mg (or equivalent) per day
  - Use of prophylactic corticosteroids to avoid allergic reactions (e.g., to paclitaxel and/or IV contrast dye) is permitted.
- Any medication prohibited in combination with chemotherapy as described in the respective product labels for nab-paclitaxel, paclitaxel, gemcitabine, and carboplatin.

The Exclusion Criteria describe other medications that are prohibited in this study.

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

5.6 Rescue Medications & Supportive Care

5.6.1 Supportive Care Guidelines for Subjects Receiving Pembrolizumab/Placebo

Subjects should receive appropriate supportive care measures as deemed necessary by the treating investigator. Suggested supportive care measures for the management of AEs with potential immunologic etiology are outlined along with the dose modification guidelines in Section 5.2.1, Table 5. Where appropriate, these guidelines include the use of oral or IV treatment with corticosteroids, as well as additional anti-inflammatory agents, if symptoms do not improve with administration of corticosteroids. Note that several courses of steroid tapering may be necessary as symptoms may worsen when the steroid dose is decreased. For each disorder, attempts should be made to rule out other causes, such as metastatic disease or bacterial or viral infection, which might require additional supportive care.

Note: If, after evaluation, the event is determined not to be related to pembrolizumab/placebo, the investigator does not need to follow the treatment guidance. Refer to Section 5.2.1 – Dose Selection/Modification and Table 5 for pembrolizumab/placebo dose modifications.

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-related Adverse Events

Paclitaxel-, nab-paclitaxel-, or gemcitabine/carboplatin-related AEs should be managed according to local guidelines and practices.

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.

5.8 Subject Withdrawal/Discontinuation Criteria

Subjects may withdraw consent at any time for any reason or be dropped from the trial at the discretion of the investigator should any untoward effect occur. In addition, a subject may be withdrawn by the investigator or the Sponsor if enrollment into the trial is inappropriate, the trial plan is violated, or for administrative and/or other safety reasons. Specific details regarding discontinuation or withdrawal procedures; including specific details regarding withdrawal from Future Biomedical Research, are provided in Section 7.1.4 – Other Procedures.

A subject must be discontinued from the trial if:

- The subject or legal representative (such as parent or legal representative) withdraws consent.

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

- The subject or legal representative (such as parent or legal guardian) withdraws consent for study treatment.
- The subject has confirmed radiographic disease progression, with the exception as outlined in Section 7.1.2.9.5 – irRECIST Assessment of Disease.
- The subject has unacceptable toxicity, as described in Section 7.2 – Assessing and Recording Adverse Events.
- The subject has an intercurrent illness that prevents further administration of treatment.
- The Investigator made a decision to discontinue subject's treatment on study.
- The subject is noncompliant with study treatment or procedural requirements.
- The subject has a confirmed positive serum pregnancy test.
- Administrative reasons.

In addition, if a subject completes 35 administrations of pembrolizumab/placebo, the subject must be discontinued from pembrolizumab/placebo study treatment but may continue chemotherapy treatment at the investigator's discretion. The subject should continue to be monitored in the trial.

Subjects who attain an investigator-determined confirmed CR may discontinue pembrolizumab/placebo after receiving at least 2 additional administrations of pembrolizumab/placebo beyond the date when the initial CR was declared and at least 8 administrations of pembrolizumab/placebo in total. (Dis)continuation of chemotherapy after confirmed CR is at the Investigator's discretion.

Subjects who are discontinued from all study treatments should continue to be monitored in the trial, as outlined in Sections 7.1.5.3 – End of Treatment and 7.1.5.4 – After Treatment Discontinuation.

Subjects who stop pembrolizumab/placebo with SD or better may be eligible for up to 17 additional treatments with pembrolizumab if they meet eligibility criteria for retreatment phase as specified in Section 7.1.5.6 – Second Course Phase (Retreatment Phase).

5.9 Subject Replacement Strategy

A subject who discontinues 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, discontinues from the trial or is lost to follow-up (i.e. the subject is unable to be contacted by the investigator).

Upon study completion, participants are discontinued and may be enrolled in a pembrolizumab extension study, if available.

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 DMC.
2. Quality of 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 from study drugs/drug combinations under investigation.
5. Plans to modify or discontinue the development of study drugs/drug combinations.

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

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

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.

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

6.0 TRIAL FLOW CHART

6.1 First Course Treatment Phase

6.1.1 Screening and Treatment Periods (Parts 1 and 2)

6.1.1.1 Pembrolizumab/Placebo Plus Taxane (Paclitaxel or Nab-Paclitaxel)

Study Period	Screening Period	Treatment Period (3-Week Cycles)												
Treatment Cycle/Title:	Screening[b]	1			2			3			4			5 and Beyond[a]
Scheduled Day:	–28 to –1	1[c]	8	15	1	8	15	1	8	15	1	8	15	1/8/15[a]
Scheduling Window (Days):	N/A	N/A	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3
Administrative Procedures														
Informed Consent	X													
Informed Consent for Future Biomedical Research	X													
Inclusion/Exclusion Criteria	X													
Subject Identification Card	X													
Demographics and Medical History	X													
Prior and Concomitant Medication Review[d]	X	X	X	X	X	X	X	X		X	X	X		X
Survival Status[t]		←----------												----------→
Clinical Procedures/Assessments														
Full Physical Examination[e]	X	X												
Directed Physical Examination[e]			X	X	X	X	X	X		X	X	X		X
12-Lead Electrocardiogram	X													
Vital Signs and Weight[f]	X	X	X	X	X	X	X	X		X	X	X		X
Pembrolizumab/Placebo Administration (Placebo given only in Part 2)[g, h]		X			X			X			X			X
Taxane Administration[g, h]		X	X	X		X	X	X		X	X	X		X
ePROs[i]		X			X			X						X
ECOG Performance Status[j]	X	X			X			X			X			X
Adverse Events Monitoring[k]	X	X	X	X	X	X	X	X		X	X	X		X
Menopausal Status	X													

Study Period	Screening Period	Treatment Period (3-Week Cycles)												
Treatment Cycle/Title:	Screening[b]	1			2			3			4			5 and Beyond[a]
Scheduled Day:	–28 to –1	1[c]	8	15	1	8	15	1	8	15	1	8	15	1/8/15[a]
Scheduling Window (Days):	N/A	N/A	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3
Laboratory Procedures/Assessments: Analysis performed by local laboratories														
CBC with Differential[j]	X	X[l]	X	X	X	X	X	X		X	X	X		X[l]
Chemistry[j]	X	X[l]			X			X			X			X[l]
Urinalysis[j]	X													
PT/INR and aPTT[j]	X													
T3 (or Free T3), Free T4, and TSH	X				X[m]						X[m]			
Serum vitamin D[j]	X													
Serum FSH and estradiol[j]	X													
Tumor markers (CA15-3, CEA, and CA27.29)	X								X[n]					X
Pregnancy Test – Serum or Urine β-Human Chorionic Gonadotropin (β-hCG)	X[o]	X			X			X			X			X
Laboratory Procedures/Assessments: Analysis performed by central laboratory														
Blood for Genetic Analyses[p]		X												
Blood for RNA Analyses[q]		X			X									X
Blood for Plasma Biomarker Analyses[q]		X			X									X
Blood for Serum Biomarker Analyses[q]		X			X									X
Efficacy Assessments														
Tumor Imaging[r]	X								X[r]					X

Study Period	Screening Period	Treatment Period (3-Week Cycles)												
Treatment Cycle/Title:	Screening[b]	1			2			3			4			5 and Beyond[a]
Scheduled Day:	–28 to –1	1[c]	8	15	1	8	15	1	8	15	1	8	15	1/8/15[a]
Scheduling Window (Days):	N/A	N/A	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3
Tumor Tissue Collection														
Recently or Newly Obtained Tumor Collection	X[s]													

a. Starting with Cycle 5, the pattern of study treatment administration and assessments and procedures performed in Cycles 1 through 4 will be repeated, unless stated otherwise.
b. Relative to day of randomization.
c. Cycle 1, Day 1, may be on the same day as randomization or at most 3 days post randomization.
d. Record all medications taken within 30 days prior to randomization and all medications taken during treatment period of the study.
e. Full physical examination and directed physical examination will include neurologic examination to be performed by the treating physician or designee.
f. Vital signs measurements include temperature, pulse, blood pressure, respiratory rate, and weight. Height is measured only at 1st clinic visit.
g. In Part 1, for subjects receiving pembrolizumab + taxane (paclitaxel or nab-paclitaxel), pembrolizumab will be administered every 3 weeks (Q3W) on Day 1 of each 3-week cycle. Paclitaxel or nab-paclitaxel will be administered on a 3-week on (Days 1, 8, and 15)/1-week off schedule every 28 days. Should an Investigator discontinue treatment with chemotherapy but continue treatment with pembrolizumab, the subject does not need to come to the clinic on dates when only the chemotherapy would have been administered. The subject should still follow the treatment and procedure schedule for pembrolizumab visits.
h. In Part 2, for subjects randomly assigned to pembrolizumab/placebo + taxane (paclitaxel or nab-paclitaxel), pembrolizumab/placebo will be administered Q3W on Day 1 of each 3-week cycle. Paclitaxel or nab-paclitaxel will be administered on a 3-week on (Days 1, 8, and 15)/1-week off schedule every 28 days. Visit schedule for subjects who discontinued treatment with chemotherapy, but continued pembrolizumab/placebo treatment remains as described above in "g".
i. The electronic Patient Reported Outcomes (ePROs) include EORTC QLQ-C30, EORTC QLQ-BR23, and EQ-5D™. Refer to Section 7.1.2.5 – Patient-Reported Outcomes for details on timing for ePROs.
j. Screening laboratory tests and ECOG must be performed within 10 days prior to the start of study treatment (serum FSH and estradiol will only be measured, if clinically indicated for determination of menopausal status). Thereafter, laboratory samples can be collected up to 72 hours prior to scheduled administration of study treatment.
k. Record all AEs occurring through the end of treatment and as described in Section 6.1.2 – End of Treatment and After Treatment Discontinuation (Parts 1 and 2).
l. The CBC and chemistry laboratory tests do not need to be performed on Cycle 1, Day 1, if obtained within 10 days prior to the start of study treatment. However, they will be performed on Day 1 of each subsequent cycle. Note: CBC will also be performed on additional days, as described in the table above.
m. Post randomization, thyroid function tests should be collected every 2 cycles.
n. CA15-3, CEA, and CA27.29 should be collected during screening and then according to the imaging schedule (can be conducted at corresponding study visit) until study treatment discontinuation (see also Section 6.1.2 – End of Treatment and After Treatment Discontinuation (Parts 1 and 2).
o. For women of reproductive potential, a urine pregnancy test will be performed within 24 hours or serum pregnancy test should be performed within 72 hours prior to the first dose of study treatment. If the urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required. While the subject is on study, pregnancy testing should be conducted as per local regulations where applicable.
p. This sample should be drawn for planned analysis of the association between genetic variants in DNA and drug response. This sample will not be collected at that site if there is either a local law or regulation prohibiting collection, or if the IRB/IEC does not approve the collection of the sample for these purposes. If the sample is collected, leftover extracted DNA will be stored for future biomedical research if the subject signs the FBR consent. If the planned genetic analyses are not approved, but FBR is approved and consent is given, this sample will be collected for the purpose of FBR.
q. Blood should be collected at pre-dose on Cycles 1, 2, and 5 or at time of discontinuation as described in Section 6.1.2 – End of Treatment and After Treatment Discontinuation (Parts 1 and 2). Leftover RNA, plasma, and serum will be stored at the end of the study for future biomedical research if the subject has consented.

r. Post-baseline imaging studies will be performed at Weeks 8 (±7 days), 16 (±7 days), and 24 (–7 days) post randomization, every 9 weeks (±7 days) thereafter during the first year, and every 12 weeks (±7 days) after the first year. Imaging at Week 24 should be performed within 24 weeks post randomization. Refer to Section 7.1.2.9 – Tumor Imaging and Assessment of Disease Status for details on tumor imaging and assessment of disease.

s. All subjects must have central confirmation of TNBC status and determination of tumor PD-L1 status prior to randomization (see Section 5.1.2 – Subject Inclusion Criteria). The same, recently or newly obtained, core or excisional tumor biopsy (fine needle aspiration [FNA] not adequate) from a locally recurrent inoperable or metastatic tumor lesion can be used for both investigations. Additional information is provided in Section 7.1.2.10 – Tumor Tissue Collection.

t. During the Survival Follow-up phase, contacts are approximately every 12 weeks by telephone (or more often as needed). Updated 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 survival status (excluding subjects that have a death event previously recorded).

6.1.1.2 Pembrolizumab/Placebo Plus Gemcitabine/Carboplatin

Study Period:	Screening Period	Treatment Period (3-Week Cycles)								
Treatment Cycle/Title:	Screening[b]	1		2		3		4		5 and Beyond[a]
Scheduled Day:	–28 to –1	1[c]	8	1	8	1	8	1	8	1/8[a]
Scheduling Window (Days):	N/A	N/A	±3	±3	±3	±3	±3	±3	±3	±3
Administrative Procedures										
Informed Consent	X									
Informed Consent for Future Biomedical Research	X									
Inclusion/Exclusion Criteria	X									
Subject Identification Card	X									
Demographics and Medical History	X									
Prior and Concomitant Medication Review[d]	X	X	X	X	X	X	X	X	X	X
Survival Status[t]		←----------								----------→
Clinical Procedures/Assessments										
Full Physical Examination[e]	X	X								
Directed Physical Examination[e]			X	X	X	X	X	X	X	X
12-Lead Electrocardiogram	X									
Vital Signs and Weight[f]	X	X	X	X	X	X	X	X	X	X
Pembrolizumab/Placebo Administration (Placebo given only in Part 2)[g, h]		X		X		X		X		X
Gemcitabine/Carboplatin Administration[g, h]		X	X	X	X	X	X	X	X	X
ePROs[i]		X		X		X				X
ECOG Performance Status[j]	X	X		X		X		X		X
Adverse Events Monitoring[k]	X	X	X	X	X	X	X	X	X	X
Menopausal Status	X									
Laboratory Procedures/Assessments: Analysis performed by local laboratories										
CBC with Differential[j]	X	X[l]	X	X	X	X	X	X	X	X[l]
Chemistry[j]	X	X[l]		X		X		X		X[l]
Urinalysis[j]	X									
PT/INR and aPTT[j]	X									
T3 (or Free T3), Free T4, and TSH	X			X[m]				X[m]		

Study Period:	Screening Period	Treatment Period (3-Week Cycles)								
Treatment Cycle/Title:	Screening[b]	1		2		3		4		5 and Beyond[a]
Scheduled Day:	–28 to –1	1[c]	8	1	8	1	8	1	8	1/8[a]
Scheduling Window (Days):	N/A	N/A	±3	±3	±3	±3	±3	±3	±3	±3
Serum vitamin D[j]	X									
Serum FSH and estradiol[j]	X									
Tumor markers (CA15-3, CEA, and CA27.29)	X						X[n]			X[n]
Pregnancy Test – Serum or Urine β-Human Chorionic Gonadotropin (β-hCG)	X[o]	X		X		X		X		X
Laboratory Procedures/Assessments: Analysis performed by central laboratory										
Blood for Genetic Analyses[p]		X								
Blood for RNA Analyses[q]		X		X						X
Blood for Plasma Biomarker Analyses[q]		X		X						X
Blood for Serum Biomarker Analyses[q]		X		X						X
Efficacy Assessments										
Tumor Imaging[r]	X						X[r]			X[r]
Tumor Tissue Collection										
Recently or Newly Obtained Tumor Collection	X[s]									

a. Starting with Cycle 5, the pattern of study treatment administration and assessments and procedures performed in Cycles 1 through 4 will be repeated, unless stated otherwise.
b. Relative to day of randomization.
c. Cycle 1, Day 1, may be on the same day as randomization or at most 3 days post randomization.
d. Record all medications taken within 30 days prior to randomization and all medications taken during treatment period of the study.
e. Full physical examination and directed physical examination will include neurologic examination to be performed by the treating physician or designee.
f. Vital signs measurements include temperature, pulse, blood pressure, respiratory rate, and weight. Height is measured only at 1st clinic visit.
g. In Part 1, for subjects receiving pembrolizumab + gemcitabine/carboplatin, pembrolizumab will be administered every 3 weeks (Q3W) on Day 1 of each 3-week cycle. Gemcitabine/carboplatin will be administered on Days 1 and 8 every 21 days. Should an Investigator discontinue treatment with chemotherapy, but continue treatment with pembrolizumab, the subject does not need to come to the clinic on dates when only the chemotherapy would have been administered The subject should still follow the treatment and procedure schedule for pembrolizumab visits.
h. In Part 2, for subjects randomly assigned to pembrolizumab/placebo + gemcitabine/carboplatin, pembrolizumab/placebo will be administered Q3W on Day 1 of each 3-week cycle. Gemcitabine/carboplatin will be administered on Days 1 and 8 every 21 days. Visit schedule for subjects who discontinued treatment with chemotherapy, but continued pembrolizumab/placebo treatment remains as described above in "g".
i. The electronic Patient Reported Outcomes (ePROs) include EORTC QLQ-C30, EORTC QLQ-BR23, and EQ-5D™. Refer to Section 7.1.2.5 – Patient-Reported Outcomes for details on timing for ePROs.
j. Screening laboratory tests and ECOG must be performed within 10 days prior to the start of study treatment (serum FSH and estradiol will only be measured, if clinically indicated for determination of menopausal status). Thereafter, laboratory samples can be collected up to 72 hours prior to scheduled administration of study treatment.

k. Record all AEs occurring through the end of treatment and as described in Section 6.1.2 – End of Treatment and After Treatment Discontinuation (Parts 1 and 2).

l. The CBC and chemistry laboratory tests do not need to be performed on Cycle 1, Day 1, if obtained within 10 days prior to the start of study treatment. However, they will be performed on Day 1 of each subsequent cycle. Note: CBC will also be performed on additional days, as described in the table above.

m. Post randomization, thyroid function tests should be collected every 2 cycles.

n. CA15-3, CEA, and CA27.29 should be collected during screening and then according to the imaging schedule (can be conducted at corresponding study visit) until study treatment discontinuation (see also Section 6.1.2 – End of Treatment and After Treatment Discontinuation (Parts 1 and 2).

o. For women of reproductive potential, a urine pregnancy test will be performed within 24 hours or serum pregnancy test should be performed within 72 hours prior to the first dose of study treatment. If the urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required. While the subject is on study, pregnancy testing should be conducted as per local regulations where applicable.

p. This sample should be drawn for planned analysis of the association between genetic variants in DNA and drug response. This sample will not be collected at that site if there is either a local law or regulation prohibiting collection, or if the IRB/IEC does not approve the collection of the sample for these purposes. If the sample is collected, leftover extracted DNA will be stored for future biomedical research if the subject signs the FBR consent. If the planned genetic analyses are not approved, but FBR is approved and consent is given, this sample will be collected for the purpose of FBR.

q. Blood should be collected at pre-dose on Cycles 1, 2, and 5 or at time of discontinuation as described in Section 6.1.2 – End of Treatment and After Treatment Discontinuation (Parts 1 and 2). Leftover RNA, plasma, and serum will be stored at the end of the study for future biomedical research if the subject has consented.

r. Post baseline imaging studies will be performed at Weeks 8 (±7 days), 16 (±7 days), and 24 (–7 days) post randomization, every 9 weeks (±7 days) thereafter during the first year, and every 12 weeks (±7 days) after the first year. Imaging at Week 24 should be performed within 24 weeks post randomization. Refer to Section 7.1.2.9 – Tumor Imaging and Assessment of Disease Status for details on tumor imaging and assessment of disease.

s. All subjects must have central confirmation of TNBC status and determination of tumor PD-L1 status prior to randomization (see Section 5.1.2 – Subject Inclusion Criteria). The same, recently or newly obtained, core or excisional tumor biopsy (fine needle aspiration [FNA] not adequate) from a locally recurrent inoperable or metastatic tumor lesion can be used for both investigations. Additional information is provided in Section 7.1.2.10– Tumor Tissue Collection.

t. During the Survival Follow-up phase, contacts are approximately every 12 weeks by telephone (or more often as needed). Updated 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 survival status (excluding subjects that have a death event previously recorded).

6.1.2 End of Treatment and After Treatment Discontinuation (Parts 1 and 2)

	End of Treatment	After Treatment Discontinuation		
	Last Dose[a]	Safety Follow-up	Disease Status Follow-up[a]	Survival Follow-up[b]
Treatment Cycle/Title	At Time of Treatment Discontinuation	30 Days Post Last Dose	Every 9 or 12 Weeks Post Last dose	Every 12 Weeks[b]
Scheduled Day	N/A	N/A	N/A	N/A
Scheduling Window (Days):	N/A	±3	±7	±7
Administrative Procedures				
Prior and Concomitant Medication Review[c]	X	X		
Clinical Procedures/Assessments				
Full Physical Examination[d]	X	X		
Vital Signs and Weight[e]	X	X		
ePROs[f]	X	X		
ECOG Performance Status	X	X		
Post-treatment Disease Status			X	
Survival Status[b]	←----------	----------	----------→	X
Adverse Events Monitoring[g]	X	X		
Laboratory Procedures/Assessments: Analysis performed by local laboratories				
CBC with Differential	X	X		
Chemistry	X	X		
T3 (or Free T3), Free T4, and TSH	X	X		
Tumor markers (CA15-3, CEA, and CA27.29)	X	X	X	
Pregnancy Test – Serum or Urine β-Human Chorionic Gonadotropin (β-hCG)[h]				
Laboratory Procedures/Assessments: Analysis performed by central laboratory				
Blood for RNA Analyses[j]	X			
Blood for Plasma Biomarker Analyses[j]	X			
Blood for Serum Biomarker Analyses[j]	X			
Efficacy Assessments				
Tumor Imaging[i]	X		X	

Treatment Cycle/Title	End of Treatment	After Treatment Discontinuation		
	Last Dose[a]	Safety Follow-up	Disease Status Follow-up[a]	Survival Follow-up[b]
	At Time of Treatment Discontinuation	30 Days Post Last Dose	Every 9 or 12 Weeks Post Last dose	Every 12 Weeks[b]
Scheduled Day	**N/A**	**N/A**	**N/A**	**N/A**
Scheduling Window (Days):	**N/A**	**±3**	**±7**	**±7**
Tumor Tissue Collection				
Optional Tumor Collection	X			

a. For subjects who discontinue study treatment without centrally verified disease progression, please see Section 7.1.4.1 – Withdrawal/Discontinuation for guidance.
b. During the Survival Follow-up phase, contacts are approximately every 12 weeks by telephone (or more often as needed). Updated 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 survival status (excluding subjects that have a death event previously recorded).
c. Record all medications taken at time of and after treatment discontinuation.
d. Full physical examination and directed physical examination will include neurologic examination to be performed by the treating physician or designee.
e. Vital signs measurements include temperature, pulse, blood pressure, respiratory rate, and weight.
f. The electronic Patient Reported Outcomes (ePROs) include EORTC QLQ-C30, EORTC QLQ-BR23, and EQ-5D™. Refer to Section 7.1.2.5 –Patient-Reported Outcomes for details on timing for ePROs.
g. Record all AEs occurring within 30 days post treatment end. Report all SAEs occurring up to 90 days post treatment end or until subject initiates new anti-cancer therapy, but for at least 30 days post treatment end, whichever occurs first. Afterwards, report only drug-related SAEs.
h. For women of reproductive potential, while the subject is on study, pregnancy testing should be conducted as per local regulations where applicable.
i. Refer to Section 7.1.2.9 – Tumor Imaging and Assessment of Disease Status for details on tumor imaging and assessment of disease.
j. Blood should be collected at time of discontinuation. Leftover RNA, plasma, and serum will be stored at the end of the study for future biomedical research if the subject has consented.

6.2 Second Course Phase (Retreatment Phase) for Part 1 Subjects or Part 2 Subjects Randomized to Pembrolizumab Plus Chemotherapy

6.2.1 Treatment Period

For subjects assigned to treatment with pembrolizumab + chemotherapy, continuation or resumption of the same chemotherapy received in the First Course Treatment Phase may be administered in the Second Course Phase at the discretion of the Investigator. Note that chemotherapy different from that received in the First Course Treatment Phase is not permitted. The Trial Flow Charts for subjects who will be administered retreatment in the Second Course Phase are provided below for subjects receiving pembrolizumab alone (Section 6.2.1.1 – Pembrolizumab), pembrolizumab + taxane (paclitaxel or nab-paclitaxel) (Section 6.2.1.2 – Pembrolizumab Plus Taxane [Paclitaxel or Nab-Paclitaxel]), or pembrolizumab + gemcitabine/carboplatin (Section 6.2.1.3 – Pembrolizumab Plus Gemcitabine/Carboplatin). Complete details regarding retreatment are provided in Section 7.1.5.6 – Second Course Phase (Retreatment Phase).

6.2.1.1 Pembrolizumab

Study Period:	Treatment Period (3-Week Cycles)[a]				
Treatment Cycle/Title:	**1**	**2**	**3**	**4**	**5 and Beyond[b]**
Scheduled Day:	**1**	**1**	**1**	**1**	**1**
Scheduling Window (Days):[a]	**N/A**	**±3**	**±3**	**±3**	**±3**
Administrative Procedures					
Eligibility Criteria[a]	X				
Concomitant Medication Review	X	X	X	X	X
Survival Status[k,l]	←	---	---	---	→
Clinical Procedures/Assessments					
Full Physical Examination	X				
Directed Physical Examination		X	X	X	X
Vital Signs and Weight	X	X	X	X	X
Pembrolizumab Administration[c]	X	X	X	X	X
ECOG Performance Status	X	X	X	X	X
Review Adverse Events[d]	X	X	X	X	X
Laboratory Procedures/Assessments: Analysis performed by local laboratories					
CBC with Differential	X[e]	X	X	X	X[e]
Chemistry	X[e]	X	X	X	X[e]
Urinalysis	X				
PT/INR and aPTT[f]	X				
T3 (or Free T3), Free T4, and TSH[g]	X[g]		X[g]		X[g]
Tumor markers (CA15-3, CEA, and CA27.29)[h]	X			X	X
Pregnancy Test – Serum or Urine β-Human Chorionic Gonadotropin (β-hCG)	X[i]	X	X	X	X

Study Period:	Treatment Period (3-Week Cycles)[a]				
Treatment Cycle/Title:	**1**	**2**	**3**	**4**	**5 and Beyond[b]**
Scheduled Day:	**1**	**1**	**1**	**1**	**1**
Scheduling Window (Days):[a]	**N/A**	**±3**	**±3**	**±3**	**±3**
Efficacy Assessments					
Tumor Imaging[j,k]	X			X	X

a. For assessment/procedure details, see Section 7.0 – Trial Procedures. For information regarding eligibility criteria for retreatment, see Section 7.1.5.6.1 – Conditions of Second Course Phase. For specific timings and windows, see Section 7.1.5.6.2 – Visit Requirements of Second Course Phase.
b. Starting with Cycle 5, the pattern of retreatment administration and assessments and procedures performed in Cycles 1 through 4 will be repeated, unless stated otherwise.
c. For retreatment, pembrolizumab will be administered every 3 weeks (Q3W) on Day 1 of each 3-week cycle.
d. Guidance on recording AEs and ECIs can be found Section 7.1.2.1 – Adverse Event Monitoring.
e. The CBC and chemistry laboratory tests do not need to be performed on Cycle 1, Day 1, if obtained within 10 days prior to the first retreatment dose of pembrolizumab. However, they will be performed on Day 1 of each subsequent cycle.
f. Any subject receiving anticoagulant therapy should have coagulation factors monitored closely throughout the study.
g. T3 or FT3 can be assayed based on local guidelines and practices. To be repeated every 2 cycles after Cycle 5.
h. Tumor markers (CA15-3, CEA, and CA27.29) should be collected according to the imaging schedule (can be conducted at corresponding study visit) until retreatment discontinuation.
i. For women of reproductive potential, a urine pregnancy test will be performed within 24 hours or serum pregnancy test should be performed within 72 hours prior to the first retreatment dose of pembrolizumab. If the urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required. While the subject is on study, pregnancy testing should be conducted as per local regulations where applicable.
j. Tumor imaging (including brain imaging in subjects with known brain metastases) must be performed within 28 days prior to starting retreatment with pembrolizumab. Tumor imaging should continue to be performed every 9 weeks (±7 days) after start of Second Course Phase or more frequently if clinically indicated, regardless of any treatment delays. Tumor imaging timing should follow calendar days and should not be adjusted for any dose modifications. The same image modality acquisition and technical parameters should be used throughout the study.
k. If a subject is discontinued from retreatment with documented PD, imaging is not performed. The subject will then enter survival follow-up.
l. During the Survival Follow-up phase, contacts are approximately every 12 weeks by telephone (or more often as needed). Updated 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 survival status (excluding subjects that have a death event previously recorded).

6.2.1.2 Pembrolizumab Plus Taxane (Paclitaxel or Nab-Paclitaxel)

Study Period:	**Treatment Period (3-Week Cycles)[a]**												
Treatment Cycle/Title:	**1**			**2**			**3**			**4**			**5 and Beyond[b]**
Scheduled Day:	**1**	**8**	**15**	**1**	**8**	**15**	**1**	**8**	**15**	**1**	**8**	**15**	**1/8/15[b]**
Scheduling Window (Days):[a]	**N/A**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**
Administrative Procedures													
Eligibility Criteria[a]	X												
Concomitant Medication Review	X	X	X	X	X	X	X		X	X	X		X
Survival Status[k,l]	←----------												----------→
Clinical Procedures/Assessments													
Full Physical Examination	X												
Directed Physical Examination		X	X	X	X	X	X		X	X	X		X
Vital Signs and Weight	X	X	X	X	X	X	X		X	X	X		X
Pembrolizumab Administration[c]	X			X			X			X			X
Taxane Administration[c]	X	X	X		X	X	X		X	X	X		X
ECOG Performance Status	X			X			X			X			X
Review Adverse Events[d]	X	X	X	X	X	X	X		X	X	X		X
Laboratory Procedures/Assessments: Analysis performed by local laboratories													
CBC with Differential	X[e]	X	X	X	X	X	X		X	X	X		X[e]
Chemistry	X[e]			X			X			X			X[e]
Urinalysis	X												
PT/INR and aPTT[f]	X												
T3 (or Free T3), Free T4, and TSH[g]	X[g]						X[g]						X[g]
Tumor markers (CA15-3, CEA, and CA27.29)[h]	X								-	X[h]			X
Pregnancy Test – Serum or Urine β-Human Chorionic Gonadotropin (β-hCG)	X[i]			X			X			X			X

Study Period:	Treatment Period (3-Week Cycles)[a]												
Treatment Cycle/Title:	1			2			3			4			5 and Beyond[b]
Scheduled Day:	1	8	15	1	8	15	1	8	15	1	8	15	1/8/15[b]
Scheduling Window (Days):[a]	N/A	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3
Efficacy Assessments													
Tumor Imaging[j]	X								-	X[k]			X

a. For assessment/procedure details, see Section 7.0 – Trial Procedures. For information regarding eligibility criteria for retreatment, see Section 7.1.5.6.1 – Conditions of Second Course Phase. For specific timings and windows, see Section 7.1.5.6.2 – Visit Requirements of Second Course Phase.

b. Starting with Cycle 5, the pattern of retreatment administration and assessments and procedures performed in Cycles 1 through 4 will be repeated, unless stated otherwise.

c. Continuation or resumption of same chemotherapy as received in the First Course Treatment Phase may be administered in the Second Course Phase at the discretion of the investigator. Note that chemotherapy different from that received in the First Course Treatment Phase is not permitted. For subjects receiving pembrolizumab + taxane (paclitaxel or nab-paclitaxel), pembrolizumab will be administered every 3 weeks (Q3W) on Day 1 of each 3-week cycle. Paclitaxel or nab-paclitaxel will be administered on a 3-week on (Days 1, 8, and 15)/1-week off schedule every 28 days. Should an Investigator discontinue treatment with chemotherapy, but continue treatment with pembrolizumab, the subject does not need to come to the clinic on dates when only the chemotherapy would have been administered. The subject should still follow the treatment and procedure schedule for pembrolizumab visits.

d. Guidance on recording AEs and ECIs can be found Section 7.1.2.1 – Adverse Event Monitoring.

e. The CBC and chemistry laboratory tests do not need to be performed on Cycle 1, Day 1, if obtained within 10 days prior to the first retreatment dose. However, they will be performed on Day 1 of each subsequent cycle. Note: CBC will also be performed on additional days, as described in the table above.

f. Any subject receiving anticoagulant therapy should have coagulation factors monitored closely throughout the study.

g. T3 or FT3 can be assayed based on local guidelines and practices. To be repeated every 2 cycles after Cycle 5.

h. Tumor markers (CA15-3, CEA, and CA27.29) should be collected according to the imaging schedule (can be conducted at corresponding study visit) until retreatment discontinuation.

i. For women of reproductive potential, a urine pregnancy test will be performed within 24 hours or serum pregnancy test should be performed within 72 hours prior to the first retreatment dose. If the urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required. While the subject is on study, pregnancy testing should be conducted as per local regulations where applicable.

j. Tumor imaging (including brain imaging in subjects with known brain metastases) must be performed within 28 days prior to starting retreatment. Tumor imaging should continue to be performed every 9 weeks (±7 days) after start of Second Course Phase or more frequently if clinically indicated, regardless of any treatment delays. Tumor imaging timing should follow calendar days and should not be adjusted for any dose modifications. The same image modality acquisition and technical parameters should be used throughout the study.

k. If a subject is discontinued from retreatment with documented PD, imaging is not performed. The subject will then enter survival follow-up.

l. During the Survival Follow-up phase, contacts are approximately every 12 weeks by telephone (or more often as needed). Updated 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 survival status (excluding subjects that have a death event previously recorded).

6.2.1.3 Pembrolizumab Plus Gemcitabine/Carboplatin

Study Period:	**Treatment Period (3-Week Cycles)[a]**								
Treatment Cycle/Title:	**1**		**2**		**3**		**4**		**5 and Beyond[b]**
Scheduled Day:	**1**	**8**	**1**	**8**	**1**	**8**	**1**	**8**	**1/8[b]**
Scheduling Window (Days):[a]	**N/A**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**
Administrative Procedures									
Eligibility Criteria[a]	X								
Concomitant Medication Review	X	X	X	X	X	X	X	X	X
Survival Status[k,l]	←----------								----------→
Clinical Procedures/Assessments									
Full Physical Examination	X								
Directed Physical Examination		X	X	X	X	X	X	X	X
Vital Signs and Weight	X	X	X	X	X	X	X	X	X
Pembrolizumab Administration[c]	X		X		X		X		X
Gemcitabine/Carboplatin Administration[c]	X	X	X	X	X	X	X	X	X
ECOG Performance Status	X		X		X		X		X
Review Adverse Events[d]	X	X	X	X	X	X	X	X	X
Laboratory Procedures/Assessments: Analysis performed by local laboratories									
CBC with Differential	X[e]	X	X	X	X	X	X	X	X[e]
Chemistry	X[e]		X		X		X		X[e]
Urinalysis	X								
PT/INR and aPTT[f]	X								
T3 (or Free T3), Free T4, and TSH[g]	X				X				X
Tumor markers (CA15-3, CEA, and CA27.29)[h]	X						X		X
Pregnancy Test – Serum or Urine β-Human Chorionic Gonadotropin (β-hCG)[i]	X		X		X		X		X

Study Period:	Treatment Period (3-Week Cycles)[a]								
Treatment Cycle/Title:	1		2		3		4		5 and Beyond[b]
Scheduled Day:	1	8	1	8	1	8	1	8	1/8[b]
Scheduling Window (Days):[a]	N/A	±3	±3	±3	±3	±3	±3	±3	±3
Efficacy Assessments									
Tumor Imaging[j]	X						X		X[k]

a. For assessment/procedure details, see Section 7.0 – Trial Procedures. For information regarding eligibility criteria for retreatment, see Section 7.1.5.6.1 – Conditions of Second Course Phase. For specific timings and windows, see Section 7.1.5.6.2 – Visit Requirements of Second Course Phase.

b. Starting with Cycle 5, the pattern of retreatment administration and assessments and procedures performed in Cycles 1 through 4 will be repeated, unless stated otherwise.

c. Continuation or resumption of same chemotherapy as received in the First Course Treatment Phase may be administered in the Second Course Phase at the discretion of the investigator. Note that chemotherapy different from that received in the First Course Treatment Phase is not permitted. For subjects receiving pembrolizumab + gemcitabine/carboplatin, pembrolizumab will be administered every 3 weeks (Q3W) on Day 1 of each 3-week cycle. Gemcitabine/carboplatin will be administered on Days 1 and 8 every 21 days. Should an Investigator discontinue treatment with chemotherapy, but continue treatment with pembrolizumab, the subject does not need to come to the clinic on dates when only the chemotherapy would have been administered. The subject should still follow the treatment and procedure schedule for pembrolizumab visits.

d. Guidance on recording AEs and ECIs can be found Section 7.1.2.1 – Adverse Event Monitoring.

e. The CBC and chemistry laboratory tests do not need to be performed on Cycle 1, Day 1, if obtained within 10 days prior to the first retreatment dose. However, they will be performed on Day 1 of each subsequent cycle. Note: CBC will also be performed on Day 8 of each cycle, as described in the table above.

f. Any subject receiving anticoagulant therapy should have coagulation factors monitored closely throughout the study.

g. T3 or FT3 can be assayed based on local guidelines and practices. To be repeated every 2 cycles after Cycle 5.

h. Tumor markers (CA15-3, CEA, and CA27.29) should be collected according to the imaging schedule (can be conducted at corresponding study visit) until retreatment discontinuation.

i. For women of reproductive potential, a urine pregnancy test will be performed within 24 hours or serum pregnancy test should be performed within 72 hours prior to the first retreatment dose. If the urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required. While the subject is on study, pregnancy testing should be conducted as per local regulations where applicable.

j. Tumor imaging (including brain imaging in subjects with known brain metastases) must be performed within 28 days prior to starting retreatment. Tumor imaging should continue to be performed every 9 weeks (±7 days) after start of Second Course Phase or more frequently if clinically indicated, regardless of any treatment delays. Tumor imaging timing should follow calendar days and should not be adjusted for any dose modifications. The same image modality acquisition and technical parameters should be used throughout the study.

k. If a subject is discontinued from retreatment with documented PD, imaging is not performed. The subject will then enter survival follow-up.

l. During the Survival Follow-up phase, contacts are approximately every 12 weeks by telephone (or more often as needed). Updated 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 survival status (excluding subjects that have a death event previously recorded).

6.2.2 End of Treatment and After Treatment Discontinuation

Study Period:	End of Treatment	After Treatment Discontinuation		
	Last Dose[a]	Safety Follow-up	Disease Status Follow-up[a]	Survival Follow-up[b]
Treatment Cycle/Title:	At Time of Treatment Discontinuation	30 Days Post Last Dose	Every 9 or 12 Weeks Post Last Dose	Every 12 Weeks[b]
Scheduled Day:	N/A	N/A	N/A	N/A
Scheduling Window (Days):[c]	N/A	±3	±7	±7
Administrative Procedures				
Concomitant Medication Review	X	X		
Clinical Procedures/Assessments				
Full Physical Examination	X			
Vital Signs and Weight	X			
ECOG Performance Status	X			
Review Adverse Events[d]	X	X	X	
Post-study Anti-Cancer Therapy Status			X	X
Survival Status[b]	←----------	----------	----------→	X
Laboratory Procedures/Assessments: Analysis performed by local laboratories				
CBC with Differential	X			
Chemistry	X			
T3 (or Free T3), Free T4, and TSH[e]	X[f]			
Tumor markers (CA15-3, CEA, and CA27.29)[f]	X		X[f]	
Pregnancy Test – Serum or Urine β-Human Chorionic Gonadotropin (β-hCG)[g]				

Study Period:	End of Treatment	After Treatment Discontinuation		
	Last Dose[a]	Safety Follow-up	Disease Status Follow-up[a]	Survival Follow-up[b]
Treatment Cycle/Title:	At Time of Treatment Discontinuation	30 Days Post Last Dose	Every 9 or 12 Weeks Post Last Dose	Every 12 Weeks[b]
Scheduled Day:	N/A	N/A	N/A	N/A
Scheduling Window (Days):[c]	N/A	±3	±7	±7
Efficacy Assessments				
Tumor Imaging[h]	X		X[i]	

a. For subjects who discontinue retreatment without centrally verified disease progression, please see Section 7.1.4.1 – Withdrawal/Discontinuation for guidance.
b. During the Survival Follow-up phase, contacts are approximately every 12 weeks by telephone (or more often as needed). Updated 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 survival status (excluding subjects that have a death event previously recorded).
c. For assessment/procedure details, see Section 7.0 – Trial Procedures. For specific timings and windows, see Section 7.1.5.6.2 – Visit Requirements of Second Course Phase.
d. Record all AEs occurring within 30 days post retreatment end. Report all SAEs occurring up to 90 days post retreatment end or until subject initiates new anti-cancer therapy, but for at least 30 days post retreatment end, whichever occurs first. Afterwards, report only drug-related SAEs.
e. T3 or FT3 can be assayed based on local guidelines and practices.
f. Tumor markers (CA15-3, CEA, and CA27.29) should be collected according to the imaging schedule (can be conducted at corresponding study visit) until retreatment discontinuation.
g. For women of reproductive potential, while the subject is on study, pregnancy testing should be conducted as per local regulations where applicable.
h. Tumor imaging (including brain imaging in subjects with known brain metastases) must be performed within 28 days prior to starting retreatment. Tumor imaging should continue to be performed every 9 weeks (±7 days) after start of Second Course Phase or more frequently if clinically indicated. Tumor imaging timing should follow calendar days and should not be adjusted for any dose modifications. The same image modality acquisition and technical parameters should be used throughout the study.
i. If a subject is discontinued from retreatment with documented PD, imaging is not performed. The subject will then enter survival follow-up, in which the subject will be contacted via a telephone call every 12 weeks (or more often as needed).

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 study.

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

7.1.1.4.1 Other Than Breast Cancer

Demographic information and medical history will be obtained by the investigator or qualified designee. Medical history will include all active conditions and any conditions diagnosed within the prior 10 years that are considered by the Investigator to be clinically significant. Any autoimmune disorders should be recorded regardless of onset date. Details regarding the subject's breast cancer history will be recorded separately and should not be listed as medical history.

7.1.1.4.2 Breast Cancer Diagnosis Details

The Investigator or qualified designee will obtain details regarding the subject's breast cancer initial diagnosis and current disease status.

7.1.1.4.3 Prior Treatments for Breast Cancer

The investigator or qualified designee will review all prior treatments for subject's breast cancer diagnosis, including systemic treatments, radiation and surgeries.

7.1.1.5 Prior and Concomitant Medications Review

7.1.1.5.1 Prior Medications

The investigator or qualified designee will review and record prior medication use, including any protocol-specified washout requirement(s), within 30 days prior to randomization.

7.1.1.5.2 Concomitant Medications

The investigator or qualified designee will record all medications taken by the subject during study. All medications related to reportable SAEs and events of clinical interest (ECIs) should be recorded as defined in Section 7.2 – Assessing and Recording Adverse Events.

7.1.1.5.3 Medications in Disease Status Follow-up Phase

The investigator or qualified designee will review all new anti-cancer therapies initiated after the last dose of study treatment. If a subject initiates a new anti-cancer therapy within 30 days after the last dose of study treatment, the 30-day Safety Follow-up visit must occur before the first dose of the new therapy. Once new anti-cancer therapy has been initiated, the subject will move into the survival follow-up (SFU) phase.

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 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.

In a situation where rerandomization of the participants is planned (eg, study extension periods), the rerandomization will be based on a new randomization schedule; however, each participant will retain his/her original treatment/randomization number. Only the study intervention regimen associated with the rerandomization period or phase may change.

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

Interruptions from the protocol specified pembrolizumab/placebo administration for >12 weeks and chemotherapy administration for >4 weeks require consultation between the investigator and the Sponsor and written documentation of the collaborative decision on subject management.

Administration of study treatments will be witnessed by the investigator and/or study staff. The total volume of pembrolizumab/placebo and chemotherapy infused will be compared to the total volume prepared to determine compliance in each dose of pembrolizumab/placebo and chemotherapy administered.

The instructions for preparing and administering pembrolizumab will be provided in the Pharmacy Manual. Chemotherapy(ies) will be prepared and administered according to local guidelines and practices.

Please refer to Section 5.2 – Trial Treatments for instructions on pembrolizumab and chemotherapy.

7.1.2 Clinical Procedures/Assessments

7.1.2.1 Adverse Event Monitoring

The investigator or qualified designee will assess each subject for potential new or worsening AEs at scheduled clinic visits or more frequently if clinically indicated. AEs will be graded according to NCI CTCAE v4.0 and recorded during study treatment and protocol-specified follow-up period post discontinuation of study treatment (Section 7.2.4 – Evaluating Adverse Events). Toxicities will be characterized in terms of seriousness, causality, toxicity grading, and action taken with regard to study treatment(s).

AEs associated with pembrolizumab/placebo exposure should be evaluated for possible immune etiology; see Section 7.2.3.2 – Events of Clinical Interest regarding the identification, evaluation, and management of AEs with potential immunologic etiology.

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 12-Lead Electrocardiogram

A standard 12-lead electrocardiogram (ECG) will be performed using local procedures during screening. Clinically significant abnormal findings should be recorded as medical history. Additional ECG evaluations may be performed as clinically necessary.

7.1.2.3 Physical Examination

7.1.2.3.1 Full Physical Examination

The investigator or clinical designee will perform a complete physical examination during screening. Clinically significant abnormal findings should be recorded as medical history. Post randomization, full physical examinations should be performed as specified in the Trial Flow Chart – Section 6.0, and new clinically significant abnormal findings should be recorded as AEs.

7.1.2.3.2 Directed Physical Examination

The investigator or clinical designee will perform directed physical examinations as specified in the Trial Flow Chart – Section 6.0 and, 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 designee will take vital signs at screening, prior to the administration of each dose of study treatment, at treatment discontinuation, and at the safety follow-up, as specified in the Trial Flow Chart – Section 6.0. Vital signs should include temperature, pulse, blood pressure respiratory rate, and weight. Height will be measured in the first course treatment phase at the 1st clinic visit only.

7.1.2.5 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 treatment, AE evaluation, and disease status notification. The ePROs are completed in the following order: EQ-5D™, then EORTC QLQ-C30, and last the EORTC QLQ-BR23 at the time points specified in the Trial Flow Chart – Section 6.0 and briefly summarized below.

7.1.2.5.1 The Patient Reported Outcomes

The Patient Reported Outcomes (PROs) are assessed as follows:

- On Day 1 of each of the first 3 cycles
- After the 3rd cycle and until the end of Year 1, they will occur every 3rd cycle (every 9 weeks) until PD, while the subject is receiving study treatment
- During Year 2, they will occur every 4th cycle (every 12 weeks) until PD, while the subject is receiving study treatment
- At the Treatment Discontinuation Visit[a]
- At 30-day Safety Follow-up Visit[a]

[a] If the Treatment Discontinuation Visit occurs 30 days from the last dose of study treatment, at the time of the mandatory Safety Follow up Visit, ePROs do not need to be repeated.

7.1.2.6 Eastern Cooperative Oncology Group (ECOG) Performance Status

The investigator or qualified designee will assess ECOG performance status (Section 12.5 – ECOG Performance Status) at screening, prior to administration of study treatment on Day 1 of each treatment cycle, at treatment discontinuation, and at the safety follow-up, as specified in Section 6.0 – Trial Flow Chart.

7.1.2.7 Post-Treatment Disease Status

After discontinuation of all study treatments for reasons other than PD, disease status will be followed as specified in Section 6.0 – Trial Flow Chart.

7.1.2.8 Menopausal Status

The menopausal status (pre-menopausal or post-menopausal) for all female subjects less than age 60 years must be determined at screening according to the definitions below. The date of the subject's last menstrual period (LMP) 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 premenopausal 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, ER 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.

7.1.2.9 Tumor Imaging and Assessment of Disease Status

The process for image collection and transmission to the CIV can be found in the Site Imaging Manual (SIM). Tumor imaging should be acquired by computed tomography (CT, strongly preferred). Magnetic resonance imaging (MRI) should be used when CT is contraindicated and for brain imaging. For each subject, the same imaging modality and consistent use of contrast should be used throughout the study to optimize assessment of existing and new tumor burden.

Brain imaging (MRI is preferred) is required at screening and during the study (at the same schedule as other imaging for evaluation of disease status) for subjects with known brain metastases and those with worsening and/or new neurological symptoms. CT imaging will be acceptable, if MRI is medically contraindicated. (See also Section 7.1.2.9.1 – Initial Tumor Imaging.)

If a subject has a history of bone metastases and/or has new bone pain or other symptoms/signs suggestive of bone metastases during screening, a bone scan (and plain X-ray, if bone scan is negative) is required prior to study entry. During the study, a bone scan (and plain X-ray, if bone scan is negative) will be performed as needed for evaluation of

worsening and/or new bone pain or other symptoms/signs suggestive of bone metastases OR if the site believes a subject has attained a CR. Any supplemental imaging done to support a positive or negative bone scan should be submitted to the CIV.

Measurable disease for subject eligibility will be determined based on RECIST 1.1 as accessed by local radiology review. Although RECIST 1.1 references a maximum of 5 target lesions in total and 2 per organ, MSD allows a maximum of 10 target lesions in total and 5 per organ. While on study, scheduled imaging studies should be submitted to the CIV. Unscheduled imaging studies obtained for assessment of disease progression or other reason, but capturing radiologic progression, should also be submitted to the CIV.

Site/investigator-assessed first radiologic evidence of PD will also be evaluated by the CIV in real time, and the results of central imaging review will be expeditiously communicated to the study site and the Sponsor (See Section 7.1.2.9.4 – RECIST 1.1 Assessment of Disease).

7.1.2.9.1 Initial Tumor Imaging

Baseline tumor imaging must be performed during the 28-day screening window prior to randomization to confirm measurable disease based on RECIST 1.1 as assessed by local radiology review. The screening images must be submitted to the CIV for retrospective review.

Scans performed as part of routine clinical management are acceptable for use as screening tumor imaging studies, if they are of diagnostic quality, were performed within 28 days prior to randomization and were submitted to the CIV for review.

Subjects with previously treated brain metastasis(es) may be eligible for study participation provided metastatic disease to the brain is radiographically stable, i.e., without site/investigator-assessed radiologic evidence of progression for ≥4 weeks prior to the screening brain imaging study. To demonstrate radiographic stability of previously treated brain metastases, a minimum of 2 post-treatment brain imaging assessments are required: 1) The first brain imaging must be acquired after treatment of brain metastases has been completed 2) The second brain imaging must be obtained during screening (i.e., within 28 days of randomization) and ≥ 4 weeks after the previous post-treatment brain imaging. Any neurologic symptoms must have returned to baseline and steroids must not have been used for management of symptoms related to brain metastases for at least 28 days prior to randomization. Subjects with carcinomatous meningitis are excluded regardless of clinical stability.

7.1.2.9.2 Tumor Imaging During the Study

Post-baseline imaging assessments should be performed at 8 weeks (±7 days), 16 weeks (±7 days), and 24 weeks (– 7 days) post randomization, and then every 9 weeks (±7 days) during the first year (or more frequently if clinically indicated). Imaging at Week 24 should be performed within 24 weeks post randomization. After 1 year, subjects who remain on treatment will have imaging performed every 12 weeks (±7 days). Imaging timing should follow calendar days and should not be adjusted for delays in cycle starts. Imaging should not be discontinued until disease progression is verified by CIV or the start of new anti-cancer treatment, withdrawal of consent, death, or end of the study, whichever occurs first.

Based on RECIST 1.1, PRs and CRs should be confirmed by repeat tumor imaging studies at ≥4 weeks from the date response was first documented. Subjects will then return to regularly scheduled imaging, starting with the next scheduled imaging time point. Subjects who obtain a confirmation scan do not need to undergo the next scheduled tumor imaging, if this is <4 weeks later; tumor imaging may resume at the subsequent scheduled imaging time point.

Based on irRECIST, for clinically stable subjects meeting the conditions detailed in Section 7.1.2.9.5 – irRECIST Assessment of Disease, study treatment may be continued until PD is locally confirmed by imaging studies performed at least 4 weeks after initial local PD by imaging. If disease progression is not confirmed and subjects remain clinically stable, they may continue study treatment and resume tumor imaging at the next scheduled imaging time point. Subjects with confirmed PD per irRECIST should discontinue study treatment and regularly scheduled imaging studies, unless PD has not been verified by CIV, in which case regularly scheduled imaging studies should continue until central verification of PD. Study treatment may continue after locally confirmed PD according to an exception detailed in Section 7.1.2.9.5 – irRECIST Assessment of Disease.

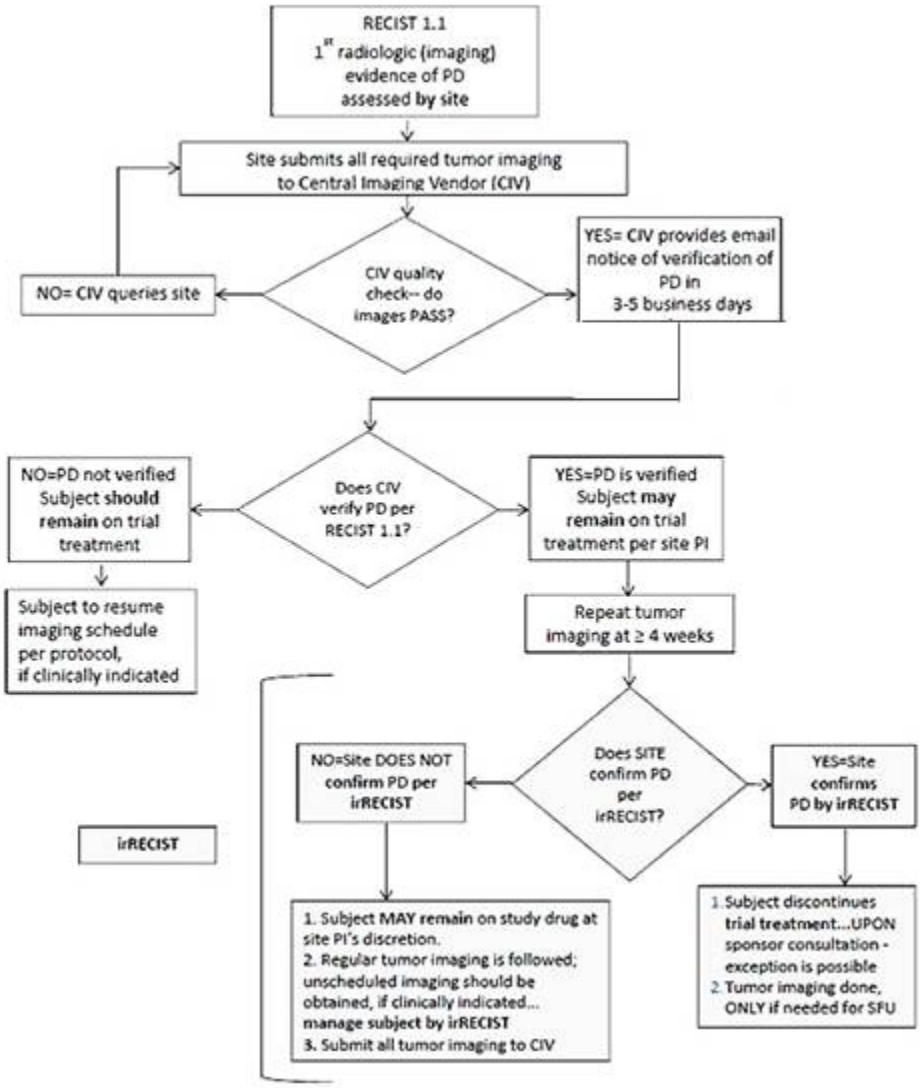
7.1.2.9.3 End of Treatment and Follow-up Tumor Imaging

In subjects who discontinue all study treatments, tumor imaging should be performed at the time of treatment discontinuation (±4-week window). If a previous scan was obtained within 4 weeks prior to the date of discontinuation, then a scan at treatment discontinuation is not mandatory. In subjects who discontinue all study treatments after central verification of disease progression, no further tumor imaging studies are required.

In subjects who discontinue all study treatments without central verification of disease progression, every effort should be made to continue monitoring of disease status by imaging performed at the same schedule as before treatment discontinuation (e.g., every 9 or 12 weeks [±7 days] during the first or second year of study, respectively, depending on time elapsed since randomization) and until (1) the start of new anti-cancer treatment, (2) disease progression verified by CIV, (3) death, (4), withdrawal of consent to study participation, or (5) the end of the study, whichever occurs first.

7.1.2.9.4 RECIST 1.1 Assessment of Disease

RECIST 1.1 [98] will be applied by local radiology review for assessing subject eligibility and by CIV as the primary measure for assessing efficacy parameters (other than OS), as described in the primary and secondary study objectives. Imaging studies showing first radiologic evidence of PD as assessed by site/investigator should be immediately submitted to the CIV, which will then notify the site and the Sponsor whether PD based on RECIST 1.1 is centrally verified or not. Figure 3 illustrates the imaging flow algorithm for verification of PD by CIV for clinically stable subjects.



Note: Verified refers to centrally verified.

Figure 3 Imaging and Treatment for Clinically Stable Subjects After First Radiologic Evidence of PD Based on RECIST 1.1 and as Assessed by Site/Investigator

7.1.2.9.5 irRECIST Assessment of Disease

Immune-related RECIST is RECIST 1.1 adapted as described below to account for the unique tumor response seen with immunotherapeutic drugs. irRECIST will be used by site/investigator to assess tumor response and make treatment decisions both before and after PD is verified by CIV (Table 8). Related imaging data will be collected in the clinical database. Treatment efficacy based on irRECIST as assessed by CIV will be evaluated retrospectively.

When feasible, study treatment should be continued until PD is confirmed by site/investigator at least 4 weeks after initial local PD. The possibility to continue study treatment past centrally verified PD takes into account the observation that subjects with a

transient tumor flare in the first few months after the start of immunotherapy may experience response at subsequent time points. Subjects who are deemed clinically unstable are not required to have repeat tumor imaging for confirmation of PD. Tumor flare includes any of the following scenarios:

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

Continuing study treatment past centrally verified PD is at the discretion of the treating physician and should be based on the subject's overall clinical condition, including performance status, clinical symptoms, and laboratory data. Clinical stability is defined by the following criteria:

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

In determining whether tumor burden has increased, decreased or remained stable per irRECIST, the site/investigator should consider all target and non-target lesions as well as any incremental new lesion(s).

PD is not confirmed based on irRECIST at repeat imaging, if ALL of the following criteria are met:

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

If PD is not confirmed based on irRECIST as assessed by site/investigator and the subject continues to be clinically stable, treatment may continue and follow the regular imaging schedule.

PD is confirmed based on irRECIST at repeat imaging, if ANY of the following occur:

- Sum of target lesion diameters remains ≥20% and at least 5 mm absolute increase compared to nadir, or
- Non-target disease resulting in initial PD is qualitatively worse, or
- New lesion resulting in initial PD is qualitatively worse, or

- Additional new lesion(s) since last evaluation, or
- Additional new non-target lesion progression since last evaluation

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

Note: If a subject has confirmed radiographic progression based on irRECIST (i.e., 2 scans at least 4 weeks apart demonstrating PD), but he/she is still deriving clinically meaningful benefit, and there is no further increase in the tumor burden at the confirmatory tumor imaging, an exception to treatment discontinuation may be considered following consultation with the Sponsor. If study treatment is continued, tumor imaging should also continue to be performed, as outlined in the Trial Flow Chart – Section 6.0, and submitted to the CIV for review.

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

Table 8 Imaging and Treatment After First Radiologic Evidence of PD

	Clinically Stable		**Clinically Unstable**	
	Imaging	**Treatment**	**Imaging**	**Treatment**
First radiologic evidence of PD based on RECIST 1.1 as assessed by site/investigator has been verified by the central imaging vendor	Repeat imaging at ≥4 weeks at site to confirm PD	May continue study treatment at site/Investigator's discretion while awaiting confirmatory tumor imaging based on irRECIST as assessed by site/investigator	No additional imaging required	Discontinue treatment
Repeat tumor imaging confirms PD based on irRECIST as assessed by site/investigator	No additional imaging required	Discontinue treatment (exception is possible upon consultation with Sponsor)	No additional imaging required	Treatment already discontinued
Repeat tumor imaging shows SD, PR or CR based on irRECIST as assessed by site/investigator	Continue regularly scheduled imaging assessments	Continue study treatment at site/ Investigator's discretion	Continue regularly scheduled imaging assessments	May restart study treatment if condition has improved and/or subject is clinically stable at site/Investigator's discretion. Next tumor imaging should occur according to the regular imaging schedule outlined in the protocol

7.1.2.10 Tumor Tissue Collection

All subjects must have central confirmation of TNBC status and determination of tumor PD-L1 status prior to randomization (Section 5.1.2 – Subject Inclusion Criteria). The same, recently or newly obtained, core or excisional tumor biopsy ([FNA not adequate) from a locally recurrent inoperable or metastatic tumor lesion can be used for both investigations.

Note: For a newly obtained tumor biopsy, tissue from 3 to 4 passes of an 18-gauge needle should be submitted as one specimen.

Note: Adequacy of biopsy specimen for the above analyses must be confirmed by the central laboratory. Submission of another tumor specimen may be required, if adequate tumor tissue was not provided the first time.

Note: An archival tumor specimen obtained before the diagnosis of locally recurrent inoperable or metastatic breast cancer may be submitted after consultation with the Sponsor, if neither a recently nor a newly obtained biopsy from a locally recurrent inoperable or a metastatic site is available.

Testing will be performed by a central vendor using commercially validated assays, and tumor status for hormone receptor and HER2 expression will be determined according to the most recent ASCO/CAP guidelines:

a. ER negative status is defined as <1% tumor cells positive for ER by IHC, irrespective of staining intensity
b. PGR negative status is defined as <1% tumor cells positive for PGR by IHC, irrespective of staining intensity
c. HER2 negative status is determined by:
    - IHC 1+, as defined by incomplete membrane staining that is faint/barely perceptible and within >10% of invasive tumor cells, OR
    - IHC 0, as defined by no staining observed or membrane staining that is incomplete and is faint/barely perceptible and within ≤10% of the invasive tumor cells, OR
    - FISH negative based on single-probe average HER2 copy number <4.0 signals/cell, or Dual-probe HER2/centromeric probe for chromosome 17 (CEP17) ratio <2.0 with an average HER2 copy number <4.0 signals/cell

Newly obtained tumor tissue should be submitted in formalin (preferred) or as formalin-fixed paraffin embedded (FFPE) tumor tissue blocks. If after agreement with the Sponsor unstained slides are submitted, the slides should be freshly cut and submitted to the testing laboratory within 14 days from site slide sectioning date; otherwise, a new specimen will be requested. A recently obtained or archival tumor specimen should be submitted as an FFPE block or unstained slides as described above.

Optional core or excisional biopsy is recommended to be obtained at disease progression.

7.1.3 Laboratory Procedures/Assessments

Details regarding specific laboratory procedures/assessments to be performed in this study are provided below. The total amount of blood/tissue to be drawn/collected over the course of the study (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 the Procedures Manual.

7.1.3.1 Laboratory Safety Evaluations

Laboratory tests to be performed in this study are specified in Table 9.

Table 9 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[b]
WBC (total and differential)	Aspartate aminotransferase (AST)	Specific gravity	Total triiodothyronine (T3) or Free T3[c]
Red Blood Cell Count	Bicarbonate or carbon dioxide (CO_2)[d]	Microscopic exam, if abnormal results noted	Free thyroxine (T4)
Absolute Neutrophil Count[e]	Calcium		Thyroid stimulating hormone (TSH)
Absolute Lymphocyte Count	Chloride		Blood for Genetic Analysis[f]
	Creatinine		Blood for RNA Analysis, Plasma and Serum Biomarker Analyses
	Glucose		Blood for PK studies
	Phosphorus		Anti-pembrolizumab Antibodies
	Potassium		FSH, estradiol[g]
	Sodium		Vitamin D levels
	Total Bilirubin		Tumor markers (CA15-3, CEA, and CA27.29)
	Direct Bilirubin, if total bilirubin is elevated above the upper limit of normal		
	Total protein		
	Blood Urea Nitrogen or Urea[h]		
	Lactate dehydrogenase (LDH)		
	Uric acid		

Hematology	Chemistry	Urinalysis	Other

a. A urine pregnancy test should be performed within 24 hours or serum pregnancy test should be performed within 72 hours prior to the first dose of study treatment in women of childbearing potential. If the urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required. While the subject is on study, pregnancy testing should be conducted as per local regulations where applicable.
b. Coagulation factors (PT/INR and aPTT) should be tested as part of the screening procedures for all subjects. Any subject receiving anticoagulant therapy should have coagulation factors monitored closely throughout the study.
c. Total T3 is preferred; if not available, free T3 may be tested.
d. Depending on local standard of care.
e. Either absolute number or % of WBC is acceptable as per institutional standards.
f. Blood for Genetic Analysis as described in Section 7.1.3.5 Planned Genetic Analysis Sample Collection and in Section 7.1.3.6 – Future Biomedical Research Sample Collection.
g. Blood for menopausal status is required only for some subjects, as described in Section 7.1.3.3 – Blood for Menopausal Status.
h. Blood Urea Nitrogen is preferred; if not available urea may be tested.

Screening laboratory tests must be performed within 10 days prior to the start of study treatment. Predose laboratory procedures can be conducted up to 72 hours prior to dosing.

Please note that only safety labs affecting potential treatment need to be reviewed prior to study therapy administration following the Screening Visit.

Vitamin D, tumor markers, and other labs which would not affect potential treatment of the subject can be reviewed, in a timely manner, by an Investigator after the date of study therapy administration. Similarly, in cases in which a site is not able to obtain the thyroid function testing (total triiodothyronine [T3], free thyroxine [free T4], and thyroid stimulating hormone [TSH]) results prior to scheduled dosing, review of the thyroid function test results after dosing is acceptable and poses no additional immediate safety risk to subjects.

7.1.3.2 Pharmacokinetic Evaluations

The accumulation of robust PK and ADA data has allowed for the adequate characterization of the clinical pharmacology of pembrolizumab across indications. Therefore, upon approval of Amendment 02 each site is to stop the collection of PK and ADA samples for all subjects. Blood samples for PK and ADA collected prior to Amendment 02 may be stored. Analysis will be performed only if required.

7.1.3.3 Blood for Menopausal Status

Blood collection at screening for biochemical evidence of menopausal status (FSH and estradiol) will be needed if subject:

1) Is ≤60 years old, **and**
2) Has not had a bilateral oophorectomy, **and**
3) Has not had a menstrual period for at least 12 months, **and**
4) Has had a hysterectomy or was on hormone replacement, ER antagonist, chemotherapy or ovarian suppression at any time since LMP.

7.1.3.4 Blood Collection for RNA Analysis and Plasma and Serum Biomarker Analyses

Blood should be collected at pre-dose on Cycles 1, 2, and 5 or at time of discontinuation. Leftover RNA, plasma, and serum will be stored at the end of the study for FBR if the subject has consented (see Section 7.1.3.6 – Future Biomedical Research Sample Collection).

Further details are provided in the Procedures Manual.

7.1.3.5 Planned Genetic Analysis Sample Collection

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

7.1.3.6 Future Biomedical Research Sample Collection

The following specimens are to be obtained as part of FBR:

- DNA for future research
- Leftover plasma and serum from biomarker analyses
- Leftover RNA
- Leftover main study tumor tissue

7.1.4 Other Procedures

7.1.4.1 Withdrawal/Discontinuation

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

When a subject discontinues/withdraws from participation in the trial, all applicable activities scheduled for the end-of-treatment 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. As noted above, subjects who are discontinued from all study treatment should continue to be monitored in the trial, as outlined in Sections 7.1.5.3 – End of Treatment and 7.1.5.4 – After Treatment Discontinuation.

7.1.4.1.1 Withdrawal From Future Biomedical Research

Subjects may withdraw their consent for Future Biomedical Research and have their specimens and all derivatives destroyed. Subjects may withdraw consent at any time by contacting the principal investigator for the main trial. If medical records for the main trial

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

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

7.1.4.2 Blinding/Unblinding

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

For emergency situations where the investigator or sub-investigator 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 sub-investigator the emergency unblinding call center will provide the information to him/her promptly and report unblinding to the sponsor. The emergency unblinding call center will make a record promptly however, the investigator or sub-investigator must enter the toxicity grade of the adverse experiences observed, their relation to study drug, the reason thereof, etc., in the medical chart etc., before unblinding is performed.

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.

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

In the event that unblinding has occurred, the circumstances around the unblinding (eg, 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 or a non-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. Subjects whose treatment assignment has been unblinded (by the investigator or through the emergency unblinding call center) must be discontinued from study drug that was blinded.

Section 5.8 outlines the criteria for allowing subjects who are discontinued from treatment to continue to be monitored in the trial.

7.1.4.3 Calibration of Critical Equipment

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

Critical Equipment for this trial includes:

- Laboratory equipment – as required for eligibility and safety assessment laboratory tests
- Imaging equipment – as required for study objectives
- Drug administration equipment – as required for storage, preparation, and administration (infusion) of study treatments.

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

7.1.5 Visit Requirements

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

7.1.5.1 Screening

Visit requirements are outlined in Section 6.0 – Trial Flow Chart.

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 randomization except for the following:

- Laboratory tests and ECOG performance status are to be performed within 10 days prior to the start of study treatment.
- For women of reproductive potential, a urine pregnancy test will be performed within 24 hours or serum pregnancy test will be performed within 72 hours prior to the subject receiving the first dose of study treatment. If the urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required.

Subjects may be rescreened once 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 corresponding inclusion criterion is met.

7.1.5.2 Treatment Period (Parts 1 and 2)

Visit timing requirements during the treatment period are as follows:

- Assessments/procedures should be performed prior to randomization and on Day 1 of each cycle unless otherwise specified in the flow chart.
- Treatment cycles are 3 weeks (starting with Day 1 of pembrolizumab administration).
- The window for each visit is ±3 days unless otherwise noted. Cycle 1 treatment should be no more than 3 days after randomization.
- Optional core or excisional biopsy is recommended to be obtained at disease progression.

In Part 1 (safety run-in; open-label) of the study, there are 3 treatment arms (pembrolizumab + nab-paclitaxel, pembrolizumab + paclitaxel, and pembrolizumab + gemcitabine/carboplatin). In Part 2 (Phase III; double-blind), there are 2 treatment arms (pembrolizumab + chemotherapy and placebo + chemotherapy).

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

7.1.5.3 End of Treatment

The End of Treatment Visit should occur at the time all study treatments are discontinued for any reason. If the End of Treatment Visit occurs 30 days from the last dose of study treatment, at the time of the mandatory Safety Follow up Visit, procedures do not need to be repeated. Visit requirements are outlined in Section 6.0 – Trial Flow Chart. Specific procedure-related details are provided above in Section 7.1 – Trial Procedures. Additional details regarding subject withdrawal and discontinuation are presented in Section 5.8 – Subject Withdrawal/Discontinuation Criteria.

7.1.5.4 After Treatment Discontinuation

7.1.5.4.1 Safety Follow-up Visit

The mandatory Safety Follow-Up Visit should be conducted approximately 30 days after the last dose of all study treatments or before the initiation of a new anti-cancer treatment, whichever comes first. All AEs that occur prior to the Safety Follow-Up Visit should be recorded. Subjects with an AE of Grade >1 will be followed until resolution of the AE to Grade 0–1 (or to subject's baseline) or until the beginning of a new anti-cancer therapy, whichever occurs first. SAEs that occur within 90 days, and ECIs that occur within 30 days, of the end of treatment or before initiation of a new anti-cancer treatment should also be followed and recorded for a minimum of 30 days.

Subjects who are eligible for retreatment with pembrolizumab (see Section 7.1.5.6.1 – Conditions of Second Course Phase) may have up to 2 safety follow-up visits, one after the Treatment Period and one after the Second Course Phase.

7.1.5.4.2 Disease Status Follow-up Visit

Subjects who discontinue all study treatments for a reason other than disease progression will move into the Disease Status Follow-Up phase and should be assessed according to the already followed tumor imaging schedule.

Every effort should be made to collect information regarding disease status until the start of new anti-cancer therapy, centrally verified disease progression, death, or end of study. Information regarding post-study anti-cancer treatment will be collected if new treatment is initiated.

Subjects who are eligible to receive retreatment with pembrolizumab according to the criteria in Section 7.1.5.6.1 – Conditions of Second Course Phase will move from the Follow-Up Phase to the Second Course Phase when they experience disease progression. Details are provided in Section 7.1.5.6 – Second Course Phase (Retreatment Phase).

7.1.5.4.3 Survival Follow-up

Subjects who experience centrally verified disease progression (or locally confirmed disease progression, if subject is further followed by irRECIST after centrally verified PD) or start a new anti-cancer therapy move into the Survival Follow-Up phase and should be contacted by telephone approximately every 12 weeks (or more often as needed) to assess for survival status until death, withdrawal of consent, or the end of the trial, whichever occurs first.

7.1.5.5 Survival Status

To ensure current and complete survival data is available at the time of database locks, updated 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 Data Monitoring Committee (eDMC) review, interim and/or final analysis. 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 survival status (excluding subjects that have a previously recorded death event in the collection tool).

7.1.5.6 Second Course Phase (Retreatment Phase)

7.1.5.6.1 Conditions of Second Course Phase

Subjects who stop pembrolizumab/placebo with SD or better may be eligible for up to 17 additional administrations of pembrolizumab, if they progress after stopping pembrolizumab/placebo and are found to have received pembrolizumab upon unblinding to pembrolizumab vs placebo administration on an individual subject basis and only after consultation with the Sponsor. Retreatment with pembrolizumab is termed the Second Course Phase of this study and is only available if the study remains open and the subject meets the following conditions:

Either

- Stopped initial treatment with pembrolizumab/placebo after attaining an investigator-determined confirmed CR based on RECIST 1.1, and

- Was treated with at least 8 cycles of pembrolizumab/placebo before discontinuing study treatment, and
- Received at least 2 cycles of pembrolizumab/placebo beyond the date when the initial CR was declared

OR

- Had SD, PR, or CR and stopped pembrolizumab/placebo treatment after 35 administrations of pembrolizumab/placebo for reasons other than disease progression or intolerability

AND

- Experienced an investigator-determined and centrally verified radiographic disease progression by RECIST 1.1 after stopping initial treatment with pembrolizumab/placebo, and
  - Upon unblinding at the time of centrally verified disease progression were found to have received pembrolizumab, and
  - No new anti-cancer treatment was administered since the last dose of pembrolizumab, and
  - The subject meets the safety parameters listed in the Inclusion/Exclusion criteria, and
  - The study is ongoing

An objective response or disease progression that occurs during the Second Course Phase for a subject will not be counted as an event for the primary analysis of either endpoint in this trial.

7.1.5.6.2 Visit Requirements of Second Course Phase

7.1.5.6.2.1 Assessments/Procedures/Windows

Assessments and procedures during the Second Course Phase will be performed as specified in the Trial Flow Charts in Section 6.2.1.1 – Pembrolizumab, Section 6.2.1.2 – Pembrolizumab Plus Taxane (Paclitaxel or Nab-Paclitaxel), and Section 6.2.1.3 – Pembrolizumab Plus Gemcitabine/Carboplatin. Treatment cycles are 3 weeks (starting with the first pembrolizumab retreatment) and visit windows are ±3 days unless otherwise noted.

For subjects assigned to treatment with pembrolizumab + chemotherapy, continuation or resumption of the same chemotherapy received in the First Course Treatment Phase may be administered during the Second Course Phase at the discretion of the investigator. Note that chemotherapy different from that received in the First Course Treatment Phase is not permitted. If toxicity occurs, refer to the dose modification guidelines provided in Section 5.6.1 – Supportive Care Guidelines for Subjects Receiving Pembrolizumab/Placebo. Imaging should always be performed every 9 weeks (±7 days), or more frequently if clinically indicated, regardless of any treatment delays.

7.1.5.6.2.2 Discontinuation During the Second Course Phase

For reasons for retreatment discontinuation during the Second Course Phase, see Section 5.8 – Subject Withdrawal/Discontinuation Criteria; subjects must discontinue pembrolizumab after 17 administrations. Imaging requirements for these subjects are described in Section 7.1.5.6.2.7 – Tumor Imaging During the Second Course Phase.

7.1.5.6.2.3 Laboratory Tests During the Second Course Phase

Laboratory tests for determining eligibility for retreatment are to be performed within 10 days prior to the first retreatment dose. See Section 7.1.3 – Laboratory Procedures/Assessments for details regarding laboratory tests.

For women of reproductive potential, a urine pregnancy test should be performed within 24 hours or serum pregnancy test should be performed within 72 hours prior to receiving the first retreatment dose. If the urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required. While the subject is on study, pregnancy testing should be conducted as per local regulations where applicable.

After Cycle 1, laboratory samples can be collected up to 72 hours prior to the scheduled time point. See Section 7.1.3 – Laboratory Procedures/Assessments for details regarding laboratory tests. T3 or FT3 can be assayed based on local standards.

Coagulation factors (PT/INR and aPTT) should be monitored closely throughout the Second Course Phase for any subject receiving anticoagulant therapy.

Clinically significant abnormal laboratory test results that are drug-related AEs should be followed until return to within the normal range or baseline. Laboratory tests do not need to be repeated after the end of retreatment if values are within normal range.

Laboratory safety measurements will be graded per NCI CTCAE v4.0.

7.1.5.6.2.4 Concomitant Medications During the Second Course Phase

Enter new medications started during the Second Course Phase through the Safety Follow-up visit. Record all medications taken for AEs as defined in Section 7.2 – Assessing and Recording Adverse Events.

7.1.5.6.2.5 Vital Signs During the Second Course Phase

Vital signs will include temperature, pulse, respiratory rate, weight, and blood pressure. Height will not be measured in the Second Course Phase (see Section 7.1.2.4 – Vital Signs). Vitals should be taken prior to retreatment administration.

7.1.5.6.2.6 Pembrolizumab Retreatment During the Second Course Phase

Subjects who start retreatment should resume pembrolizumab at 200 mg IV Q3W. If chemotherapy is also given at physician's discretion, subjects must receive the same chemotherapy agent(s) as used in the First Course Phase (see Section 6.2 – Second Course Phase [Retreatment Phase] for Part 1 Subjects or Part 2 Subjects Randomized to Pembrolizumab Plus Chemotherapy).

7.1.5.6.2.7 Tumor Imaging During the Second Course Phase

Tumor imaging scans must be performed within 28 days prior to starting retreatment. Local readings (investigator assessment with site radiology readings) will be used to determine eligibility. Imaging should be submitted to the CIV for retrospective review.

The first on-study imaging assessment should be performed at 9 weeks (±7 days) after the start of retreatment. Subsequent tumor imaging should be performed every 9 weeks (±7 days) or more frequently if clinically indicated.

Per irRECIST (Section 7.1.2.9.5 – irRECIST Assessment of Disease), if tumor imaging shows initial PD, tumor assessment should be repeated ≥4 weeks later in order to confirm PD with the option of continuing retreatment while awaiting radiologic confirmation of progression. Subjects who obtain a confirmation scan do not need to undergo scheduled tumor imaging, if it is <4 weeks later, and may wait until the next scheduled imaging time point if clinically stable.

Imaging should continue to be performed until disease progression, the start of new anti-cancer treatment, withdrawal of consent, death, or notification by the Sponsor, whichever occurs first. Disease progression may be confirmed at least 4 weeks after the first tumor imaging indicating PD in clinically stable subjects.

In subjects who discontinue retreatment, tumor imaging should be performed at the time of retreatment discontinuation (±4-week window). If a previous scan was obtained within 4 weeks prior to the date of discontinuation, then a scan at treatment discontinuation is not mandatory. In subjects who discontinue retreatment due to confirmed disease progression, this is the final required tumor imaging.

In subjects who discontinue retreatment without further documented disease progression, every effort should be made to continue monitoring their disease status by radiologic imaging every 9 weeks (±7 days) until (1) the start of new anti-cancer treatment, (2) disease progression verified by CIV, (3) death, or (4) the end of the study, whichever occurs first.

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).

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

For purposes of this study, an overdose will be defined as ≥1000 mg (5 times the dose) of pembrolizumab and as any dose ≥20% over the prescribed dose for chemotherapies included in KN355. No specific information is available on the treatment of pembrolizumab or chemotherapy overdose. In the event of an overdose, study treatment 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 treatment if the subject initiates new anticancer therapy, whichever is earlier, must be reported by the investigator. All reported pregnancies must be followed to the completion/termination of the pregnancy. Pregnancy outcomes of spontaneous abortion, missed abortion, benign hydatidiform mole, blighted ovum, fetal death, intrauterine death, miscarriage and stillbirth must be reported as serious events (Important Medical Events). If the pregnancy continues to term, the outcome (health of infant) must also be reported.

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

7.2.3 Immediate Reporting of Adverse Events to the Sponsor

7.2.3.1 Serious Adverse Events

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

- Results in death;
- Is life threatening;
- Results in persistent or significant disability/incapacity;
- Results in or prolongs an existing inpatient hospitalization;
- Is a congenital anomaly/birth defect;
- Is an other important medical event.

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

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

Refer to Table 10 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 treatment, or 30 days following cessation of treatment if the subject initiates new anticancer therapy, whichever is earlier, any serious adverse event, or follow up to a serious adverse event, including death due to any cause other than progression of the cancer under study (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 blinded efficacy endpoint events and safety data to ensure the safety of the subjects in the study. 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 10 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 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, but prior to analysis unblinding, 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 plan as well as biomarker analysis plan may be provided as appropriate. Post-hoc exploratory analyses will be clearly identified in the CSR. The 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 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
Treatment Assignment	Part 1: Approximately 30 subjects will be partially-randomized (unblinded open-label) among 3 treatment arms: (1) pembrolizumab + nab-paclitaxel, (2) pembrolizumab + paclitaxel and (3) pembrolizumab + gemcitabine/carboplatin. Part 2: Approximately 828 subjects will be randomized (double-blind) in a 2:1 ratio between 2 treatment arms: (1) pembrolizumab + chemotherapy and (2) placebo + chemotherapy. Stratification factors are as follows: 1. Chemotherapy on study (taxane [i.e., paclitaxel or nab-paclitaxel] vs gemcitabine/carboplatin). 2. Tumor PD-L1 status (CPS ≥1 vs CPS <1). 3. Prior treatment with same class of chemotherapy in the (neo)adjuvant setting (yes vs no).
Analysis Populations	Part 1 and Part 2 subjects will be analyzed separately. Part 1 Efficacy: All Subjects as Treated (ASaT) Part 2 Efficacy: Intention-to-Treat Population (ITT) Safety: All Subjects as Treated (ASaT)
Primary Endpoint(s)	Part 1: Safety and tolerability. Part 2: 1. Progression-free survival (PFS) based on Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST 1.1) as assessed by a blinded central imaging vendor (CIV) in all subjects. 2. PFS based on RECIST 1.1 as assessed by a blinded CIV in subjects with PD-L1 positive tumors (CPS ≥1). 3. PFS based on RECIST 1.1 as assessed by a blinded CIV in subjects with PD-L1 positive tumors (CPS ≥10). 4. Overall survival (OS) in all subjects. 5. OS in subjects with PD-L1 positive tumors (CPS ≥1). 6. OS in subjects with PD-L1 positive tumors (CPS ≥10).
Key Secondary Endpoint(s)	Part 2: Objective response rate (ORR) based on RECIST 1.1 as assessed by a blinded CIV in all subjects and in subjects with PD-L1 positive tumors (CPS ≥1).

Statistical Methods for Key Efficacy Analyses	Part 2: The primary hypotheses will be evaluated by comparing pembrolizumab + chemotherapy vs placebo + chemotherapy in PFS and OS using a stratified log-rank test. The hazard ratio (HR) will be estimated using a stratified Cox model. The key secondary hypotheses of ORR will be evaluated by comparing pembrolizumab + chemotherapy vs placebo + chemotherapy in ORR using a stratified Miettinen and Nurminen method.
Statistical Methods for Key Safety Analyses	Part 1: Descriptive summary statistics will be provided for safety endpoints by treatment as appropriate. Part 2: The analysis of safety will follow a tiered approach. There is no Tier 1 safety endpoint for this trial. 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	One safety interim analysis for Part 1 and 3 efficacy interim analyses for Part 2 will be performed. Results will be reviewed by an external DMC. Details are provided in Section 8.7 – Interim Analyses. Part 1 – Safety Interim Analysis: ~ 3 months after first subject randomized. o Timing: after all Part 1 subjects have completed the first 21 or 28 days (depending on chemotherapy treatment) of study treatment. o Primary purpose: interim safety evaluation. Part 2 – Efficacy Interim and Final Analyses • Interim analysis 1 (IA1): ~ 9 months after first 640 Part 2 subjects are randomized. o Primary purpose: final ORR analysis, interim PFS and interim OS analysis. • Interim analysis 2 (IA2): after ~ 185 OS events among subjects with CPS ≥10 have been observed. o Primary purpose: interim OS analysis and final PFS analysis. • Interim analysis 3 (IA3): after ~ 210 OS events among subjects with CPS ≥10 have been observed. o Primary purpose: interim OS analysis. • Final analysis (FA): after ~ 664 OS events among all subjects, ~ 482 OS events among subjects with CPS ≥1, and ~ 240 OS events among subjects with CPS ≥10 have been observed. o Primary purpose: final OS analysis.
Multiplicity	Part 1: Multiplicity adjustment not applicable. Part 2: The family-wise type-I error rate over the 6 primary hypotheses and the 2 secondary hypotheses will be strongly controlled at 2.5% (one-sided) with 0.5% allocated to PFS, 1.8% allocated to OS, and 0.2% allocated to ORR hypotheses. An extension [99] of the graphical approach of Maurer and Bretz [100] will be applied to re-allocate alpha between PFS, OS and ORR hypotheses. The Spiessens and Debois method [101] will be used to adjust the nominal alphas in ORR between all subjects and subjects with CPS ≥1. Group sequential methods will be used to allocate alpha between the interim and final analyses for OS endpoints.

Sample Size and Power	Part 1: Approximately **30** subjects will be enrolled. Part 2: It is expected that ~ 664 OS events among all subjects, ~ 482 OS events among subjects with CPS ≥1, and ~ 240 OS events among subjects with CPS ≥10 have been observed at the FA. The planned sample size is approximately **828** subjects. (1) PFS in all subjects: at IA2 the analysis has ~ 89% power at a one-sided 0.111% alpha level, if the true HR is 0.70. At IA2, with ~ 634 events the HR at boundary for success is ~ 0.77 (~ 1.6 months improvement over control median PFS of 5.5 months). At IA2, PFS in all subjects can only be tested if both hypotheses of PFS in subjects with CPS ≥10 and PFS in subjects with CPS ≥1 are supported. (2) PFS in subjects with CPS ≥1: at IA2 the analysis has ~ 97% power at a one-sided 0.111% alpha level, if the true HR is 0.62. At IA2, with ~ 463 events the HR at boundary for success is ~ 0.74 (~ 1.9 months improvement over control median PFS of 5.5 months). At IA2, PFS in all subjects with CPS ≥1 can only be tested if the hypothesis of PFS in subjects with CPS ≥10 is supported. (3) PFS in subjects with CPS ≥10: at IA2 the analysis has ~ 86% power at a one-sided 0.411% alpha level, if the true HR is 0.60. At IA2, with ~ 235 events the HR at boundary for success is ~ 0.69 (~ 2.4 months improvement over control median PFS of 5.5 months). (4) OS in all subjects: the trial has ~ 60% power at a one-sided 0.75% alpha level, if the true HR is 0.80. With ~ 664 events, the HR at boundary for success at FA is ~ 0.81 (~ 4.0 months improvement over control median OS of 17.5 months). After IA1, OS in all subjects can be tested if hypothesis of OS in subjects with CPS ≥1 is supported. (5) OS in subjects with CPS ≥1: the trial has ~ 87% power at a one-sided 0.75% alpha level, if the true HR is 0.71. With ~ 482 events, the HR at boundary for success at FA is ~ 0.78 (~ 4.8 months improvement over control median OS of 17.5 months). (6) OS in subjects with CPS ≥10: the trial has ~ 79% power at a one-sided 1.011% alpha level, if the true HR is 0.65. With ~ 240 events, the HR at boundary for success at FA is ~ 0.72 (~ 6.8 months improvement over control median OS of 17.5 months).

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.

Part 1:

Part 1 of this study is being conducted as a partially randomized, open-label study, i.e., subjects, investigators, and Sponsor personnel will be aware of subject treatment assignments after each subject is enrolled and treatment is assigned.

Planned safety interim analysis is described in Section 8.7 – Interim Analyses. Study enrollment is likely to be ongoing at the time of the safety interim analysis (i.e., no planned enrollment pause between Part 1 and Part 2).

The external DMC will serve as the primary reviewer of the results of the safety interim analysis and will make recommendations for discontinuation of the study or modification to

an EOC of the Sponsor. Additional logistical details, revisions to the above plan and data monitoring guidance will be provided in the DMC Charter. Key aspects of the interim analysis are described in Section 8.7 – Interim Analyses.

Part 2:

Part 2 of this study will be conducted as a double-blind, Phase III study part under in-house blinding procedures. The official, final database of Part 2 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 independent radiologist(s) will perform the central imaging review without knowledge of treatment group assignment. The Investigators, other study site staff, and subjects will be blinded to subject-level PD-L1 biomarker results. Analysis or summaries generated by PD-L1 status will be limited and documented. Additional details regarding trial blinding/unblinding including unblinding required for operational purposes (e.g., unblinded pharmacist) are described in Section 5.2.3 – Trial Blinding.

Planned efficacy interim analyses are described in Section 8.7 – Interim Analyses. Study enrollment is likely to be ongoing at the time of any efficacy interim analyses. Blinding to treatment assignment will be maintained at all investigational sites.

Treatment-level results of the efficacy interim analyses 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 interim analyses and will make recommendations for discontinuation of the study or modification to an EOC of the Sponsor. Depending on the recommendation of the DMC, the Sponsor may prepare a regulatory submission. If the DMC recommends modifications to the design of the protocol or discontinuation of the study, this EOC may be unblinded to results at the treatment level in order to act on these recommendations or facilitate regulatory filing. Limited additional Sponsor personnel may be unblinded to the treatment level results of the interim analysis (analyses), if required, in order to act on the recommendations of the DMC or facilitate regulatory filing. The extent to which individuals are unblinded with respect to results of interim analyses will be documented. Additional logistical details, revisions to the above plan and data monitoring guidance will be provided in the DMC Charter. Key aspects of the interim analyses are described in Section 8.7 – Interim Analyses.

Prior to final study unblinding, the 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 interim analyses.

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

Progression-free survival (PFS) – based on RECIST 1.1 as assessed by a CIV

Progression-free survival is defined as the time from randomization to the first documented disease progression per RECIST 1.1 based on assessments by a CIV or death due to any cause, whichever occurs first. See Section 8.6.1 – Statistical Methods for Efficacy Analyses for the definition of censoring.

Overall Survival (OS)

Overall survival 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.

Secondary

Objective Response Rate (ORR) – based on RECIST 1.1 as assessed by a CIV

Objective response rate is defined as the proportion of the subjects in the analysis population who have a CR or PR. Responses are based on assessments by a CIV per RECIST 1.1.

Duration of Overall Response (DOR) – based on RECIST 1.1 as assessed by a CIV

For subjects who demonstrate CR or PR, duration of response is defined as the time from first documented evidence of CR or PR until disease progression or death due to any cause, whichever occurs first, based on assessments by a CIV per RECIST 1.1. See Section 8.6.1 – Statistical Methods for Efficacy Analyses for the definition of censoring.

Disease Control Rate (DCR) – based on RECIST 1.1 as assessed by a CIV

Disease control rate is defined as the percentage of subjects who have achieved CR or PR or have demonstrated SD for at least 24 weeks, based on assessments by a CIV per RECIST 1.1.

8.4.2 Safety Endpoints

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

8.5 Analysis Populations

8.5.1 Efficacy Analysis Populations

The ITT population will serve as the population for primary efficacy analysis of Part 2. All randomized subjects will be included in this population. Subjects will be included in the treatment group to which they are randomized.

Part 1 subjects will be excluded from all Part 2 efficacy analyses and therefore will not contribute to the analyses to address the primary/secondary objectives of Part 2. The All Subjects as Treated (ASaT) population will be used for the analysis of Part 1 efficacy in this study. The ASaT population consists of all randomized subjects who received at least one dose of study treatment. Subjects will be included in the treatment group corresponding to the study treatment they actually received for the analysis of Part 1 efficacy 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 correct treatment group.

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 dose of 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 correct 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.

Part 1 and Part 2 subjects will be analyzed separately.

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

8.6 Statistical Methods

This section describes the statistical methods that address the primary and secondary efficacy and safety objectives. Methods related to PRO objectives and exploratory objectives will be described in the sSAP(s).

8.6.1 Statistical Methods for Efficacy Analyses

For Part 1, descriptive summaries will be provided for efficacy endpoints (e.g., PFS, OS, ORR, DOR, DCR) as appropriate.

The efficacy analysis methods specified in this section apply to Part 2. Part 1 subjects will be excluded from all Part 2 efficacy analyses and therefore will not contribute to the analyses to address the primary/secondary objectives of Part 2.

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 Progression-Free Survival (PFS)

The non-parametric Kaplan-Meier method will be used to estimate the PFS curve in each treatment group. The treatment difference in PFS 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 (i.e., HR) between the treatment arms. The HR and its 95% confidence interval (CI) from the stratified Cox model with Efron's method of tie handling and 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.

Since disease progression is assessed periodically, PD can occur any time in the time interval between the last assessment in which PD was not documented and the assessment when PD is documented. For subjects who have PD, the true date of disease progression will be approximated by the date of the first assessment at which PD is objectively documented based on RECIST 1.1 as assessed by a CIV. Death is always considered as a confirmed PD event. Subjects who do not experience a PFS event will be censored at the last disease assessment.

In order to evaluate the robustness of the PFS endpoint based on RECIST 1.1 as assessed by a CIV, one primary and two sensitivity analyses with a different set of censoring rules will be performed. For the primary analysis, if the events (PD or death) are immediately after more than one missed disease assessment, the data are censored at the last disease assessment prior to missing visits. Also, data after new anti-cancer therapy are censored at the last disease assessment prior to the initiation of new anti-cancer therapy. The first sensitivity analysis follows the intention-to-treat principle. That is, PDs/deaths are counted as events regardless of missed study visits or initiation of new anti-cancer therapy. The second sensitivity analysis considers initiation of new anticancer treatment or discontinuation of treatment due to reasons other than complete response to be a PD event for subjects without documented PD or death. The censoring rules for primary and sensitivity analyses are summarized in Table 11.

Table 11 Censoring Rules for Primary and Sensitivity Analyses of PFS

Situation	Primary Analysis	Sensitivity Analysis 1	Sensitivity Analysis 2
No PD and no death; and new anticancer treatment is not initiated	Censored at last disease assessment	Censored at last disease assessment	Progressed at treatment discontinuation due to reasons other than complete response; otherwise censored at last disease assessment if still on study treatment or completed study treatment.
No PD and no death; new anticancer treatment is initiated	Censored at last disease assessment before new anticancer treatment	Censored at last disease assessment	Progressed at date of new anticancer treatment
PD or death documented after ≤1 missed disease assessment, and before new anti-cancer therapy, if any	Progressed at date of documented PD or death	Progressed at date of documented PD or death	Progressed at date of documented PD or death
PD or death documented immediately after ≥2 consecutive missed disease assessments or after new anti-cancer therapy, if any	Censored at last disease assessment prior to the earlier date of ≥2 consecutive missed disease assessment and new anti-cancer therapy, if any	Progressed at date of documented PD or death	Progressed at date of documented PD or death

The proportional hazards assumption on PFS will be examined using both graphical and analytical methods if warranted. The log[-log] of the survival function vs time for PFS may be plotted for the comparison between the pembrolizumab + chemotherapy and placebo + chemotherapy 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; for example, using Restricted Mean Survival Time (RMST) method [102] and parametric method [103].

One assumption for stratified Cox proportional hazard model is that the treatment HR is constant across the strata. If strong departures from the assumption of the HR being the same for all the strata 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 [104], 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.

Sensitivity analyses will be performed for PFS based on site investigator/local radiology review. Additional supportive unstratified analyses may also be provided. Further details of sensitivity analyses will be described in the sSAP.

8.6.1.2 Overall Survival (OS)

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 (i.e., the HR). 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.

Subjects in the placebo + chemotherapy arm are expected to discontinue treatment earlier compared to subjects in the pembrolizumab + chemotherapy arm and are not allowed to crossover to the pembrolizumab + chemotherapy arm; however, they may be treated with another anti–PD-1 drug following the verification of PD by a blinded CIV. As an exploratory analysis, adjustment for the effect of crossover on OS may be performed based on recognized methods (e.g., the Rank Preserving Structural Failure Time (RPSFT) model proposed by Robins and Tsiatis [105], 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.

8.6.1.3 Objective Response Rate (ORR)

The stratified Miettinen and Nurminen method will be used for the comparison of ORR between 2 treatment arms. The difference in ORR and its 95% CI from the stratified Miettinen and Nurminen method with strata weighting by sample size will be reported. The stratification factors used for randomization (see Section 5.4 – Stratification) will be applied to the analysis.

The ORR hypotheses will be tested according to the hypotheses testing plan as described in Section 8.8 – Multiplicity.

Sensitivity analyses will be performed for ORR based on site investigator/local radiology review. 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 Disease Control Rate (DCR)

The stratified Miettinen and Nurminen method will be used for the comparison of DCR between 2 treatment arms. The difference in DCR and its 95% CI from the stratified Miettinen and Nurminen method with strata weighting by sample size will be reported. The stratification factors used for randomization (see Section 5.4 – Stratification) will be applied to the analysis.

Sensitivity analyses will be performed for DCR based on site investigator/local radiology review. Further details of sensitivity analyses will be described in the sSAP as needed.

8.6.1.5 Duration of Response (DOR)

If sample size permits, DOR will be summarized descriptively using the non-parametric Kaplan-Meier method. Only the subset of subjects who achieved CR or PR will be included in this analysis.

Censoring rules for DOR are summarized in Table 12.

Sensitivity analyses will be performed for DOR based on site investigator/local radiology review. Further details of sensitivity analyses will be described in the sSAP as needed.

Table 12 Censoring Rules for DOR

Situation	**Date of Progression or Censoring**	**Outcome**
No progression nor death, no new anti-cancer therapy initiated	Last adequate disease assessment	Censor (non-event)
No progression nor death, new anti-cancer therapy initiated	Last adequate disease assessment before new anti-cancer therapy initiated	Censor (non-event)
Death or progression immediately after ≥2 consecutive missed disease assessments or after new anti-cancer therapy, if any	Earlier date of last adequate disease assessment prior to ≥2 missed adequate disease assessments and new anti-cancer therapy, if any	Censor (non-event)
Death or progression after ≤1 missed disease assessments and before new anti-cancer therapy, if any	PD or death	End of response (Event)
A missed disease assessment includes any assessment that is not obtained or is considered inadequate for evaluation of response.		

8.6.1.6 Summary of Statistical Methods for Efficacy

Table 13 summarizes the primary analysis approach for primary and secondary efficacy endpoints of Part 2. 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 interim analyses is described in Section 8.7 – Interim Analyses and in Section 8.8 – Multiplicity.

Table 13 Analysis Strategy for Key Efficacy Endpoints (Part 2)

Endpoint/Variable (Description, Time Point)	Statistical Method[a]	Analysis Population	Missing Data Approach
Primary Hypothesis 1			
PFS based on RECIST 1.1 assessed by a blinded CIV in all subjects	Test: Stratified log-rank test Estimation: Stratified Cox model with Efron's tie handling method	ITT	• Primary censoring rule • Sensitivity analysis 1 • Sensitivity analysis 2 (More details are in Table 11)
Primary Hypothesis 2			
PFS based on RECIST 1.1 assessed by a blinded CIV in subjects with PD-L1 positive tumors (CPS ≥1)	Test: Stratified log-rank test Estimation: Stratified Cox model with Efron's tie handling method	ITT	• Primary censoring rule • Sensitivity analysis 1 • Sensitivity analysis 2 (More details are in Table 11)
Primary Hypothesis 3			
PFS based on RECIST 1.1 assessed by a blinded CIV in subjects with PD-L1 positive tumors (CPS ≥10)	Test: Stratified log-rank test Estimation: Stratified Cox model with Efron's tie handling method	ITT	• Primary censoring rule • Sensitivity analysis 1 • Sensitivity analysis 2 (More details are in Table 11)
Primary Hypothesis 4			
OS in all subjects	Test: Stratified log-rank test Estimation: Stratified Cox model with Efron's tie handling method	ITT	Censored at last known alive date
Primary Hypothesis 5			
OS in subjects with PD-L1 positive tumors (CPS ≥1)	Test: Stratified log-rank test Estimation: Stratified Cox model with Efron's tie handling method	ITT	Censored at last known alive date
Primary Hypothesis 6			
OS in subjects with PD-L1 positive tumors (CPS ≥10)	Test: Stratified log-rank test Estimation: Stratified Cox model with Efron's tie handling method	ITT	Censored at last known alive date
Key Secondary Hypothesis 1 (Hypothesis 7)			
ORR based on RECIST 1.1 assessed by a blinded CIV in all subjects	Stratified M & N method[b]	The first ~ 640 subjects randomized in Part 2 (a subset of ITT)	Subjects with relevant data missing are considered non-responders
Key Secondary Hypothesis 2 (Hypothesis 8)			
ORR based on RECIST 1.1 assessed by a blinded CIV in subjects with PD-L1 positive tumors (CPS ≥1)	Stratified M & N method[b]	The first ~ 640 subjects randomized in Part 2 (a subset of ITT)	Subjects with relevant data missing are considered non-responders

Endpoint/Variable (Description, Time Point)	Statistical Method[a]	Analysis Population	Missing Data Approach
Other Secondary Endpoints			
ORR based on RECIST 1.1 assessed by a blinded CIV in subjects with PD-L1 positive tumors (CPS ≥10)	Stratified M & N method[b]	ITT	Subjects with relevant data missing are considered non-responders
DCR based on RECIST 1.1 assessed by a blinded CIV in all subjects and in subjects with PD-L1 positive tumors (CPS ≥1 and CPS ≥10)	Stratified M & N method[b]	ITT	Subjects with relevant data missing are considered non-responders
DOR based on RECIST 1.1 assessed by a blinded CIV in all subjects and in subjects with PD-L1 positive tumors (CPS ≥1 and CPS ≥10)	Summary statistics using Kaplan-Meier method	All responders in ITT	See Table 12

CIV=central imaging vendor; CPS=combined positive score; DCR=disease control rate; DOR=duration of response; ITT=intention-to-treat; M & N=Miettinen and Nurminen; ORR=objective response rate; OS=overall survival; PD-L1=programmed cell death ligand 1; PFS=progression-free survival; RECIST 1.1= Response Evaluation Criteria in Solid Tumors version 1.1.

[a] Statistical models are described in further detail in the text. For stratified analyses, the stratification factors used for randomization will be used as stratification factors for analysis.

[b] Miettinen and Nurminen method.

8.6.2 Statistical Methods for Safety Analyses

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

Part 1

Descriptive summary statistics (e.g., counts, percentage, mean, standard deviation) will be provided for safety endpoints by treatment for Part 1 as appropriate.

Part 2

The analysis of safety results will follow a tiered approach [Table 14]. The tiers differ with respect to the analyses that will be performed. For this protocol, there are no Tier 1 safety endpoints. 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.

Adverse experiences (specific terms as well as system organ class terms) will be classified as belonging to "Tier 2" or "Tier 3", based on the number or percent of subjects with events observed. Specific AEs occurring in ≥5% of subjects in one or more treatment groups will be considered Tier 2 endpoints. Specific Serious and Grade 3-5 AEs occurring in at least 8 subjects in the pembrolizumab + chemotherapy group, or at least 2 subjects in the placebo + chemotherapy group will also 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. The threshold of at least 8 subjects in the pembrolizumab + chemotherapy group, or at least 2 subjects in the placebo + chemotherapy group was chosen for specific Serious and Grade 3-5 AEs because the 95% CI for the between-group difference in percent incidence will always include zero with 2 to 1 randomization ratio if there are less than 8 subjects with events in the treatment group and less than 2 subjects with events in the control group, and thus would add little to the interpretation of potentially meaningful differences. 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 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 serious AE, 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 14 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 or more treatment groups)	X	X
	Specific Serious AEs, SOCs (incidence ≥8 subjects in the pembrolizumab + chemotherapy group, or ≥2 subjects in the placebo + chemotherapy group)	X	X
	Specific Grade 3-5 AEs, SOCs (incidence ≥8 subjects in the pembrolizumab + chemotherapy group, or ≥2 subjects in the placebo + chemotherapy group)	X	X
Tier 3	Specific AEs, SOCs (incidence <5% of subjects in both treatment groups) or PDLCs		X
	Specific Serious AEs, SOCs (incidence <8 subjects in the pembrolizumab + chemotherapy group and <2 subjects in the placebo + chemotherapy group)		X
	Specific Grade 3-5 AEs, SOCs (incidence <8 subjects in the pembrolizumab + chemotherapy group and <2 subjects in the placebo + chemotherapy group)		X
	Change from Baseline Results (Labs, 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

Part 1 and Part 2

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 reason for discontinuation will be displayed. Demographic variables (e.g., age) and baseline characteristics will be summarized by treatment either by descriptive statistics or categorical tables.

8.7 Interim Analyses

The study has 1 planned safety interim analysis for Part 1 and 3 planned efficacy interim analyses for Part 2. Results will be reviewed by the external DMC.

8.7.1 Part 1: Safety Interim Analysis

A safety interim analysis will be performed after all Part 1 subjects have completed the first 21 or 28 days (depending on chemotherapy treatment) of study treatment (unless early discontinued), i.e., 21 days after the first study treatment administration if the subject is in the pembrolizumab + gemcitabine/carboplatin arm or 28 days after the first study treatment administration if the subject is in either of the pembrolizumab + taxane arms. Interim safety data will be reviewed by the DMC. It is estimated that the safety interim analysis will occur approximately 3 months after the first subject is randomized (depending on enrollment rate).

In addition, continuous safety monitoring will be performed for Part 1 prior to the safety interim analysis by the study team. If a potential safety issue signal is observed before 10 subjects are enrolled in a treatment arm, the DMC will be notified to review data prior to the pre-specified safety interim analysis.

8.7.2 Part 2: Efficacy Interim Analyses

There are 3 planned efficacy interim analyses for Part 2 in this trial. Results will be reviewed by the DMC. Of note, the boundaries for the analyses in this section may be adjusted, as appropriate, using the graphical approach discussed in Section 8.8 – Multiplicity.

The boundaries provided in this section are calculated based on the estimated number of events at each analysis, and the actual interim boundaries will be determined using the actual observed and the planned numbers of events at the time of interim analyses with the rules and spending functions specified in Section 8.8 – Multiplicity. The actual final boundaries will be adjusted accordingly. Any changes to the timing of the analyses, along with its rationale, will be documented in the sSAP or a memo to the study file before the database lock.

Of note, Amendment 05 occurred after the conduct of efficacy interim analysis 1 (IA1), and the following information regarding IA1 is based on the planned number of events and original multiplicity strategy specified in the protocol prior to Amendment 05.

Interim Analysis 1 (Final ORR, Interim PFS and Interim OS Analysis)

The primary purpose of efficacy IA1 is to perform the final ORR, interim PFS and interim OS analysis. The ORR analysis at IA1 is considered the final ORR analysis of the study. IA1 will be performed after: (1) enrollment is completed, and (2) ~ 9 months after the first 640 subjects randomized to Part 2.

At IA1, ORR analyses will be based on data from the first ~ 640 subjects randomized to Part 2 and be tested in 1) all subjects and, 2) subjects with CPS ≥1. All subjects randomized on or prior to the date the 640th Part 2 subject is randomized will be included in the ORR analysis.

The success boundary to demonstrate ORR superiority at IA1 approximately corresponds to an observed ORR difference of ~ 12.6 percentage points at $\alpha = 0.1\%$ (one-sided) for all subjects, and an observed ORR difference of ~ 14.1 percentage points at nominal

$\alpha = \sim 0.145\%$ (one-sided) for subjects with CPS ≥1, if there are 640 subjects in all subjects and 480 subjects in subjects with CPS ≥1 available for analysis (assuming PD-L1 positivity prevalence CPS ≥1 of 75%), respectively.

The estimated boundaries for PFS and OS endpoints at IA1 are provided in Table 15, assuming the planned numbers of events are analyzed.

Interim Analysis 2 (Interim OS Analysis and Final PFS Analysis)

The primary purpose of efficacy interim analysis 2 (IA2) is to evaluate superiority of pembrolizumab + chemotherapy vs placebo + chemotherapy in OS, and to perform final PFS analysis. The analysis will be performed after ~ 185 OS events among subjects with CPS ≥10 have been observed. It is estimated that at IA2 ~ 523 OS events among all subjects and ~ 375 OS events among subjects with CPS ≥1 have been observed. The analysis may be delayed for up to 4 months if the planned number of OS events has not been reached in all subjects or in subjects with CPS ≥1. It is estimated that IA2 is expected to occur ~ 22 months after last subject randomized.

The estimated boundaries for PFS and OS endpoints at IA2 are provided in Table 15 and Table 16, assuming the planned numbers of events are analyzed.

Interim Analysis 3 (Interim OS Analysis)

The primary purpose of efficacy interim analysis 3 (IA3) is to evaluate superiority of pembrolizumab + chemotherapy vs placebo + chemotherapy in OS. The analysis will be performed after ~ 210 OS events among subjects with CPS ≥10 have been observed. It is estimated at IA3 ~ 589 OS events among all subjects and ~ 424 OS events among subjects with CPS ≥1 have been observed. The analysis may be delayed for up to 4 months if the planned number of OS events has not been reached in all subjects or in subjects with CPS ≥1. It is estimated that IA3 is expected to occur ~ 30 months after last subject randomized.

The estimated boundaries for OS endpoints at IA3 are provided in Table 15 and Table 16, assuming the planned numbers of events are analyzed.

Final Analysis (Final OS Analysis)

The final analysis (FA) of the study is event driven and will be conducted after approximately ~ 664 OS events among all subjects, ~ 482 OS events among subjects with CPS ≥1, and ~ 240 OS events among subjects with CPS ≥10 have been observed. It is estimated that FA is expected to occur ~ 43 months after last subject randomized. If after 43 months after last subject randomized, the planned numbers of OS events still have not been observed, then the final OS analysis may be conducted at that time regardless. The success boundaries to demonstrate OS superiority at FA are presented in Table 15 and Table 16, if the planned numbers of OS events are analyzed.

Table 15 summarizes the timing, sample size and decision guidance of the 3 efficacy interim analyses and FA, assuming there is no alpha re-allocation among hypotheses. ORR boundaries are based on the assumptions of 640 randomized subjects and 75% PD-L1 CPS ≥1 prevalence, and may be updated at time of the analyses using the actual observed numbers. PFS and OS boundaries are based on planned number of events and may be updated at times of the analyses according to the actual observed number of events, spending functions, and the spending time approach as specified in Section 8.8 – Multiplicity.

Table 15 Summary of Timing, Sample Size and Decision Guidance of Efficacy Interim Analyses and Final Analysis (Part 2, at Initial Alpha)

Analysis	Criteria for Conduct of Analysis	Endpoint and Testing Population	Parameter	Efficacy Bar[a, b]
Interim Analysis 1: Final ORR, Interim PFS and Interim OS Analysis	IA1 occurred ~ 4 months after last subject randomized. IA1 was to be conducted when: (1) enrollment is completed, and (2) ~ 9 months after first 640 subjects are randomized in Part 2 It was estimated that at IA1: ~ 500 PFS events among all subjects, ~ 360 PFS events among subjects with CPS ≥1, ~ 260 OS events among all subjects, and ~ 185 OS events among subjects with CPS ≥1 have been observed.	ORR in all subjects	p-value (1-sided) at boundary ~ ORR difference at boundary	0.001 ~ 12.6 percentage points
		ORR in subjects with CPS ≥1	p-value (1-sided) at boundary ~ ORR difference at boundary	~ 0.00145[c] ~ 14.1 percentage points
		PFS in all subjects	p-value (1-sided) at boundary ~ HR at boundary	0.0005 ~ 0.73
		PFS in subjects with CPS ≥1	p-value (1-sided) at boundary ~ HR at boundary	0.0005 ~ 0.69
		OS in all subjects	p-value (1-sided) at boundary ~ HR at boundary	0.0004 ~ 0.64
		OS in subjects with CPS ≥1	p-value (1-sided) at boundary ~ HR at boundary	0.0004 ~ 0.59
Interim Analysis 2: Interim OS Analysis/Final PFS Analysis	IA2 will be conducted after ~ 185 OS events among subjects with CPS ≥10 have been observed[d]. It is estimated that at IA2: ~ 523 OS events among all subjects, ~ 375 OS events among subjects with CPS ≥1, ~ 634 PFS events among all subjects, ~ 463 PFS events among subjects with CPS ≥1, and ~ 235 PFS events among subjects with CPS ≥10 have been observed.	PFS in subjects with CPS ≥10	p-value (1-sided) at boundary ~ HR at boundary	0.00411 ~ 0.69
		OS in subjects with CPS ≥1	p-value (1-sided) at boundary ~ HR at boundary	0.0022 ~ 0.73
		OS in subjects with CPS ≥10	p-value (1-sided) at boundary ~ HR at boundary	0.0034 ~ 0.66
Interim Analysis 3: Interim OS Analysis	IA3 will be conducted after ~ 210 OS events among subjects with CPS ≥10 have been observed[d]. It is estimated that at IA3: ~ 589 OS events among all subjects, ~ 424 OS events among subjects with CPS ≥1 have been observed.	OS in subjects with CPS ≥1	p-value (1-sided) at boundary ~ HR at boundary	0.0036 ~ 0.76
		OS in subjects with CPS ≥10	p-value (1-sided) at boundary ~ HR at boundary	0.0050 ~ 0.69

Analysis	Criteria for Conduct of Analysis	Endpoint and Testing Population	Parameter	Efficacy Bar[a, b]
Final Analysis (FA): Final OS Analysis	FA will be conducted after [e]: ~ 664 OS events among all subjects, ~ 482 OS events among subjects with CPS ≥1, and ~ 240 OS events among subjects with CPS ≥10 have been observed.	OS in subjects with CPS ≥1	p-value (1-sided) at boundary ~ HR at boundary	0.0060 ~ 0.78
		OS in subjects with CPS ≥10	p-value (1-sided) at boundary ~ HR at boundary	0.0082 ~ 0.72

[a.] Efficacy bar represents boundary at which statistical significance supporting pembrolizumab + chemotherapy is superior to placebo + chemotherapy can be claimed.
[b.] Efficacy bars at IA1 are based on planned number of events and original multiplicity strategy specified in the protocol prior to Amendment 05. Efficacy bars at IA2/IA3/FA for OS in subjects with CPS ≥1 are based on the actual number of events at IA1 and planned numbers of events at IA2/IA3/FA.
[c.] Approximate nominal alpha based on the Spiessens and Debois method accounting for correlation between ORR in all subjects and ORR in subjects with CPS ≥1. The actual nominal alpha will be calculated based on the actual correlation between these two populations for testing.
[d.] IA2 and IA3 may be delayed for up to 4 months if the planned number of OS events in all subjects or in subjects with CPS ≥1 has not yet been reached.
[e.] FA may be conducted after 43 months post last patient randomized even if the planned numbers of events are not reached at that time.

If a hypothesis is supported, the alpha can be re-allocated to another hypothesis following the pre-specified rules in Section 8.8 – Multiplicity. The hypotheses of PFS in all subjects, PFS in subjects with CPS ≥1, and OS in all subjects have initial alpha of 0% at IA2 (PFS) or IA2/IA3/FA (OS). As such, after IA1 they can only be tested after alpha re-allocation if relevant hypothesis(es) is supported. The efficacy decision guidance for these endpoints with respect to the re-allocated alpha from the support of other hypothesis(es) is summarized in Table 16 below (selected scenarios), assuming the planned numbers of events specified in Table 15 are available for analyses at each time point.

If an efficacy boundary is crossed at IA1 or IA2 for PFS, or at an interim analysis or the FA for OS, in either all subjects or subjects with CPS ≥1 or CPS ≥10, the study will be declared to have met its primary objective. The study may continue till completion regardless of the results of the interim analyses to obtain mature OS data.

Of note, an assumption of 75% prevalence of PD-L1 CPS ≥1, and 38% prevalence of PD-L1 CPS ≥10 in mTNBC subjects were made in above calculations. The above timing, estimated event count, and criteria for interim and final analyses are subject to modification in the sSAP as needed based on emerging data on PD-L1 prevalence in mTNBC.

Table 16 Summary of Efficacy Decision Guidance After Alpha Re-Allocation (Part 2, Selected Scenarios)

Endpoint	Scenario	Total Alpha Allocated	Analysis	Efficacy Boundary (After Alpha Re-Allocation)	
				p-value (1-sided) at Boundary	Approx. HR at Boundary
H1: PFS in all subjects (IA2)	H2 and H3 supported	0.00111	IA2	0.00111	0.77
H2: PFS in subjects with CPS ≥1 (IA2)	H3 supported	0.00111	IA2	0.00111	0.74
H4: OS in all subjects (IA2/IA3/FA)	H5 supported	0.0075	IA2	0.0026	0.77
			IA3	0.0038	0.79
			FA	0.0060	0.81

8.8 Multiplicity

Part 1

Multiplicity adjustment is not applicable.

Part 2

The multiplicity strategy specified in this section will be applied to the 6 primary hypotheses and the 2 secondary hypotheses of Part 2: primary hypotheses of superiority of pembrolizumab + chemotherapy compared to placebo + chemotherapy in PFS and OS in all subjects and in subjects with PD-L1 positive tumors (CPS ≥1 and CPS ≥10), and secondary hypotheses of superiority of pembrolizumab + chemotherapy compared to placebo + chemotherapy in ORR in all subjects and in subjects with PD-L1 positive tumors (CPS ≥1).

Based on emerging biomarker data external to this study, the initial alpha allocation among the 6 primary hypotheses and 2 secondary hypotheses is revised in Amendment 05. The revision of the alpha allocation occurs after the conduct of efficacy IA1. The family-wise Type-I error rate for this study is strongly controlled at 2.5% (one-sided) across all 6 primary hypotheses on PFS and OS as well as 2 secondary hypotheses on ORR.

Figure 4 displays the revised multiplicity strategy diagram of the study. The initial one-sided alpha allocation for each hypothesis is shown in the rectangle representing the hypothesis. The weights for re-allocation from each hypothesis to the others are represented in the numbers along the lines connecting hypotheses. Overall, a total of 0.5% alpha is allocated to PFS endpoints, a total of 1.8% alpha is allocated to OS endpoints, and a total of 0.2% alpha is allocated to ORR endpoints.

Table 17 also summarizes the revised initial alpha allocation before any alpha re-allocation.

Table 17 Initial Alpha Allocation

Hypothesis	Initial Alpha Allocation
H1: PFS in all subjects	• 0.043% allocated at IA1 (already spent at IA1). • 0% allocated at IA2.
H2: PFS in subjects with CPS ≥1	• 0.046% allocated at IA1 (already spent at IA1). • 0% allocated at IA2.
H3: PFS in subjects with CPS ≥10	• 0.411% allocated at IA2 only.
H4: OS in all subjects	• 0.039% allocated at IA1 (already spent at IA1). • 0% allocated at IA2/IA3/FA (group sequential).
H5: OS in subjects with CPS ≥1	• 0.75% allocated to IA1/IA2/IA3/FA (group sequential), which includes 0.036% spent at IA1.
H6: OS in subjects with CPS ≥10	• 1.011% allocated to IA2/IA3/FA (group sequential).
H7: ORR in all subjects	• 0.1% allocated at IA1 only (already spent at IA1).
H8: ORR in subjects with CPS ≥1	• 0.1% allocated at IA1 only (already spent at IA1).

An extension [99] of the graphical approach of Maurer and Bretz [100] will be used with Figure 4 to allocate and re-allocate alpha between hypotheses. Testing will first be performed in subjects with CPS ≥1 for a treatment effect on ORR (H8). If H8 is supported (ie, the null hypothesis is rejected), then the corresponding alpha can be added to that allocated for evaluating the treatment effect on ORR in all subjects (H7). If H7 is supported, then the corresponding alpha can be re-allocated to PFS in subjects with CPS ≥10 (H3). If H3 is supported, then the corresponding alpha can be re-allocated, 27% to PFS in subjects with CPS ≥1 (H2 at IA2 only), and 73% to OS in subjects with CPS ≥10 (H6). If H2 is supported, the alpha for that hypothesis can be re-allocated to PFS in all subjects (H1 at IA2 only). If H1 is supported, the alpha for that hypothesis can be re-allocated to OS in subjects with CPS ≥10 (H6). If H6 is supported, the alpha for that hypothesis can then be re-allocated to OS in subjects with CPS ≥1 (H5). If H5 is supported, the alpha for that hypothesis can then be re-allocated to OS in all subjects (H4 at IA2/IA3/FA). If H4 is supported, at IA2/IA3/FA, the alpha for that hypothesis can be re-allocated back to H7.

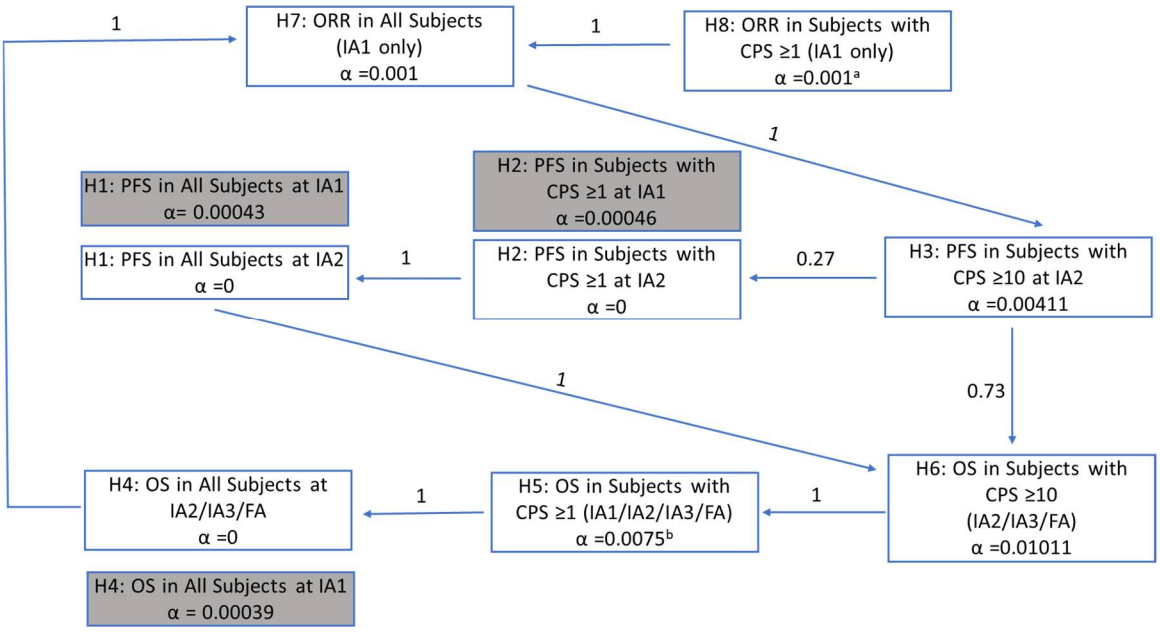
In the above multiplicity strategy, actual alpha spent at IA1 was calculated based on the original pre-specified alpha allocation strategy prior to Amendment 05 by the pre-specified alpha spending functions, using the actual spending time calculated from the planned and observed information fractions at IA1. Under the revised alpha allocation, actual alpha spent at IA1 for PFS in all subjects (H1), PFS in subjects with CPS ≥1 (H2), and OS in all subjects (H4) will be kept intact by a Bonferroni approach to strongly control the family-wise Type-I error rate at one-sided 2.5%. After IA1, these alphas will no longer be re-allocated to other hypotheses under the graphical approach, nor can they be used to account for correlation among group sequential tests within each endpoint across different time points. As such, the revised total alpha after IA1 is now 2.5% - 0.043% (alpha spent at IA1 for H1) - 0.046% (alpha spent at IA1 for H2) - 0.039% (alpha spent at IA1 for H4) ~= 2.37% for all hypotheses (all numbers rounded, the actual alpha for testing will be calculated based on the

actual alpha spent for H1, H2 and H4 at IA1 with high precision). The 0.036% alpha spent at IA1 for H5 will be part of the new initial alpha of 0.75% for H5. Of note, a 0% initial alpha is now assigned to PFS in all subjects at IA2, PFS in subjects with CPS ≥1 at IA2, and OS in all subjects at IA2/IA3/FA. These endpoints at these specific timepoints are now part of the graphical approach and can still be tested if a positive alpha can be re-allocated to them after the success of testing relevant hypothesis(es). For example, if PFS in CPS ≥10 is supported at IA2, a one-sided alpha of 0.111% (0.411% × 0.27) will be re-allocated to PFS in CPS ≥1 at IA2 for testing. In addition, if a positive alpha can be re-allocated to OS in all subjects (H4) at either IA2, IA3 or FA, then a Lan-DeMets O'Brien-Fleming alpha-spending function will be used to distribute the alpha among IA2, IA3, and FA for appropriate testing at each time point, respectively.

For OS endpoints, a Lan-DeMets O'Brien-Fleming approximation alpha-spending function is constructed to implement group sequential boundaries that control the Type-I error. Spending time will be plugged into the pre-specified spending function to calculate alpha spending. At the time of IA1 (as applicable), IA2, and IA3 for OS, the spending time will be the minimum of the actual observed information fraction and the planned information fraction for each endpoint, respectively (with the exception of OS in subjects with CPS ≥1 at IA1, please see next paragraph). At the time of FA for OS endpoints, the spending time will be 1. Of note, while the spending time used for alpha-spending calculation will be the minimum of the actual observed information fraction and the planned information fraction, the correlations used for computing bounds for each endpoint will still be from that endpoint depending on the actual event counts. The rationale for the above strategy is to ensure that full Type-I error is spent at the final analysis without overspending at the interim. Justification for the spending time approach can be found in Anderson et.al. [99]. Of note, prior to Amendment 05, a Hwang-Shih-DeCani alpha-spending function with gamma parameter (-4) was constructed to implement group sequential boundaries that control the Type-I error for PFS endpoints, and it is no longer applicable under Amendment 05.

For OS in subjects with CPS ≥1 (H5), the revised initial alpha is 0.75% which includes 0.036% already spent at IA1. In order to account for the 0.036% alpha already spent at IA1 for H5 under initial alpha allocation, the spending time at IA1 will be fixed at 56.1% such that the corresponding alpha distributed at IA1 using the Lan-DeMets O'Brien-Fleming spending function with a total initial alpha of 0.75% remains 0.036%.

The Spiessens and Debois method [101] will be used to calculate the nominal alpha of ORR in subjects with CPS ≥1 after accounting for the correlation between ORR endpoints in these 2 populations, while fixing the nominal alpha at 0.001 for ORR in all subjects. The actual observed correlation will be used for this adjustment in the analysis. Of note, if at IA2, IA3 or FA, additional alpha can be reallocated to H7 (e.g., H4 is not successful at IA1 but successful at IA2), the p-value of ORR in all subjects obtained from IA1 will be re-evaluated using the updated alpha threshold at that time. Similarly, if at IA3 or FA additional alpha can be re-allocated to PFS endpoint(s), the p-value of PFS endpoint(s) obtained from IA2 will be re-evaluated using the updated alpha threshold at that time.



[a] Nominal alpha for testing will be calculated based on Spiessens and Debois method accounting for correlation between ORR in all subjects and ORR in subjects with CPS ≥1. Of note, while the nominal alpha will be calculated and used for testing, the allocated alpha (0.001) will be passed to H7 when applicable.
[b] H5 α=0.0075 which includes 0.00036 already spent at IA1.
Note: The shaded boxes in this figure represent alpha that has already been spent at IA1 and will be considered lost for future analyses. These alphas will no longer be re-allocated to other hypotheses under the graphical approach, nor can they be used to account for correlation among group sequential tests within each endpoint across different time points.

Figure 4 Multiplicity Strategy

8.9 Sample Size and Power Calculations

Part 1

Part 1 of the study will enroll approximately 30 subjects. For each treatment with 10 subjects available for analysis, if the underlying incidence rate of a given type of AE is 5% or 10%, there is 40% or 65% chance of observing at least one AE among the 10 subjects, respectively. If no AE of a given type is observed among the 10 subjects, this study part will provide 80% confidence that the underlying percentage of subjects with the AE is <14.9% (90% confidence that the underlying rate of the AE is <20.6%) in the study population treated with the study treatment.

Part 2

Part 2 of the study will randomize approximately 828 subjects in a 2:1 ratio between the pembrolizumab + chemotherapy and the placebo + chemotherapy arms.

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.

Power considerations for each endpoint are described below.

PFS

The PFS power calculation is based on the following assumptions: 1) PFS follows an exponential distribution with a median of 5.5 months in the placebo + chemotherapy arm in all populations (all subjects, subjects with CPS ≥1, and subjects with CPS ≥10); 2) An enrollment period of 17 months for Part 2; 3) A yearly drop-out rate of 30%; 4) the true HR is 0.70, 0.62, and 0.60 for PFS in all subjects, subjects with CPS ≥1, and subjects with CPS ≥10, respectively. In addition, prior to Amendment 05, a Hwang-Shih-DeCani alpha-spending function with gamma parameter (-4) was constructed to implement group sequential boundaries that control the Type-I error for PFS endpoints.

Any change to the timing of the PFS analyses, along with its rationale, will be documented in the sSAP or a memo to the study file before the database lock.

PFS in all subjects

At IA1 it was expected that approximately 500 PFS events would have been accumulated among all subjects. An alpha of ~ 0.05% was to be allocated to PFS in all subjects at this analysis (subject to change according to the actual number of PFS events at IA1, based on the alpha-spending function with a total of 0.1% alpha originally allocated to PFS in all subjects). If the planned number of events of 500 was analyzed, this analysis had ~ 67% power to demonstrate that pembrolizumab + chemotherapy is superior to placebo + chemotherapy, if the underlying HR is 0.70.

At IA2 of the study, PFS in all subjects will only be tested if both hypotheses of PFS in subjects with CPS ≥1 and PFS in subjects with CPS ≥10 are supported. It is expected that approximately 634 PFS events will be observed among all subjects at IA2. A final PFS analysis will be performed at IA2. This analysis has ~ 89% power to demonstrate that pembrolizumab + chemotherapy is superior to placebo + chemotherapy for PFS in all subjects at a one-sided 0.111% alpha level, if the underlying HR is 0.70.

PFS in subjects with CPS ≥1

At IA1 it was expected that approximately 360 PFS events would have been observed among subjects with CPS ≥1. An alpha of ~ 0.05% was to be allocated to PFS in subjects with CPS ≥1 at this analysis (subject to change according to the actual number of PFS events at IA1, based on the alpha-spending function with a total of 0.1% alpha originally allocated to PFS in subjects with CPS ≥1). If the planned number of events of 360 was analyzed, this analysis had ~ 83% power to demonstrate that pembrolizumab + chemotherapy is superior to placebo + chemotherapy, if the underlying HR is 0.62.

At IA2 of the study, PFS in subjects with CPS ≥1 will only be tested if the hypothesis of PFS in subjects with CPS ≥10 is supported. It is expected that approximately 463 PFS events will be observed among subjects with CPS ≥1 at IA2. A final PFS analysis will be performed at IA2. This analysis has ~ 97% power to demonstrate that pembrolizumab + chemotherapy is superior to placebo + chemotherapy for PFS in subjects with CPS ≥1 at a one-sided 0.111% alpha level, if the underlying HR is 0.62.

PFS in subjects with CPS ≥10

At IA2 of the study, it is expected that approximately 235 PFS events would have been observed among subjects with CPS ≥10. The only PFS analysis in subjects with CPS ≥10 will be performed at IA2. The analysis has ~ 86% power to demonstrate that pembrolizumab + chemotherapy is superior to placebo + chemotherapy for PFS in subjects with CPS ≥10 at a one-sided 0.411% alpha level, if the underlying HR is 0.60.

OS

The sample size and OS power calculation is based on the following assumptions: 1) OS follows an exponential distribution with a median of 17.5 months in the placebo + chemotherapy arm in all populations (all subjects, subjects with CPS ≥1 and subjects with CPS ≥10); 2) An enrollment period of 17 months for Part 2 and a minimum of 43 months follow-up after enrollment completion; 3) A yearly dropout rate of 3%; 4) the true HR is 0.80, 0.71, and 0.65 for OS in all subjects, subjects with CPS ≥1, and subjects with CPS ≥10, respectively. In addition, a Lan-DeMets O'Brien-Fleming approximation alpha-spending function was constructed to implement group sequential boundaries that control the Type-I error for OS endpoints.

Any change to the timing of the OS analyses, along with its rationale, will be documented in the sSAP or a memo to the study file before the database lock.

OS in all subjects

After IA1, OS in all subjects can be tested if hypothesis of OS in subjects with CPS ≥1 is supported. With ~ 664 OS events among all subjects at the final OS analysis, the trial has ~ 60% power to demonstrate that pembrolizumab + chemotherapy is superior to placebo + chemotherapy at a one-sided 0.75% alpha level, if the underlying HR is 0.80. If the planned numbers of events are analyzed, success boundary for OS in all subjects at FA approximately corresponds to an observed HR of ~ 0.81 (~ 4.0 months improvement over a control median OS of 17.5 months).

OS in subjects with CPS ≥1

It is expected that ~ 482 OS events will have occurred among subjects with CPS ≥1 at the final OS analysis. For OS in subjects with CPS ≥1, the trial has ~ 87% power to demonstrate that pembrolizumab + chemotherapy is superior to placebo + chemotherapy at a one-sided 0.75% alpha-level, if the underlying HR is 0.71. If the planned numbers of events are analyzed at IA2/IA3/FA, success boundary for OS in subjects with CPS ≥1 at FA approximately corresponds to an observed HR of ~ 0.78 (~ 4.8 months improvement over a control median OS of 17.5 months).

OS in subjects with CPS ≥10

It is expected that ~ 240 OS events will have occurred among subjects with CPS ≥10 at the final OS analysis. For OS in subjects with CPS ≥10, the trial has ~ 79% power to demonstrate that pembrolizumab + chemotherapy is superior to placebo + chemotherapy at a one-sided 1.011% alpha-level, if the underlying HR is 0.65. If the planned numbers of events are analyzed, success boundary for OS in subjects with CPS ≥10 at FA approximately corresponds to an observed HR of ~ 0.72 (~ 6.8 months improvement over a control median OS of 17.5 months).

ORR

The ORR power calculation is based on the following assumptions: 1) under initial alpha allocated to ORR hypotheses; 2) the underlying ORR is 29% in the placebo + chemotherapy arm, and there is 15 or 18 percentage points increase in ORR in the pembrolizumab + chemotherapy arm (ORR of 44% or 47%), in both all subjects and in subjects with CPS ≥1, respectively. The power for ORR endpoints is summarized in Table 18.

Table 18 Power for ORR

Population	N	Nominal Alpha	~ ORR Difference at Success Boundary	True ORR Difference	Power
All Subjects	640	0.001	12.6 percentage points	15 percentage points	72%
				18 percentage points	91%
Subjects with CPS ≥1	480	0.00145[a]	14.1 percentage points	15 percentage points	58%
				18 percentage points	80%

[a] Approximate nominal alpha based on the Spiessens and Debois method accounting for correlation between ORR in all subjects and ORR in subjects with CPS ≥1. The actual nominal alpha will be calculated based on the actual correlation between these two populations.
Assume 29% ORR in the placebo + chemotherapy arm
Assume 75% PD-L1 CPS ≥1 prevalence.

The assumptions for a median PFS of 5.5 months, median OS of 17.5 months, and an ORR of 29% in the placebo + chemotherapy arm are based on the estimates from Miles et al., 2013 [78], and the Phase III trial reported in O'Shaughnessy et al., 2014 [71].

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

Of note, the assumptions of 75% prevalence of PD-L1 CPS ≥1, 38% prevalence of PD-L1 CPS ≥10 in mTNBC subjects, and low discrepancy rate (e.g., <10%) between central and local determinations of baseline measurable disease were made in above calculations. The above assumptions and sample size calculations are subject to modification in the sSAP as needed based on emerging data on PD-L1 prevalence in mTNBC as well as correlation between PD-L1 expression and treatment effect, and/or emerging data on the discrepancy rate between central and local determinations of baseline measurable disease in mTNBC subjects.

Although safety issues are not expected for any of the pembrolizumab and chemotherapy combinations in this study, if one or more of the chemotherapy options (i.e., nab-paclitaxel, paclitaxel, or gemcitabine/carboplatin) is stopped because of a safety issue, then the Part 2 primary analyses will be restricted to the remaining chemotherapy option(s) and the Part 2 sample size will be based on only those remaining option(s).

8.10 Subgroup Analyses and Effect of Baseline Factors

Part 1

There is no planned subgroup analysis for Part 1.

Part 2

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:

- Chemotherapy on study (nab-paclitaxel vs paclitaxel vs gemcitabine/carboplatin; taxane vs gemcitabine/carboplatin).
- Tumor PD-L1 status (CPS ≥1 vs CPS <1; CPS ≥5 vs CPS <5; CPS ≥10 vs CPS <10; CPS ≥15 vs CPS <15; CPS ≥20 vs CPS <20). Note: these subgroup analyses will only be conducted in the all subjects population.
- Prior treatment with same class of chemotherapy in the (neo)adjuvant setting (yes vs no).
- Prior (neo)adjuvant chemotherapy (yes vs no)
- Prior (neo)adjuvant taxane treatment (yes vs no)
- Prior (neo)adjuvant platinum treatment (yes vs no)
- 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 status (0 vs 1)
- HER2 status (2+ by IHC vs 0-1+ by IHC)
- Disease-free interval (de novo metastasis vs <12 months vs ≥12 months)
- Number of metastatic sites (<3 vs ≥3)
- Visceral disease (yes vs no)
- LDH (≥2.0 x Upper Limit of Normal [ULN] vs <2.0 x ULN)

8.11 Compliance (Medication Adherence)

Part 1 and Part 2

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

Part 1 and Part 2

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 19.

Table 19 Product Descriptions

Product Name & Potency	Dosage Form	Source/Additional Information
Pembrolizumab (MK-3475) 100 mg/4 mL	Solution for Infusion	Provided centrally by the Sponsor
Nab-paclitaxel 5 mg/mL	Powder for Infusion	Provided centrally by the Sponsor or locally by the trial site, subsidiary, or designee
Paclitaxel 6 mg/mL (potency may vary by country/source)	Solution for Infusion (dosage form may vary by country/source)	Provided centrally by the Sponsor or locally by the trial site, subsidiary, or designee
Gemcitabine (potency may vary by country/source)	Lyophilized powder for IV infusion (dosage form may vary by country/source)	Provided centrally by the Sponsor or locally by the trial site, subsidiary, or designee
Carboplatin 10 mg/mL (potency may vary by country/source)	Solution for infusion (dosage form may vary by country/source)	Provided centrally by the Sponsor or locally by the trial site, subsidiary, or designee

All supplies indicated in Table 19 will be provided per the "Source/Additional Information" column depending on local country operational requirements.

Any commercially available product not included in Table 19 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 for Part 2 of this trial. 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.

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 or a non-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.

Section 5.8 outlines the criteria for allowing subjects who are discontinued from treatment to continue to be monitored in the trial.

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 Modernization Act (FDAMA) and the Food and Drug Administration Amendments Act (FDAAA), the Sponsor of the trial is solely responsible for determining whether the trial and its results are subject to the requirements for submission to the Clinical Trials Data Bank, http://www.clinicaltrials.gov. 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 FDAMA/FDAAA 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 FDAMA/FDAAA are that of the Sponsor and agrees not to submit any information about this trial or its results to the Clinical Trials Data Bank.

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 collected in this trial as outlined in Section 7.1.3.6 – Future Biomedical Research Sample Collection7.1.3.6 – Future Biomedical Research Sample Collection will be used to study various causes for how subjects may respond to a drug/vaccine. Future biomedical research specimen(s) will be stored to provide a resource for future trials conducted by the Sponsor focused on the study of biomarkers responsible for how a drug/vaccine enters and is removed by the body, how a drug/vaccine works, other pathways a drug/vaccine may interact with, or other aspects of disease. The specimen(s) may be used for future assay development and/or drug/vaccine development.

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

3. Summary of Procedures for Future Biomedical Research

a. Subjects for Enrollment

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

b. Informed Consent

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

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

c. eCRF Documentation for Future Biomedical Research Specimens

Documentation of 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 Collections

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

4. Confidential Subject Information for Future Biomedical Research

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

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

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

5. Biorepository Specimen Usage

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

6. Withdrawal From Future Biomedical Research

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

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

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

7. Retention of Specimens

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

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

8. Data Security

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

9. Reporting of Future Biomedical Research Data to Subjects

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

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

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

10. Future Biomedical Research Study Population

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

11. Risks Versus Benefits of Future Biomedical Research

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

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

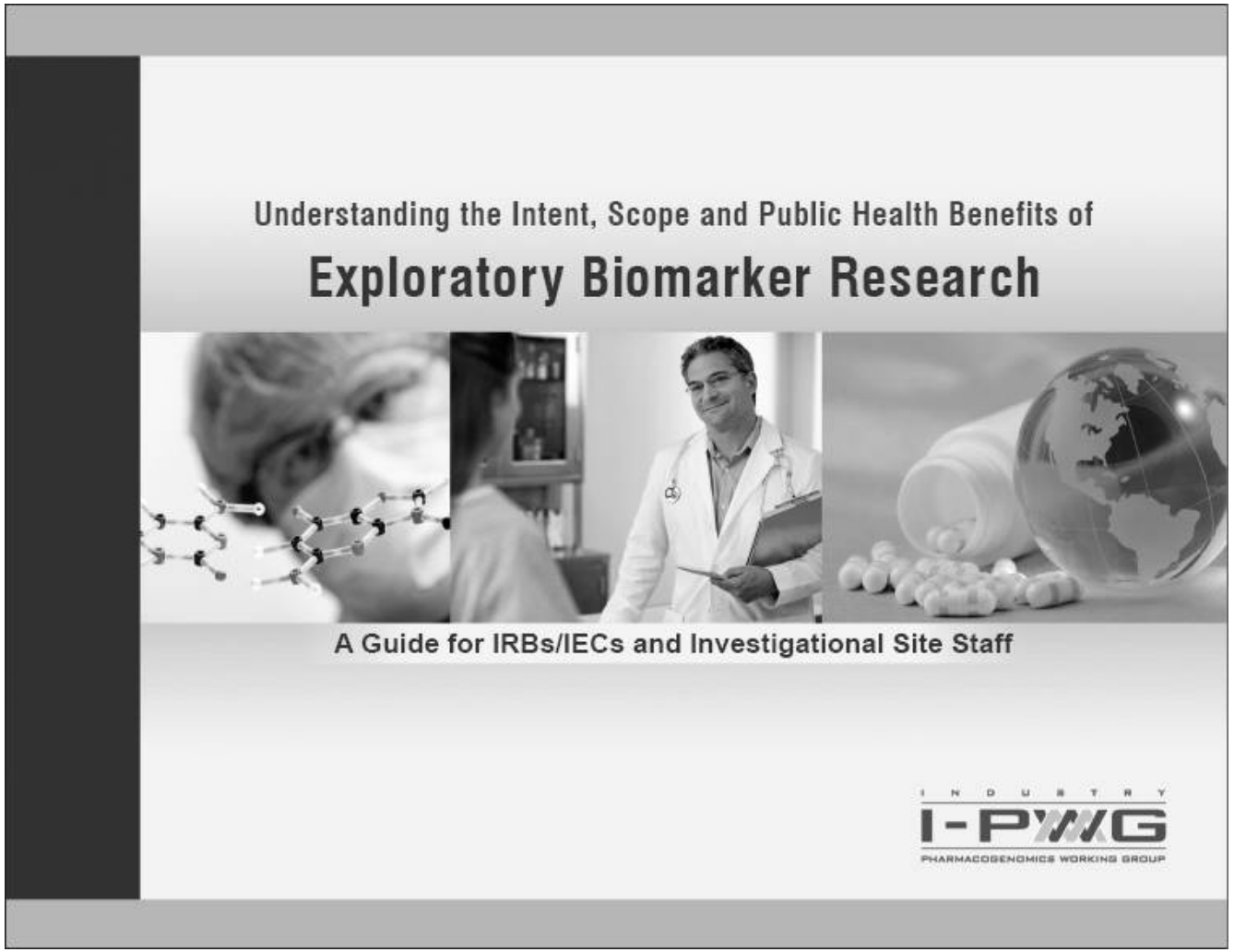
12. Questions

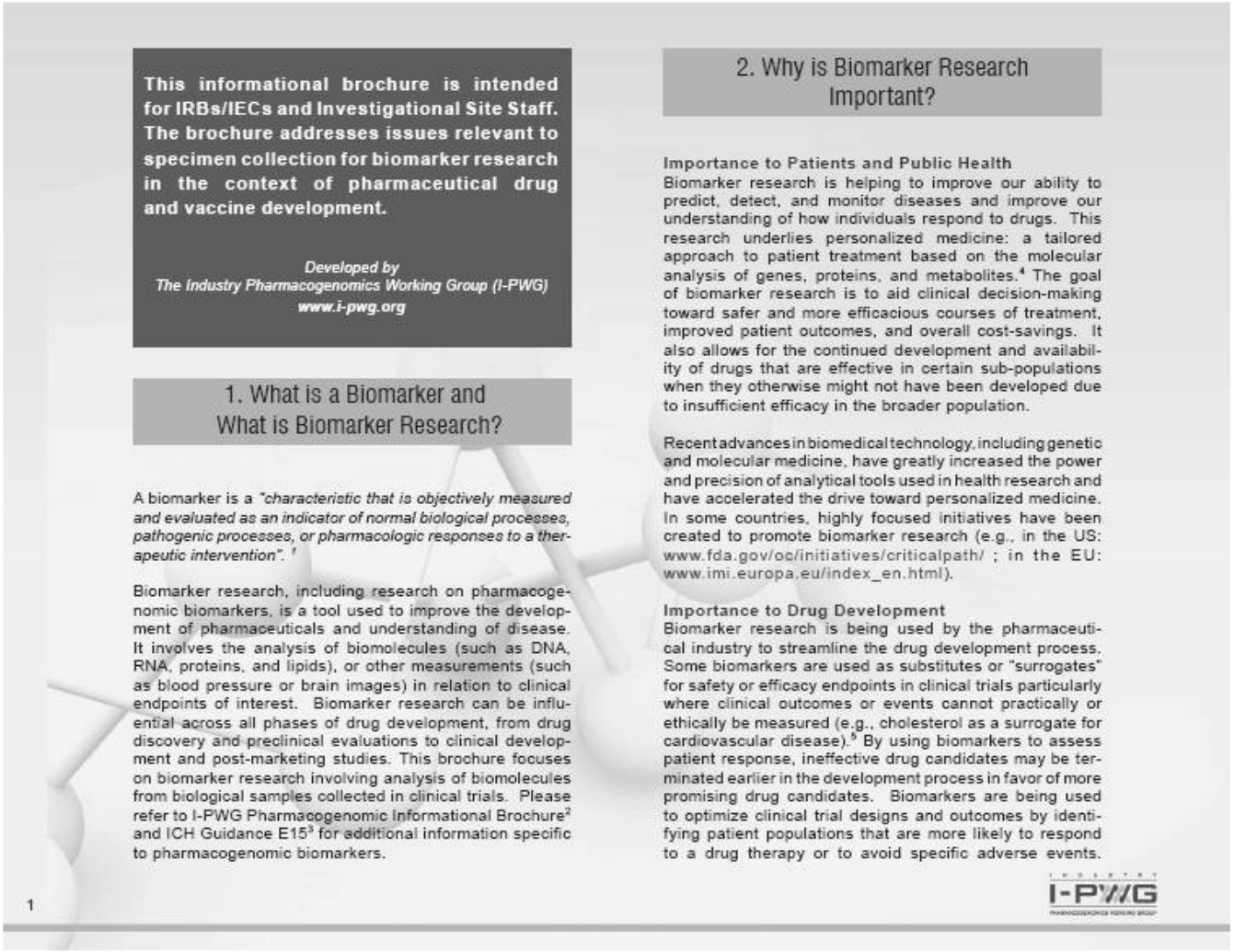
Any questions related to the future biomedical research should be e-mailed directly to clinical.specimen.management@MSD.com.

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

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





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

Developed by
The Industry Pharmacogenomics Working Group (I-PWG)
www.i-pwg.org

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

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

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

2. Why is Biomarker Research Important?

Importance to Patients and Public Health

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

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

Importance to Drug Development

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

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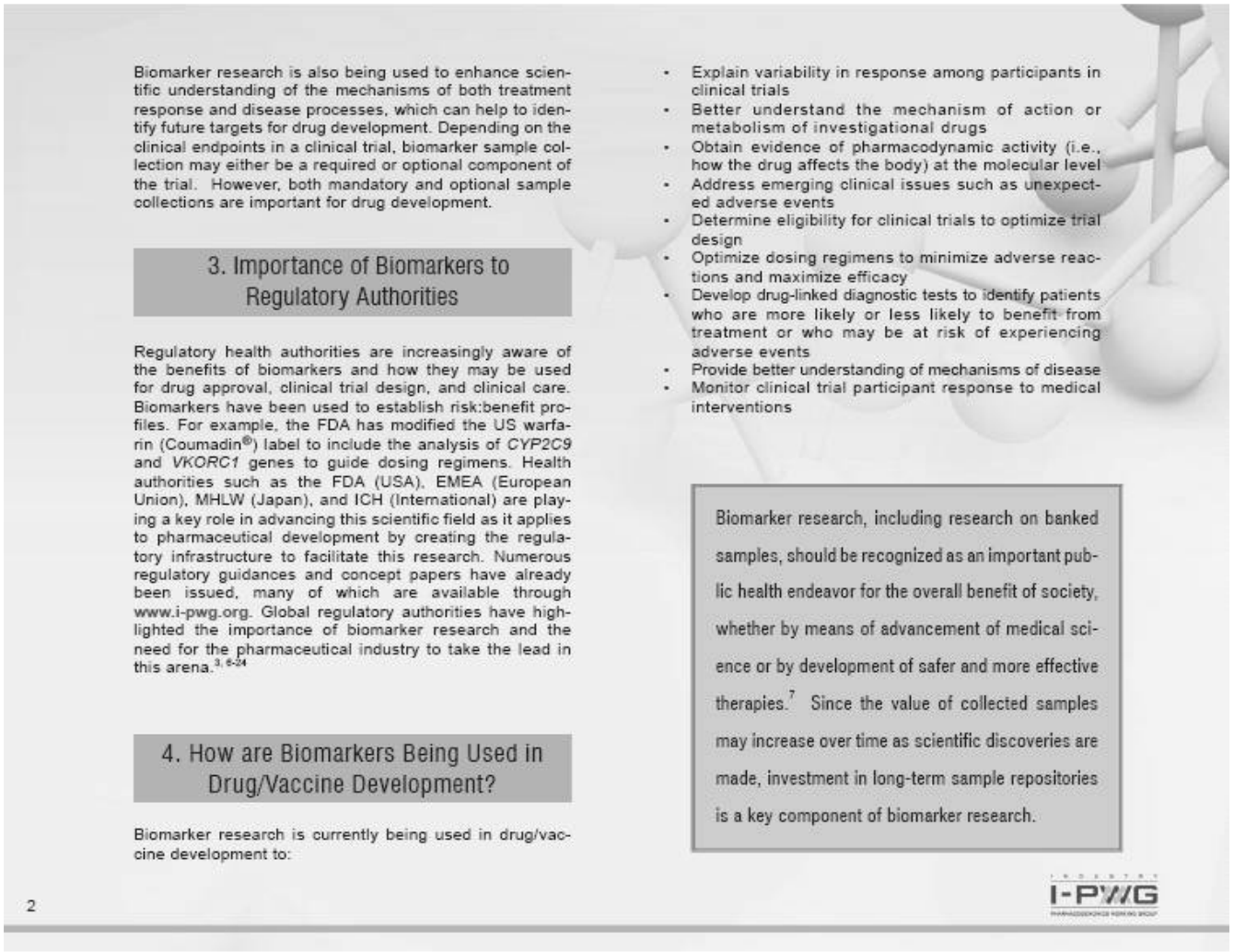

Biomarker research is also being used to enhance scientific understanding of the mechanisms of both treatment response and disease processes, which can help to identify future targets for drug development. Depending on the clinical endpoints in a clinical trial, biomarker sample collection may either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

3. Importance of Biomarkers to Regulatory Authorities

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

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

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

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

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

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5. Biomarkers are Already a Reality in Health Care

A number of drugs now have biomarker information included in their labels.[25] Biomarker tests are already being used in clinical practice to serve various purposes:

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

Predictive biomarkers (safety) – In clinical practice, predictive safety biomarkers are used to select the proper drug dose or to evaluate the appropriateness of continued therapy in the event of a safety concern. Examples include: i) monitoring of blood potassium levels in patients receiving drospirenone and ethinyl estradiol (Yasmin®) together with daily long-term drug regimens that may increase serum potassium, and ii) prospective *HLA-B*5701* screening to identify those at increased risk for hypersensitivity to abacavir (Ziagen®).

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

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

6. Biomarker Samples from Clinical Trials: An Invaluable Resource

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

7. Informed Consent for Collection & Banking of Biomarker Samples

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

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and regulations for legally-appropriate informed consent vary on national, state, and local levels, but are generally based on internationally recognized pillars of ethical conduct for research on human subjects.[28-31]

Optional vs. Required Subject Participation

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

Consent for Future Research Use

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

Important elements of informed consent for **future use** of samples include, but are not limited to:[39]

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

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

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

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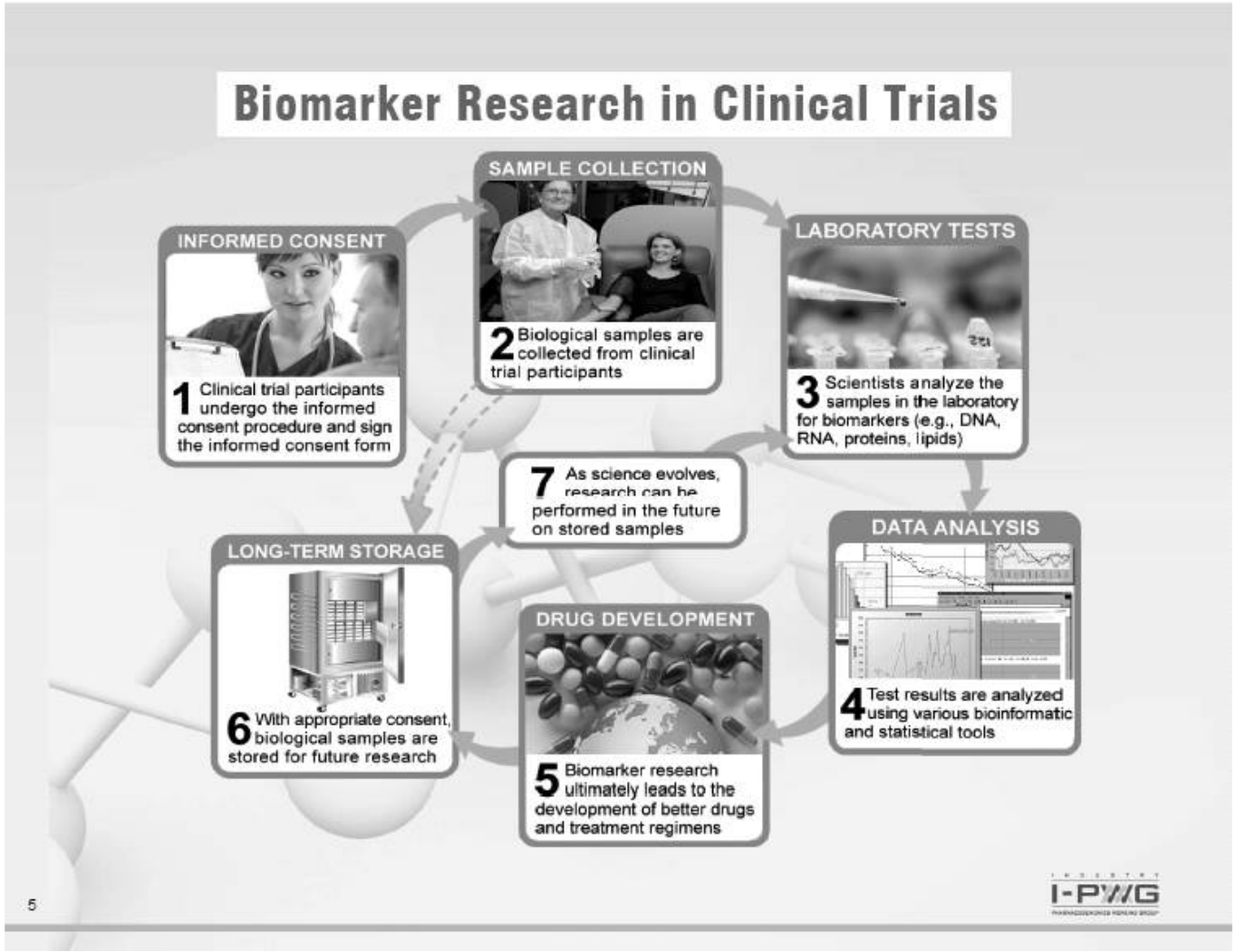
Biomarker Research in Clinical Trials
SAMPLE COLLECTION
2 Biological samples are collected from clinical trial participants
LABORATORY TESTS
3 Scientists analyze the samples in the laboratory for biomarkers (e.g., DNA, RNA, proteins, lipids)
INFORMED CONSENT
1 Clinical trial participants undergo the informed consent procedure and sign the informed consent form
7 As science evolves, research can be performed in the future on stored samples
DATA ANALYSIS
4 Test results are analyzed using various bioinformatic and statistical tools
LONG-TERM STORAGE
6 With appropriate consent, biological samples are stored for future research
DRUG DEVELOPMENT
5 Biomarker research ultimately leads to the development of better drugs and treatment regimens
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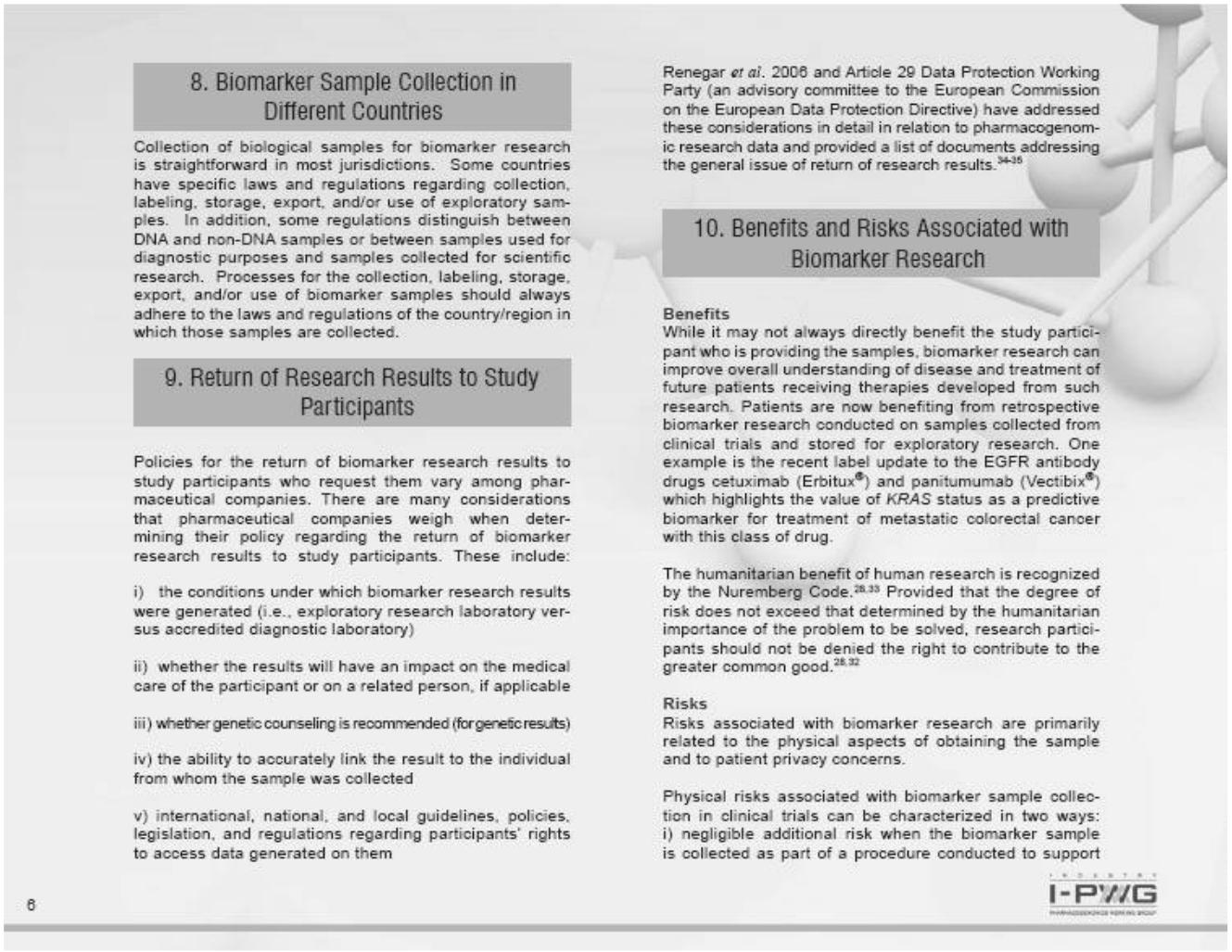

8. Biomarker Sample Collection in Different Countries

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

9. Return of Research Results to Study Participants

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

i) the conditions under which biomarker research results were generated (i.e., exploratory research laboratory versus accredited diagnostic laboratory)

ii) whether the results will have an impact on the medical care of the participant or on a related person, if applicable

iii) whether genetic counseling is recommended (for genetic results)

iv) the ability to accurately link the result to the individual from whom the sample was collected

v) international, national, and local guidelines, policies, legislation, and regulations regarding participants' rights to access data generated on them

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

10. Benefits and Risks Associated with Biomarker Research

Benefits

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

The humanitarian benefit of human research is recognized by the Nuremberg Code.[28,33] Provided that the degree of risk does not exceed that determined by the humanitarian importance of the problem to be solved, research participants should not be denied the right to contribute to the greater common good.[28,32]

Risks

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

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

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

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

11. Privacy, Confidentiality, and Patient Rights

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

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

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

This standard dictates that *"the confidentiality of records that could identify subjects should be protected, respecting the privacy and confidentiality rules in accordance with applicable regulatory requirements."* [31]

Exploratory biomarker research in pharmaceutical development is commonly conducted in research laboratories that are not accredited to perform diagnostic tests used for healthcare decision-making. Therefore, results from exploratory biomarker research usually are not appropriate for use in making decisions about a trial participant's health. In addition, exploratory research data should not be included as part of a participant's medical record accessible for use by insurance companies. Legislation and policies to protect individuals against discrimination based on genetic information continually evolve based on social, ethical, and legal considerations. Examples of such legislation include the Human Tissue Act 2004 (UK) and the Genetic Information Nondiscrimination Act (GINA) 2008 (USA).[36-37]

12.Where to Get More Information?

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

13. What is I-PWG?

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

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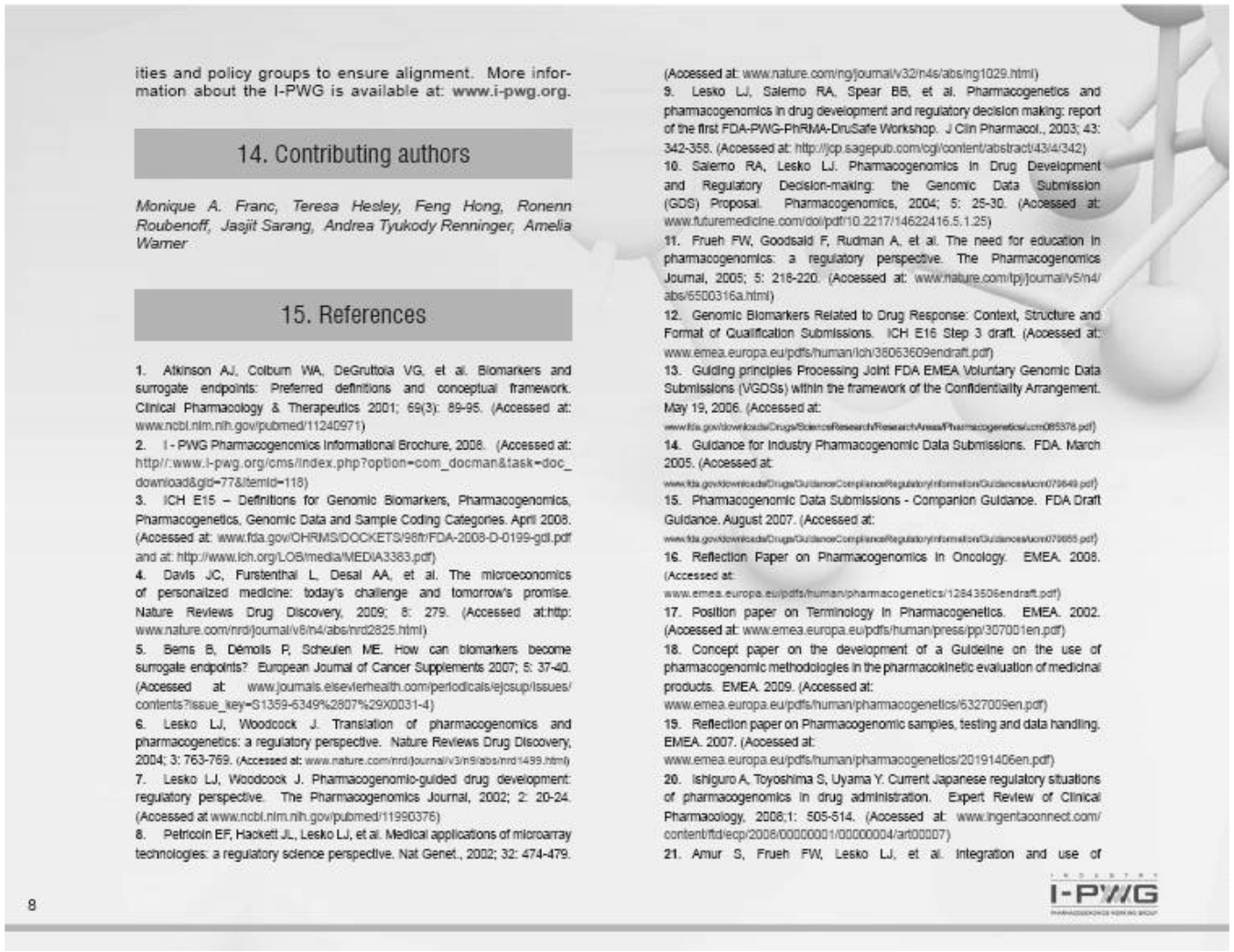

ities and policy groups to ensure alignment. More information about the I-PWG is available at: www.i-pwg.org.

14. Contributing authors

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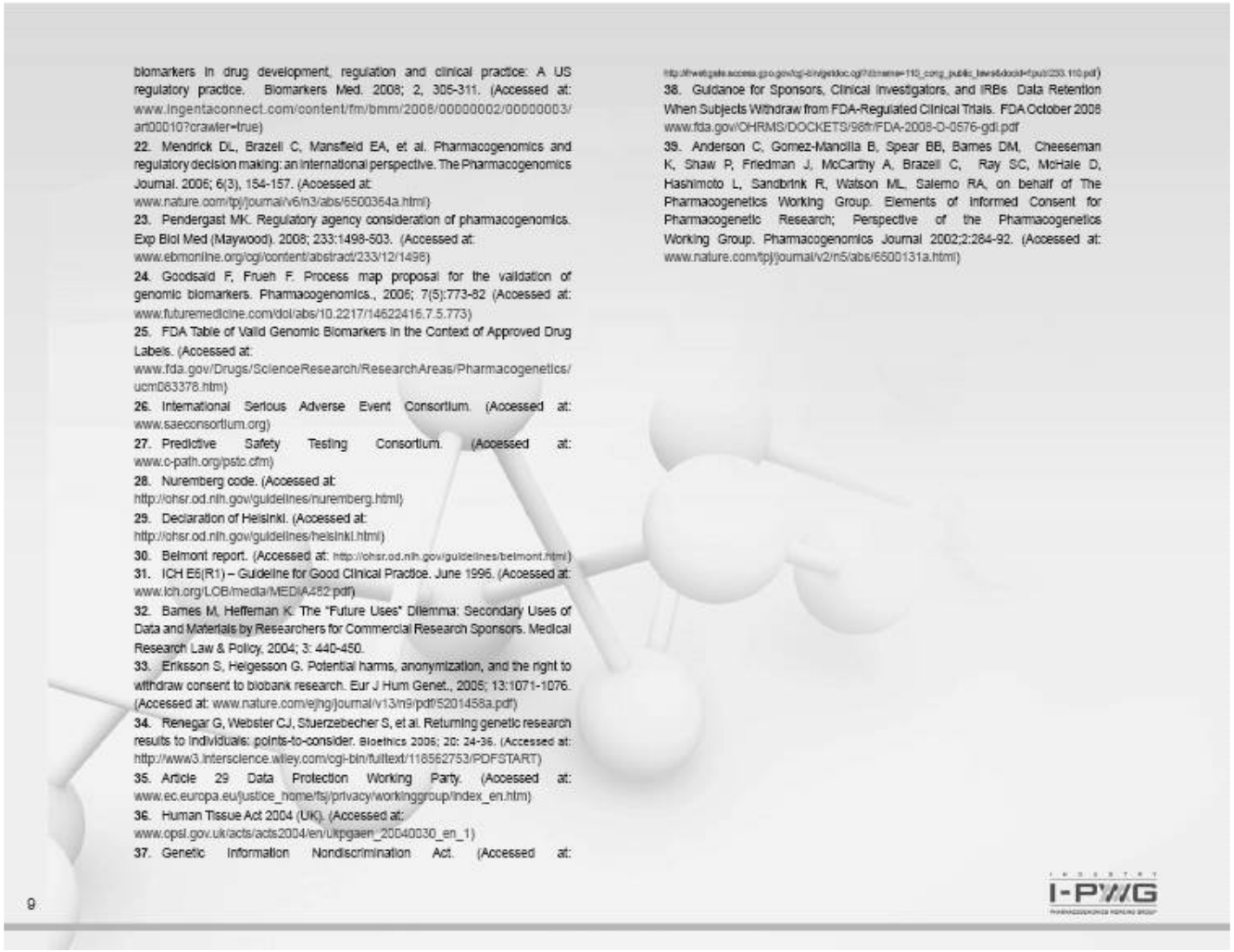

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www.i-pwg.org

12.4 Abbreviations

Abbreviation/Term	Definition
1L	First Line
2L	Second Line
AE	Adverse Event
ADA	Anti-Drug Antibodies
AJCC	American Joint Committee on Cancer
ALK	Anaplastic Lymphoma Kinase
ALT	Alanine Aminotransferase
ANC	Absolute Neutrophil Count
aPTT	Activated Partial Thromboplastin Time
AR	Androgen Receptor
ASCO	American Society of Clinical Oncology
ASaT	All Subjects as Treated
AST	Aspartate Aminotransferase
AUC	Area Under the Concentration-Time Curve
ß-hCG	Beta Human Chorionic Gonadotropin
BCG	Bacillus Calmette–Guérin
BRAF	B-Raf proto-oncogene, serine-threonine kinase
BRCA1	Breast Cancer 1
BRCA2	Breast Cancer 2
CAP	College of American Pathologists
CBC	Complete Blood Count
CD	Cluster of Differentiation
CD8+	Cluster of Differentiation 8–positive
CEP17	centromeric probe for chromosome 17
CI	Confidence Interval
CIV	Central Imaging Vendor
CNS	Central Nervous System
CPS	Combined Positive Score
CR	Complete Response
CrEL	Cremofor EL
CSR	Clinical Study Report
CSR CI	Clinical Study Report Coordinating Investigator
CT	Computed Tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTLA-4	Cytotoxic T-Lymphocyte–Associated Antigen-4
DCR	Disease control rate

Abbreviation/Term	Definition
DIC	Disseminated Intravascular Coagulate
DKA	Diabetic Ketoacidosis
DMC	Data Monitoring Committee
DNA	Deoxyribonucleic acid
DOR	Duration of Response
DRFS	Distant Recurrence-Free Survival
ECI	Events of Clinical Interest
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EGFR	Epidermal Growth Factor Receptor
EOC	Executive Oversight Committee
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 Quality of Life Questionnaire Core 30
ePRO	Electronic Patient Reported Outcomes
EQ-5D™	EuroQol-5 Dimension Questionnaire
ER	Estrogen Receptor
ERC	Ethics Review Committee
EU	European Union
FA	Final Analysis
FBR	Future Biomedical Research
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act
FDAMA	Food and Drug Administration Modernization Act
FFPE	Formalin-Fixed Paraffin Embedded
FGFR	Fibroblast Growth Factor Receptor
FISH	Fluorescence In Situ Hybridization
FNA	Fine Needle Aspiration
FSH	Follicle Stimulating Hormone
GCP	Good Clinical Practice
HBsAg	Hepatitis B surface Antigen
HER2	Human Epidermal Growth Factor Receptor-2
HCV	Hepatitis C Virus
HIV	Human Immunodeficiency Virus
HLA	Human Leukocyte Antigen
HNSCC	Head and Neck Squamous Cell Carcinoma

Abbreviation/Term	Definition
HPV	Human Papillomavirus
HR	Hazard Ratio
HRD	Homologous Recombination Defect
IA(1, 2, 3)	Interim Analysis (Interim Analysis 1, Interim Analysis 2, Interim Analysis 3)
IB	Investigator's Brochure
ICH	International Conference on Harmonization
IDO1	indoleamine 2.3-dioxygenase 1
IEC	Independent Ethics Committee
IFN-γ	Interferon Gamma
Ig	Immunoglobulin
IHC	Immunohistochemistry
IL-10	Interleukin 10
INR	International Normalized Ratio
IRB	Institutional Review Board
irRECIST	Immune-related Response Evaluation Criteria in Solid Tumors
ITIM	Immunoreceptor Tyrosine-based Inhibition Motif
ITSM	Immunoreceptor Tyrosine-based Switch Motif
ITT	Intention-To-Treat
IUD	Intrauterine Device
IV	Intravenous(ly)
IVRS	Interactive Voice Response System
IWRS	Integrated Web Response System
LDH	Lactate Dehydrogenase
LMP	Last Menstrual Period
mAb	Monoclonal Antibody
mBC	Metastatic Breast Cancer
MHC	Major Histocompatibility Complex
mRNA	Messenger Ribonucleic Acid
MRI	Magnetic Resonance Imaging
MSI	Microsatellite Instability
MTD	Maximum Tolerated Dose
mTNBC	Metastatic Triple Negative Breast Cancer
NA or N/A	Not Applicable
NCI	National Cancer Institute
NKC	Natural Killer Cell
NMR	Nuclear Magnetic Resonance
NSAID	Nonsteroidal Anti-inflammatory Drug

Abbreviation/Term	Definition
NSCLC	Non-Small Cell Lung Cancer
ORR	Objective Response Rate
OS	Overall Survival
OTC	Over-the-counter
Protocol CI	Protocol Coordinating Investigator
PD	Progressive Disease
PD-1	Programmed Cell Death 1
PD-L1	Programmed Cell Death Ligand 1
PD-L2	Programmed Cell Death Ligand 2
PFS	Progression-Free Survival
PGR	Progesterone Receptor
PIN	Personal Identification Number
PK	Pharmacokinetic
PKCθ	Protein kinase C-theta
PR	Partial Response
PT	Prothrombin Time
PTEN	Phosphatase and Tensin Homolog
Q2W	Every 2 Weeks
Q3W	Every 3 Weeks
QoL	Quality of Life
R/M	Recurrent or Metastatic
RECIST/RECIST 1.1	Response Evaluation Criteria in Solid Tumors/version 1.1
RMST	Restricted Mean Survival Time
RNA	Ribonucleic Acid
RPSFT	Rank Preserving Structural Failure Time
SABCS	San Antonio Breast Cancer Symposium
SAC	Scientific Advisory Committee
SAE	Serious Adverse Events
SAP	Statistical Analysis Plan
SD	Stable Disease
SFU	Survival Follow-Up
SHP-1	Src Homology Phosphatase 1
SHP-2	Src Homology Phosphatase 2
SIM	Site Imaging Manual
SNP	Single Nucleotide Polymorphism
SOC	Standard of Care
SOP	Standard Operating Procedures
sSAP	Supplemental Statistical Analysis Plan

Abbreviation/Term	Definition
T3	Triiodothyronine
T4	Thyroxine
TB	Bacillus Tuberculosis
TCGA	The Cancer Genome Atlas
TIL	Tumor Infiltrating Lymphocytes
TNBC	Triple Negative Breast Cancer
TSH	Thyroid Stimulating Hormone
TTP	Time to Disease Progression
ULN	Upper Limit of Normal
US	United States
UV	Ultraviolet
V-type	Variable Type
WBC	White Blood Cell
ZAP70	Zeta-Chain-Associated Protein Kinase 70kDa

12.5 ECOG Performance Status

GRADE	ECOG PERFORMANCE STATUS
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all selfcare but unable to carry out any work activities; up and about more than 50% of waking hours
3	Capable of only limited selfcare; confined to bed or chair more than 50% of waking hours
4	Completely disabled; cannot carry on any selfcare; totally confined to bed or chair
5	Dead

Source: 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

12.6 Contraceptive Guidance

12.6.1 Definitions

Women of Childbearing Potential (WOCBP)

A woman is considered fertile following menarche and until becoming postmenopausal unless permanently sterile (see below):

If fertility is unclear (eg, amenorrhea in adolescents or athletes) and a menstrual cycle cannot be confirmed before first dose of study intervention, additional evaluation should be considered.

Women in the following categories are not considered WOCBP:

- Premenarchal
- Premenopausal female with 1 of the following:
  - Documented hysterectomy
  - Documented bilateral salpingectomy
  - Documented bilateral oophorectomy

For individuals with permanent infertility due to an alternate medical cause other than the above (eg, Mullerian agenesis, androgen insensitivity), investigator discretion should be applied to determining study entry.

Note: Documentation can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.

- Postmenopausal female
  - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.
  - A high FSH level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or HRT. However, in the absence of 12 months of amenorrhea, confirmation with two FSH measurements in the postmenopausal range is required.
  - Females on HRT and whose menopausal status is in doubt will be required to use one of the non-hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

12.6.2 Contraception Requirements

Contraceptives allowed during the study include[a]:
Highly Effective Contraceptive Methods That Have Low User Dependency *Failure rate of <1% per year when used consistently and correctly.*
Progestogen-only subdermal contraceptive implant[b,c] IUS[c] Non-hormonal IUD Bilateral tubal occlusion
Azoospermic partner (vasectomized or secondary to medical cause) This is a highly effective contraception method provided that the partner is the sole male sexual partner of the WOCBP and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used. A spermatogenesis cycle is approximately 90 days. Note: Documentation of azoospermia for a male participant can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview.
Sexual Abstinence Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study intervention. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.
a Contraceptive use by men or women should be consistent with local regulations regarding the use of contraceptive methods for participants of clinical studies. b If locally required, in accordance with CTFG guidelines, acceptable contraceptive implants are limited to those which inhibit ovulation. c IUS is a progestin releasing IUD. Note: The following are not acceptable methods of contraception: - Periodic abstinence (calendar, symptothermal, post-ovulation methods), withdrawal (coitus interruptus), spermicides only, and LAM. - Male condom with cap, diaphragm, or sponge with spermicide. - Male and female condom should not be used together (due to risk of failure with friction).

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	