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SUMMARY OF CHANGES

PRIMARY REASON(S) FOR THIS AMENDMENT:

Section Number (s)	Section Title(s)	Description of Change (s)	Rationale
3.0 8.0	Objective(s) & Hypothesis(es) Statistical Analysis Plan	Revised objectives, hypotheses, and statistical analysis plan to include subjects with PD-L1 positive tumors with a higher combined positive score (CPS) cutoff of ≥10 (CPS ≥10)	Data from other indications of pembrolizumab monotherapy in the second-line setting demonstrate an enriched treatment effect with increasing PD-L1 level. The cutoff of CPS ≥10 has been included to identify an enriched population of patients that could potentially benefit more from pembrolizumab monotherapy as second- or third-line in metastatic triple negative breast cancer.
8.1 8.8	Statistical Analysis Plan Summary Multiplicity	Updated multiplicity strategy of the analyses.	The updated multiplicity strategy reflects the updated primary and secondary hypotheses and rationales. Initial alpha is split between OS endpoints in subjects with CPS ≥10 and CPS ≥1 to ensure maximum power to identify an enriched population of patients that could potentially benefit more from pembrolizumab monotherapy as second- or third-line in metastatic triple negative breast cancer. The OS in all subjects hypothesis can be tested if OS in subjects with CPS ≥1 is successful.

Section Number (s)	Section Title(s)	Description of Change (s)	Rationale
8.1 8.7 8.9	Statistical Analysis Plan Summary Interim Analyses Sample Size and Power Calculations	Updated the following: timing of the interim/final analysis; the target events for final analysis, and sample size and power calculations.	These changes were made to be consistent with the addition of primary OS endpoint in subjects with CPS ≥10 and the updated multiplicity strategy. The updated timing and planned number of events at IA and FA were driven by the updated power / success HR boundary calculation based on the updated multiplicity strategy to ensure adequate power of each primary endpoint at the time of each analysis. The study now has only one interim analysis as at the time of IA the information fraction is expected to be approximately 85% and adding another IA will be little value added. For power calculation, the true hazard ratio assumptions were updated based on recent data observed from other indications of pembrolizumab monotherapy in the second-line setting. The enrollment duration and drop-out rate assumptions were updated based on recent available information.

ADDITIONAL CHANGE(S) FOR THIS AMENDMENT:

Section Number (s)	Section Title(s)	Description of Change (s)	Rationale
4.2.1	Rationale for the Trial and Selected Subject Population	Rationale was added for the inclusion of CPS ≥10.	Data from other indications of pembrolizumab monotherapy in the second-line setting demonstrate an enriched treatment effect with increasing PD-L1 level. The cutoff of CPS ≥10 has been included to identify an enriched population of patients with metastatic triple negative breast cancer that could potentially benefit more from pembrolizumab monotherapy.
6.1.1 7.1.3.3 8.0	Trial Flow Chart – Pembrolizumab Monotherapy Pharmacokinetic/Pharmacodynamic Evaluations Statistical Analysis Plan	Sampling for pembrolizumab PK and anti-drug antibodies (ADA) has been removed. Clarified that PK analysis will be performed only if required.	Based on feedback from regulatory agencies, sufficient PK/ADA data has been collected for pembrolizumab and samples are no longer needed.
8.1	Statistical Analysis Plan Summary	Corrected that the unstratified Miettinen and Nurminen method will be used for safety analysis.	To be consistent with Section 8.6.2.
8.2	Responsibility for Analysis/In-House Blinding	The interim efficacy to be provided by the external unblinded statistician to eDMC is not restricted to OS and PFS.	Updated language to be consistent with the updated hypotheses (addition of ORR hypothesis).

Section Number (s)	Section Title(s)	Description of Change (s)	Rationale
8.2	Responsibility for Analysis/In-House Blinding	The external unblinded statistician will not be monitoring OS events in subjects with PD-L1 positive tumors to inform the analysis timing. Instead, the unblinded Sponsor biomarker statistician will have this responsibility.	To allow monitoring of number of OS events to ensure timely analysis.
8.4.1 8.6.1.2	Efficacy Endpoints Progression-Free Survival	Updated the censoring rules for primary and sensitivity analyses of PFS.	Recent changes in the therapeutic standard PFS censoring rules; the primary analysis closely follows FDA guidance, and the first sensitivity analysis closely follows the "intent-to-treat (ITT) complete follow-up principle".
8.4.1 8.6.1.4	Efficacy Endpoints Duration of Response	Updated the censoring rules for primary and sensitivity analyses of DOR.	To be aligned with the updated censoring rule for PFS.
8.4.1	Efficacy Endpoints	Clarified the PFS, ORR, DOR and DCR endpoints based on irRECSIT by Investigator review may be performed as supportive analysis as needed.	Clarification.
8.6.2	Statistical Methods for Safety Analyses	Updated that safety analysis will be performed in all subjects only.	It is expected that the safety profile for subjects with PD-L1 positive tumors is similar as that in all subjects. As such, safety analysis in all subjects provides most information.

Section Number (s)	Section Title(s)	Description of Change (s)	Rationale
8.10 4.2.3.4	Subgroup Analyses and Effect of Baseline Factors Planned Exploratory Biomarker Research.	Removed BRCA1/2 status, homologous recombination defect score, and microsatellite stability status as categories for the subgroup analysis. Instead, these analyses may be performed as separate exploratory biomarker analyses.	These may be evaluated as exploratory analyses to correlate efficacy/resistance biomarkers with response to pembrolizumab. Allows flexibility for effective use of collected tumor samples depending on emerging data regarding the effect of these biomarkers in the TNBC population.
8.10	Subgroup Analyses and Effect of Baseline Factors	Updated subgroup categorization for Age and PD-L1 status.	To be aligned with the current guidance for age category and updated PD-L1 cutoff.
Global	Global	Corrections to minor typographical or formatting errors have been incorporated.	

1.0 TRIAL SUMMARY

Abbreviated Title	A Randomized Open-Label Phase III Study of Single Agent Pembrolizumab versus Single Agent Chemotherapy per Physician's Choice for Metastatic Triple Negative Breast Cancer (mTNBC) – (KEYNOTE 119)
Trial Phase	III
Clinical Indication	Metastatic (Stage IV/M1) Triple Negative Breast Cancer
Trial Type	Interventional
Type of control	Active Control
Route of administration	Intravenous or oral
Trial Blinding	Unblinded Open-label
Treatment Groups	Pembrolizumab: 200 mg intravenously (IV) Q3W Medications used as treatments of physician's choice (TPC) will be handled according to local regulations and guidelines in participating countries. Sites may choose any ONE drug from the following: Capecitabine Eribulin Gemcitabine Vinorelbine
Number of trial subjects	Approximately 600 subjects will be enrolled.
Estimated duration of trial	The sponsor estimates that the trial will require approximately 40 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 trial from the time he/she signs the Informed Consent Form (ICF) until withdrawing consent, becoming lost-to-follow-up, death, or end of study. After the screening phase, eligible subjects will be stratified according to 2 stratification factors [PD-L1 tumor status (positive [combined positive score ≥1] vs negative [combined positive score <1]), and history of prior (neo) adjuvant therapy vs. de novo metastatic disease at initial diagnosis], and then randomized 1:1 to single agent pembrolizumab or single agent chemotherapy per physician's choice. Study treatment will continue until disease progression (verified by blinded central imaging vendor, unless subject is then managed by immune-related response evaluation criteria in solid tumors [irRECIST]), unacceptable adverse event(s), intercurrent illness that prevents further administration of study treatment, Investigator's decision to withdraw the subject from study treatment, pregnancy of the subject, noncompliance with study treatment or procedure requirements, 35 treatments have been completed (pembrolizumab arm only), consent withdrawal, becoming lost-to-follow-up, death or for administrative reasons requiring cessation of treatment. After discontinuation of study treatment, each subject will be followed for 30 days for adverse event (AE) and events of clinical interest (ECI) monitoring. Serious adverse events (SAEs) will be collected for 90 days after the end of study treatment. Subjects who discontinue study treatment for reasons other than disease progression will have post-treatment follow-up for disease status until disease progression (verified by blinded central imaging vendor), start of a non-study anticancer

	treatment, consent withdrawal, becoming lost to follow-up, death or end of the study. All subjects will be followed by telephone for overall survival until consent withdrawal, becoming lost to follow-up, death or end of the study. Subjects who stop pembrolizumab after achieving a CR and subjects who, after receiving 35 cycles, stop pembrolizumab for reasons other than disease progression or intolerability may be eligible for up to one year of retreatment with pembrolizumab upon experiencing disease progression. The decision to retreat with pembrolizumab will be at the discretion of the Investigator, only if subjects meet the criteria for retreatment and the trial is ongoing. Subjects may be transitioned to an extension study if/when an extension study becomes available.
Randomization Ratio	1:1

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

2.0 TRIAL DESIGN

2.1 Trial Design

This is a randomized, open-label, active-controlled, multicenter, international Phase III trial of single agent pembrolizumab versus single agent chemotherapy per physician's choice (Treatment of Physician's Choice, TPC) for subjects receiving second line (2L) or third line (3L) treatment for metastatic triple negative breast cancer (mTNBC). The study will be conducted in conformance with Good Clinical Practices (GCPs).

Subjects must have centrally confirmed mTNBC, have received either one or two prior systemic treatments for metastatic breast cancer, and have documented disease progression on or after the most recent therapy. Subjects must have been previously treated with an anthracycline and/or a taxane in the (neo)adjuvant or metastatic setting.

All subjects in this study will be required to provide fresh newly obtained core or excisional biopsy from a metastatic, not previously irradiated, tumor lesion to be evaluated at a central laboratory for 1) triple-negative breast cancer status by determination of estrogen receptor (ER), progesterone receptor and human epidermal growth factor receptor-2 (HER2) expression, and 2) programmed death-ligand 1 (PD-L1) expression by immunohistochemistry (IHC). Samples will be sent to a central laboratory for real time evaluation to ensure adequate tumor tissue is present and eligibility requirements are fulfilled.

After the screening phase, eligible subjects will be first stratified according to 2 stratification factors [PD-L1 tumor status (positive [combined positive score (CPS) ≥1] vs. negative [CPS <1]), and history of prior (neo)adjuvant treatment vs. *de novo* metastatic disease at initial diagnosis]. Subjects will then be randomized 1:1 to receive single agent pembrolizumab 200 mg IV once every 3 weeks (Q3W) or single agent chemotherapy per physician's choice (TPC): capecitabine, eribulin, gemcitabine, **or** vinorelbine. For the TPC arm, there is a maximum enrollment cap of 60% of total enrollment for each chemotherapy

drug. The TPC dosing and frequency will be handled according to local regulations and guidelines in participating countries.

Study treatment will continue until disease progression (verified by blinded central imaging vendor unless subject is then managed by irRECIST), unacceptable adverse event(s) (AE[s]), intercurrent illness that prevents further administration of study treatment, Investigator's decision to withdraw the subject from study treatment, pregnancy of the subject, noncompliance with study treatment or procedure requirements, 35 treatments have been completed (pembrolizumab arm only), consent withdrawal, becoming lost-to-follow-up, death or for administrative reasons requiring cessation of treatment.

After discontinuation of study treatment, each subject will be followed for 30 days for AE and events of clinical interest (ECIs). Serious AEs (SAEs) will be collected for 90 days after the end of study treatment.

Subjects who discontinue study treatment for reasons other than disease progression will have post-treatment follow-up for disease status every 3 cycles (± 7 days) until disease progression (verified by blinded central imaging vendor), start of a non-study anticancer treatment, consent withdrawal, becoming lost to follow-up, death or end of the study.

All subjects will be followed by telephone every 4 cycles (± 7 days) for overall survival (OS) until consent withdrawal, becoming lost to follow-up, death or end of the study.

Subjects may have the opportunity to transition to a pembrolizumab extension study if available in the future after closure of this study.

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.

In this trial, pembrolizumab will be compared to TPC as 2L or 3L monotherapy in subjects with centrally confirmed mTNBC. The study objectives are defined in in Section 3.0.

A multiplicity approach will be followed as described in Section 8.0. The size of this trial is ~600 subjects. The OS events required in subjects with PD-L1 positive tumors (CPS ≥1 and CPS ≥10) was estimated based on the estimation of the prevalence of PD-L1 positive tumors with CPS ≥1 (65%) and CPS ≥10 (31%). The prevalence of PD-L1 positivity (CPS ≥1) in mTNBC was ~55% in the proof-of-principle study KN012 (Section 4.2).

One interim efficacy analysis is planned in this study (Section 8.7). The interim efficacy analysis is to assess efficacy based on OS in subjects with PD-L1 positive tumors (CPS ≥10 and CPS ≥1) and in all subjects.

2.2 Trial Diagram

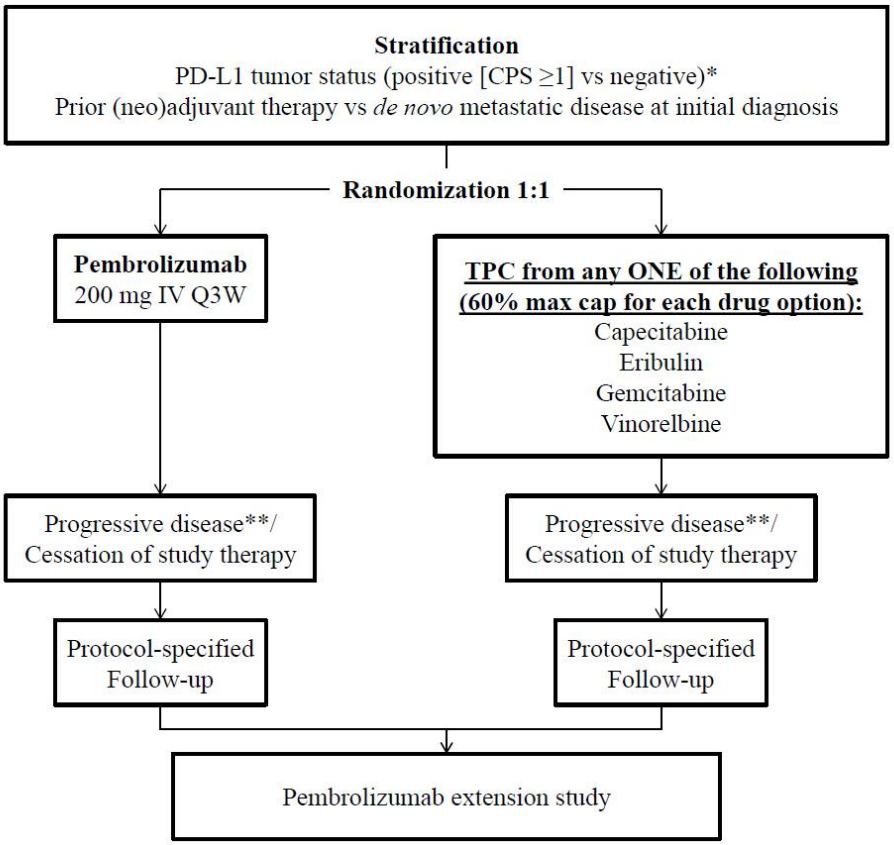


Figure 1 Trial Design

Abbreviations: CPS = combined positive score; irRECIST = immune-related Response Evaluation Criteria in Solid Tumors; IV = intravenous; PD-L1 = programmed cell death ligand 1; Q3W = every 3 weeks; TPC = chemotherapy per physician's choice.

* In the event that treatment with pembrolizumab is found to be futile in subjects with PD-L1 negative tumors, stratification for PD-L1 status will be abandoned.

** Treatment may be continued beyond verified 1st radiologic evidence of disease progression according to irRECIST criteria.

3.0 OBJECTIVE(S) & HYPOTHESIS(ES)

3.1 Primary Objective(s) & Hypothesis(es)

Pembrolizumab will be compared to TPC as 2L or 3L monotherapy in subjects with centrally confirmed mTNBC:

PD-L1 Positive Populations: subjects with PD-L1 positive expression defined by ≥10 Combined Positive Score (CPS) and by ≥1 CPS; henceforth abbreviated as CPS ≥10 and CPS ≥1 respectively.

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

Hypothesis (H1): Pembrolizumab prolongs OS compared to TPC in subjects with PD-L1 positive tumors (CPS ≥10).

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

Hypothesis (H2): Pembrolizumab prolongs OS compared to TPC in subjects with PD-L1 positive tumors (CPS ≥1).

(3) **Objective:** To compare OS in all subjects.

Hypothesis (H3): Pembrolizumab prolongs OS compared to TPC in all subjects.

The study is considered to have met its primary objective if pembrolizumab is superior to TPC in OS in either subjects with PD-L1 positive tumors (CPS ≥10 [H1] or CPS ≥1 [H2]) or in all subjects (H3), at either the interim analysis or the final analysis.

3.2 Secondary Objective(s) & Hypothesis(es)

Pembrolizumab will be compared to TPC as 2L or 3L monotherapy in subjects with centrally confirmed mTNBC:

(1) **Objective:** To compare progression-free survival (PFS) based on RECIST 1.1 as assessed by blinded central imaging vendor in all subjects.

Hypothesis (H4): Pembrolizumab prolongs PFS based on RECIST 1.1 as assessed by blinded central imaging vendor compared to TPC in all subjects.

(2) **Objective:** To compare overall response rate (ORR) per RECIST 1.1 by blinded central imaging vendor in all subjects.

Hypothesis (H5): Pembrolizumab increases ORR per RECIST 1.1 by blinded central imaging vendor compared to TPC in all subjects.

(3) **Objective:** To evaluate PFS and ORR based on RECIST 1.1 as assessed by blinded central imaging vendor in subjects with PD-L1 positive tumors (CPS ≥10 and CPS ≥1).

(4) **Objective:** To evaluate duration of response (DOR), and disease control rate (DCR) based on RECIST 1.1 as assessed by blinded central imaging vendor in subjects with PD-L1 positive tumors (CPS ≥10 and CPS ≥1) and in all subjects.

(5) **Objective:** To determine the safety and tolerability of pembrolizumab.

The secondary hypotheses regarding PFS in all subjects (H4) and ORR in all subjects (H5) can only be formally tested once the null hypothesis regarding the primary endpoint OS in all subjects (H3) has been rejected..

3.3 Exploratory Objectives

Pembrolizumab will be compared to TPC as 2L or 3L monotherapy in subjects with centrally confirmed mTNBC:

(1) **Objective:** To evaluate PFS, ORR, DOR, and DCR based on irRECIST as assessed by blinded central imaging review in subjects with PD-L1 positive tumors (CPS ≥10 and CPS≥1) and all subjects.

(2) **Objective:** To evaluate changes in health-related quality-of-life assessments from baseline in subjects with PD-L1 positive tumors (CPS ≥10 and CPS ≥1) and all subjects using the European Organisation for Research and Treatment of Cancer (EORTC) QLQ-C30 and QLQ-BR23.

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

(4) **Objective:** To investigate the association between antitumor activity of pembrolizumab in mTNBC and efficacy/resistance biomarkers, utilizing tumor and blood specimens obtained before/during treatment and at disease progression.

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

4.0 BACKGROUND & RATIONALE

4.1 Background

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

4.1.1 Pharmaceutical and Therapeutic Background

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 [2-14]. In particular, the presence of 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 [10, 15-21].

The PD-1 receptor-ligand interaction is a major pathway hijacked by tumors to suppress immune control [22]. The normal function of PD-1, which is 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 a member of the Ig superfamily 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 PD-L2). The structures of murine PD-1 alone [23] and in complex with its ligands were first resolved [24, 25]. More recently the 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 important for ligand binding and a cytoplasmic tail which is responsible for the activation of downstream signaling molecules. The cytoplasmic tail of PD-1 contains 2 tyrosine-based signaling motifs, an immunoreceptor tyrosine-based inhibition motif (ITIM) and an immunoreceptor tyrosine-based switch motif (ITSM). Following T cell stimulation, PD-1 recruits the tyrosine phosphatases SHP-1 and SHP-2 to the ITSM motif within its cytoplasmic tail, leading to the dephosphorylation of effector molecules, such as CD3ζ, PKCθ and ZAP70, which are involved in the CD3 T cell signaling cascade [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 [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 non-hematopoietic tissues, most notably on vascular endothelium, whereas PD-L2 protein is only detectably expressed on antigen-presenting cells found in lymphoid tissue or chronic inflammatory environments [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].

4.1.2 Immunotherapy: Preclinical 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 [38-40]. Anti-mouse PD-1 or anti-mouse PD-L1 antibodies have demonstrated antitumor responses in models of squamous cell carcinoma, pancreatic carcinoma, melanoma, acute myeloid leukemia and colorectal carcinoma [41-45]. In such studies, tumor infiltration by CD8+ T-cells and increased IFN-γ, granzyme B and perforin expression were observed, indicating that the mechanism underlying the antitumor activity of PD-1 checkpoint inhibition involved local infiltration and activation of effector T cell function *in vivo* [42]. 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).

4.1.3 Pembrolizumab: Ongoing Clinical Trials in Other Tumor Types

Pembrolizumab – Clinical trials. 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 recently approved in the US for the treatment of advanced, unresectable or metastatic malignant melanoma, and for use in melanoma subjects with disease progression after prior treatment with (a) ipilimumab or (b) a BRAF inhibitor, in the case of BRAF V600-mutant disease [46]. It is the first anti-PD-1 therapy to receive regulatory approval in the US, and is currently under regulatory review in the EU. Ongoing clinical trials of pembrolizumab are being conducted in advanced melanoma, non-small cell lung cancer, and a number of other advanced solid tumor indications and hematologic malignancies. For study details please refer to the IB.

4.1.4 Information on Disease to be Treated – mTNBC

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 were expected in women in the United States in 2014 [47]. Triple-negative breast cancer (TNBC) is phenotypically defined by a lack of estrogen receptor (ER) and progesterone receptor expression and the absence of human epidermal growth factor receptor-2 (HER2) overexpression and/or amplification [48].

TNBC represents 15-20% of all breast cancers [49] and is overlapping, but not synonymous, with the basal-like subtype defined by gene expression, as about 70% of TNBCs have basal-like characteristics [50, 51].

TNBC is a molecularly heterogeneous disease and includes tumor subsets with different prognosis. For example, the claudin-low subtype, which is characterized by low expression of claudin genes and often presents with stem cell features and epithelial-to-mesenchymal transition (EMT), is associated with poor prognosis [52]. Recent gene expression profiling has identified up to six distinct TNBC subtypes (two basal-like, an immunomodulatory, a mesenchymal, a mesenchymal stem-like and a luminal androgen receptor subtype) [53].

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 [49]. 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 1-3 years after initial diagnosis, and decreases significantly thereafter; subjects with TNBC also have shorter OS compared to subjects with non-TNBC (4.2 versus 6.0 years) [48]. 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 [54].

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) [55]. 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 OS of all (at any line of therapy) subjects with mTNBC was 13.3 months; median duration of first line (1L) therapy for mTNBC was 11.9 weeks; 80% of subjects received second line (2L) therapy with a median duration of 9 weeks, and about 50% received third line (3L) therapy with a median duration of 4 weeks [56].

Immune checkpoint inhibition for the treatment of TNBC. Several studies have demonstrated that presence of TILs has prognostic significance 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 [57, 58]. In addition, unsupervised gene expression profiling of TNBCs has identified a gene signature enriched for cytotoxic CD8+ T cell genes and natural killer cell (NKC) activity, which is predictive of good clinical outcomes [59]. 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 [60].

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 (HR)-negative and high grade, proliferative tumors [61]. 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 [62]. 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 expression of the proliferation marker Ki-67 [63]. A recent publication reported that PD-L1 messenger ribonucleic acid (mRNA) is expressed in nearly 60% of breast tumors, independently of HR status, and is positively correlated with PD-L1 protein expression and increased TILs [64]. Another study mining the Cancer Genome Atlas (TCGA) RNA sequencing data showed that PD-L1 gene expression is significantly higher in TNBCs compared to non-TNBCs, and is associated with Phosphatase and Tensin Homolog (PTEN) loss; in the same study, PD-L1 was found expressed in 20% of TNBCs [65]. 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 androgen receptor (AR)-negative and BRCA1-mutant TNBC [104]. 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.

4.1.5 Proof-of-Principle Study for Pembrolizumab use in mTNBC

KN-012 - Clinical data supporting pembrolizumab use for the treatment of mTNBC. In the first report of clinical activity of an immune checkpoint inhibitor in TNBC, a Merck-sponsored multi-center, non-randomized Phase Ib trial (KN-012) showed that single agent pembrolizumab given at 10 mg/kg IV Q2W is a well-tolerated and effective treatment with significant therapeutic activity in a subset of heavily pre-treated subjects with mTNBC.

Methods: PD-L1 expression in ≥1% tumor cells or in stroma (ie, PD-L1 positive mTNBC) was required for study entry. PD-L1 tumor status was determined by immunohistochemical analysis of archival tumor specimens using the Merck proprietary 22C3 antibody (Qualtek assay). Primary objectives of this study were to determine the safety, tolerability, and antitumor activity of pembrolizumab in subjects with PD-L1 positive mTNBC. Secondary objectives included assessments of PFS, OS, and DOR. Adverse events (AEs) reported in any subject receiving at least 1 dose of study treatment were monitored and graded using National Cancer Institute Common Terminology Criteria for Adverse Events version 4.0 (National Cancer Institute [NCI] CTCAE v. 4.0). Tumor imaging was obtained every 8 weeks and evaluated by both Investigator and a central imaging vendor to assess clinical responses as defined by RECIST 1.1.

Results: A total of 32 female subjects with a median age of 50.5 years (range 29-72 years) and PD-L1 positive mTNBC were enrolled in the study (the prevalence of PD-L1 tumor

positivity in mTNBC was 58%, as determined by the Qualtek assay). Most of these subjects had received and progressed on multiple lines of therapy for advanced disease (47% of subjects had received ≥ 3 prior treatments in the metastatic setting). According to data through 06-Nov-2014, five subjects (15.6%) experienced at least one drug-related SAE; each of four subjects experienced one of the following: Grade 3 anemia, headache, aseptic meningitis or pyrexia, and a fifth subject experienced Grade 5 disseminated intravascular coagulation (DIC) with thrombocytopenia and decreased blood fibrinogen. Of the 27 subjects with centrally confirmed measurable disease, one subject (3.7%) had a complete response (CR), 4 subjects (14.8%) had a confirmed partial response (PR), 25.9% had stable disease (SD), and 44.4% had progressive disease (PD) based on RECIST 1.1 as assessed by central imaging vendor. As of 06-Nov-2014, the median duration of response had not been reached (range 15 to 40+ weeks), and three subjects (1 CR; 2 PR) were still on treatment after at least 11 months.

Conclusions: This is the first report of clinical activity of an immune checkpoint inhibitor in TNBC. The preliminary results from this study suggest that single agent MK-3475 is a well-tolerated and effective treatment with significant therapeutic activity in a subset of heavily pre-treated subjects with recurrent/metastatic triple-negative breast cancer.

4.2 Rationale

4.2.1 Rationale for the Trial and Selected Subject Population

KN-119: Rationale for using pembrolizumab as 2-3L monotherapy for mTNBC. Subjects with TNBC whose disease has progressed on at least one systemic treatment for mTNBC have a dismal prognosis with a PFS of 2-3 months and OS of 9-12 months [66-71]. Nearly all have been previously treated with anthracyclines(s) and taxane(s), and will receive single agent chemotherapy as a 2L+ regimen [72]. As there is no established standard of care (SOC) for mTNBC, any drug approved for the treatment of metastatic breast cancer, such as capecitabine, eribulin, gemcitabine, or vinorelbine, may be used. To date, no mTNBC-focused clinical trial has evaluated the efficacy of any of the above mentioned agents; historical data comes from pre-specified (1 study) and, more commonly, retrospective TNBC subgroup analysis of randomized Phase III studies in metastatic breast cancer (MBC; all subtypes or excluding HER2-positive disease) (Table 1). In a retrospective TNBC subgroup analysis of the randomized Phase III RIBBON-2 trial, which investigated the combination of bevacizumab with chemotherapy for MBC [73], single agent taxane, gemcitabine, capecitabine, or vinorelbine as 2L monotherapy for mTNBC resulted in an ORR of 18%, PFS of 2.7 months, and OS of 12.6 months [74] In the Phase III study comparing the combination of capecitabine and ixabepilone to single agent capecitabine as 2L+ treatment for MBC, capecitabine showed an ORR of 9%, PFS of 2.1 months, and OS of 9 months in mTNBC, according to a pre-specified subgroup analysis [76]. In the EMBRACE Phase III open-label, randomized study comparing eribulin to TPC (TPC, including single agent taxane, gemcitabine, capecitabine, and vinorelbine among others) as 3L+ therapy for MBC, eribulin showed an ORR of 12%, PFS of 3.7 months, and OS of 13.1 months compared to ORR of 5%, PFS of 2.1 months, and OS of 10.6 months (HR 0.81; $P = 0.041$) for TPC in all subjects independent of breast cancer subtype [75]; however, efficacies of eribulin and TPC in mTNBC were not reported. According to a pooled retrospective

subgroup analysis of EMBRACE and study #301 (eribulin vs capecitabine as 1-3L monotherapy for MBC), eribulin extended OS compared to TPC in subjects receiving 1-3L+ treatment for mTNBC, as it showed a OS of 12.4 months compared to 8.2 months for TPC (HR 0.74; $P = 0.006$) [95]; PFS was also longer for eribulin (2.8 months) compared to TPC (2.6 months), but the difference was small and not clinically significant, despite reaching statistical significance (HR 0.78; $P = 0.018$).

Table 1 Efficacy of Currently Used 2L+ Monotherapy Regimens in mTNBC

Study	Line Tx	Drug/Drug combo	ORR%/PFSmo/OSmo	Reference
RIBBON-2 Phase III study-Retrospective TNBC subgroup analysis	2L	Taxane or capecitabine or gemcitabine or vinorelbine	18/2.7/12.6	[74]
Phase III study-prespecified TNBC subgroup analysis	2L+	Capecitabine	9/2.1/9	[76]
EMBRACE and #301 Phase III studies-Retrospective TNBC subgroup analysis	1-3L+	Eribulin	NR/2.8/12.4	[95]
		TPC (taxane, capecitabine, gemcitabine, vinorelbine, etc.)	NR/2.6/8.2	

Given (1) the poor outcome of subjects with advanced mTNBC, (2) the lack of TNBC-specific standard of care for the treatment of mTNBC, (3) the paucity of published results from Phase III clinical trials prospectively enrolling mTNBC subjects, and (4) the promising antitumor and safety profile of pembrolizumab in heavily pretreated mTNBC as demonstrated by the proof-of-concept KN-012 study, which showed an ORR of 18.5% and response durability, potential use of pembrolizumab as a 2-3L monotherapy for mTNBC will be further investigated in a large randomized open-label Phase 3 study (KN-119) comparing single agent pembrolizumab to TPC monotherapy.

KN-119: Rationale for choice of anticancer drugs in the comparator arm. At present there are no drugs specifically approved or considered SOC for the treatment of mTNBC. Instead, drugs approved for metastatic breast cancer are also used for mTNBC. The Treatment of Physician's Choice (TPC) is based on common usage of these drugs for metastatic breast cancer, prior inclusion of these drugs as TPC in Phase III studies for metastatic breast cancer, and input from scientific leaders.

The EMBRACE study, a pivotal study leading to the approval of eribulin for metastatic breast cancer, did not restrict the number of drugs that could be used as TPC in the comparator arm. However, one of the criticisms of the EMBRACE study design was that allowing several different chemotherapies, each with their own toxicity profile, precluded detailed comparisons with eribulin [75]. KN-119 aims to restrict the TPC to four frequently used chemotherapies, namely capecitabine, eribulin, gemcitabine, or vinorelbine, based on geographical, institutional and physician's preference in order to perform a more detailed comparison with pembrolizumab. The anticancer drugs included as TPC will be handled

according to local regulations and guidelines in participating countries. Furthermore, if a TPC is not approved in a particular country, this particular agent cannot be used and selected via interactive voice response system (IVRS) during randomization.

Capecitabine has a registered indication for the treatment of subjects with metastatic breast cancer resistant to both paclitaxel and an anthracycline-containing chemotherapy regimen or resistant to paclitaxel and for whom further anthracycline therapy is not indicated. Resistance is defined as progressive disease while on treatment, with or without an initial response, or relapse within 6 months of completing treatment with an anthracycline-containing adjuvant regimen.

Eribulin has a registered indication for usage as a single agent in the treatment of metastatic breast cancer subjects who have previously received at least one (in EU) or two (in US) chemotherapeutic regimens for the treatment of metastatic disease. Prior therapy must also have included anthracycline and a taxane in either the adjuvant or metastatic setting.

Gemcitabine has a registered indication in combination with paclitaxel for first line treatment of metastatic breast cancer after failure of prior anthracyline-containing adjuvant chemotherapy unless anthracyclines were clinically contraindicated.

Vinorelbine has a registered indication in the US for usage as a single agent or in combination with cisplatin for first line treatment of subjects with unresectable, advanced non-small cell lung cancer (NSCLC). Although not formally approved in the US for the treatment of metastatic breast cancer, vinorelbine is included in the NCCN breast cancer treatment guidelines and is commonly used as 2L+ monotherapy. In most European countries, vinorelbine is approved for metastatic breast cancer treatment.

Rationale for including subjects with PD-L1 negative tumors. The KN-012 TNBC proof-of-concept data was obtained in subjects with PD-L1 positive tumors (ie, PD-L1 staining in ≥1% tumor cells or in stroma); no data is currently available on the performance of pembrolizumab in TNBC subjects with PD-L1 negative tumors (ie PD-L1 staining in <1% tumor cells <u>and</u> no stromal staining). Due to the limited efficacy of treatment options currently available in later (2L+) line TNBC, subjects with PD-L1 negative tumors may benefit from pembrolizumab.

KN-086: The performance of pembrolizumab in subjects with PD-L1 negative tumors will first be explored in KN-086, a two-part, non-randomized, multi-site, open-label trial of pembrolizumab monotherapy in subjects with mTNBC.

In <u>Part 1</u>, subjects will be enrolled in 2 cohorts, **Cohort A** (2L+ monotherapy for mTNBC independent of PD-L1 status, ~160 subjects) and **Cohort B** (1L monotherapy for PD-L1 positive mTNBC, ~40 subjects) to examine the efficacy and safety of single agent pembrolizumab in the treatment of mTNBC. The relationship between response to treatment and PD-L1 protein expression in mTNBC will be explored in Cohort A.

Two interim efficacy analyses (IA 1 and 2) will be performed on Cohort A.

IA 1: Subjects in Cohort A will initially be enrolled independent of PD-L1 tumor status. A futility analysis (IA 1) will be done on the PD-L1 negative subpopulation of Cohort A to evaluate response in this group. If treatment with pembrolizumab is found to be futile in subjects with PD-L1 negative tumors, then further enrollment in Cohort A will be limited to subjects with PD-L1 positive tumors, including PD-L1 strong positive tumors.

IA 2 will be done in Cohort A to look at responses in subjects with PD-L1 strong positive tumors. In this subpopulation, at least 10 subjects with PD-L1 strong positive tumors need to be enrolled for response assessment and at least one responder is required to initiate Part 2, which will open after enrollment in Cohort A is completed.

Part 2 will examine whether higher tumor PD-L1 expression, as determined by a prototype immunohistochemistry (IHC) assay, is associated with increased probability of response to pembrolizumab in mTNBC, as it has been shown to be in other tumor types, such as advanced NSCLC [103].

KN-119: **Rationale for Including Subjects with PD-L1 positive tumors (CPS ≥1).** The PD-L1 IHC assay (Dako assay), which will be used in KN-119, is being developed as a companion diagnostic and will be available prior to initiation of KN-119. In KN-012, PD-L1-positivity was defined as ≥1% tumor cell staining or stromal staining, and was determined by a PD-L1 prototype IHC assay (Qualtek assay) that is different than the assay planned for KN-119 (Dako assay). The definition of PD-L1 positivity in KN-119 will be generally equivalent to the definition used in KN-012; however, the actual percent of minimum positive staining required may be different in the new assay. It is also possible that the prevalence of PD-L1 tumor positivity is different between the two assays, in which case the sample size and statistical considerations may need to be adjusted accordingly.

KN-119: **Rationale for Including Subjects with PD-L1 positive tumors (CPS ≥10).** Evaluation of OS efficacy by different CPS cutoffs from other indications of pembrolizumab monotherapy in the 2L+ setting (ie, head and neck squamous cell carcinoma [HNSCC], gastric cancer, and bladder cancer), demonstrate an enriched treatment effect with increasing PD-L1 expression level. Based on these finding, and to improve the usage of biomarkers to enhance the overall benefit:risk profile of pembrolizumab, CPS ≥10 by the Dako assay is included in order to identify an enriched subpopulation of patients with mTNBC who could potentially benefit more from pembrolizumab monotherapy.

KN-119: Rationale for requiring central confirmation of TNBC status. Several studies have reported discordance in evaluation of ER, progesterone receptor, and HER2 status between local and central laboratories, due to both technical issues in IHC testing and interpretation issues in FISH testing [77-79]. It is, thus, recommended that central testing should be performed to determine trial eligibility, particularly in large studies involving multiple collaborating institutions in several countries [77].

KN-119: Rationale for selection of stratification factors. Given that the primary objectives of KN-119 are OS in subjects with PD-L1 positive mTNBC and in all subjects, stratification for PD-L1 tumor status (positive [CPS ≥1] vs. negative [CPS <1]) will be applied to ensure equal distribution of subjects with PD-L1 positive tumors and negative tumors between the two study arms.

Given that subjects who are diagnosed with metastatic disease at the time of initial breast cancer diagnosis generally have more aggressive, and possibly of different biology, disease than subjects who initially present with early or locally advanced TNBC, stratification for prior (neo)adjuvant therapy vs *de novo* metastatic disease at initial diagnosis will be applied.

4.2.2 Rationale for Dose Selection/Regimen/Modification

The planned dose of pembrolizumab for this trial is 200 mg every 3 weeks (Q3W). Based on the totality of data generated in the Keytruda development program, 200 mg Q3W is the appropriate dose of pembrolizumab 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 8 randomized dose-comparison studies, 2262 subjects were enrolled with melanoma and non-small cell lung cancer (NSCLC), covering different disease settings (treatment naïve, previously treated, PD-L1 enriched and all-comers) and different treatment settings (monotherapy and in combination with chemotherapy). Five studies compared 2 mg/kg Q3W vs. 10 mg/kg Q3W (KN001 B2, KN001 D, KN002, KN010 and KN021), and 3 studies compared 10 mg/kg Q3W vs. 10 mg/kg Q2W (KN001 B3, KN001 F2 and KN006). All 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.

4.2.3 Rationale for Endpoints

4.2.3.1 Efficacy Endpoints

Primary: OS was selected as the primary endpoint for KN-119, because OS has been recognized as the gold standard for demonstration of superiority of a new antineoplastic therapy in a randomized Phase III trial.

Secondary: PFS, ORR, duration of response (DOR) and DCR based on RECIST 1.1 are commonly used efficacy endpoints in Phase III clinical trials. To minimize bias in central response assessments, imaging scans will be assessed by blinded central imaging vendor. In addition, radiologic progression by RECIST 1.1 will be based on the central assessment of progression, rather than site assessment.

Exploratory: irRECIST is an adaptation of RECIST 1.1 to account for the unique tumor response characteristics to treatment with new immunotherapeutic agents, including pembrolizumab. RECIST 1.1 was developed based on treatment with cytotoxic agents. Immunotherapeutic drugs, such as pembrolizumab, may produce antitumor effects by potentiating endogenous cancer-specific immune responses. The response patterns seen with such an approach may extend beyond the typical time course of responses seen with cytotoxic agents, and can manifest as clinical responses after initial increases in tumor burden or even the appearance of new lesions. Standard RECIST 1.1 may, thus, not provide an accurate assessment of response to immunotherapeutic agents, such as pembrolizumab, and will therefore be used with the adaptations described in Section 7.1.2.7 and referred to as irRECIST.

4.2.3.2 Selection of Patient Reported Outcomes Instruments

EORTC QLQ-C30 was developed to assess the quality of life of cancer subjects. It has been translated and validated into 81 languages and used in more than 3,000 studies worldwide. It contains 5 functioning scales (physical, role, cognitive, emotional, and social), 3 symptom scales (fatigue, nausea, pain) and additional single symptom items. It is scored on a 4 point scale (1=not at all, 2=a little, 3=quite a bit, 4=very much). The EORTC QLQ-C30 instrument also contains 2 global scales that use 7 point scale scoring with anchors (1=very poor and 7=excellent).

EORTC QLQ-BR23 is a quality of life questionnaire developed to assess the extent of symptoms or problems in subjects receiving treatment for breast cancer. The tool is used in conjunction with the EORTC QLQ-C30 and follows the same 4-point scale described above. Tumor location, treatment, and quality of life dimensions are disease-specific aspects incorporated into question design. The tool consists of 23 questions and is divided into two sections; one section with a recall period of one week and one section with a recall period of four weeks.

The EuroQol-5D (EQ-5D) is a standardized instrument for use as a measure of health outcome. The EQ-5D-3L will be used to calculate utility values to incorporate into QTWiST and health economic models. The five health state dimensions in this instrument include the following: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension is rated on a 3-point scale from 1 (extreme problem) to 3 (no problem). The eEQ-5D will always be completed by subjects first before completing the eEORTC QLQ-C30 and eEORTC QLQ-BR23.

4.2.3.3 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, Version 4.0.

4.2.3.4 Planned Exploratory Biomarker Research

Newly obtained core or excisional biopsies obtained from metastatic, not previously irradiated, lesions will be used for PD-L1 assessment by IHC. Archival tumor biopsies will also be obtained, when available, to compare the performance of the PD-L1 IHC assay in archived versus newly obtained tumor tissues.

Additional biomarker and other biomedical research to identify factors important for predicting responsiveness or resistance to pembrolizumab therapy in mTNBC will also be pursued. Pre-treatment, on treatment, and at the time of disease progression tumor biopsies and blood samples (including serum and plasma) will be collected as described in Section 6.0. Tumor and blood specimens may be evaluated by histopathologic, transcriptional, genomic [including targeted next generation sequencing (NGS), whole exome sequencing (WES) and whole genome sequencing (WGS)] and proteomic analyses, as described below. Portions of tumor and blood specimens will be stored for future analyses.

Assays may include, but are not be limited, to:

Immunohistochemistry

In addition to determining PD-L1 expression in tumor tissues by IHC as described earlier, other exploratory biomarkers (eg PD-1 expression, markers of T cell phenotype) may also be evaluated.

Tissue Infiltrating Lymphocytes

Tissue infiltrating lymphocytes have been shown to provide prognostic and potentially predictive value, particularly in TNBC [64, 80-82] and HER2-overexpressing breast cancer [81, 83, 84]. Hematoxylin and eosin (H&E)-stained breast tumor sections can be evaluated for TILs, according to a recently published standardized methodology [3].

Transcriptional Analyses

Messenger RNA (mRNA) expression profiling in tumor specimens and peripheral blood will be completed to assess expression either by RNAseq or mid-density RNA platform of approximately 700 genes and attempt to define a gene set critical for clinical response to pembrolizumab. The hypothesis to be tested is that pembrolizumab induces responses in tumors that reflect an inflammatory/immune cell-rich phenotype based on gene expression signatures capturing PD-L1 and IFN-γ transcriptional programs. Global profiling may also be pursued. Expression of individual genes related to the immune system may also be evaluated, such as immune signatures and critical cytokines (eg, IL-10). MicroRNA profiling may also be pursued in serum samples.

Genomic Analyses

The application of new technologies such as NGS, WES, and WGS has provided the opportunity to define certain tumor types at the genetic level as being 'hypermutated' and to detect the presence of specific T cell clones within the tumor microenvironment or in the peripheral blood [85-87]. It is possible that the hypermutated state (and/or increased T cell clonality) or the hypomutated state (and/or lack of dominant T cell clones) may correlate with response to pembrolizumab in TNBC.

In addition, understanding somatic and germline genetic determinants of drug response is an important endeavor during medical research. Targeted NGS may be used to evaluate whether somatic genetic variations, ie, in tumors, circulating tumor cells (CTCs) and circulating tumor DNA [88], and/or germline DNA mutations correlate with response to pembrolizumab in mTNBC. Particular emphasis will be placed on the following biological determinants/pathways: BRCA1/2, PI3K, PTEN, EGFR, MEK, FGFR, MET, and Notch signaling [89-92]. Microsatellite instability may also be evaluated. A homologous recombination defect (HRD) assay may be used in this study. If genetic variation is found to predict efficacy or adverse events, this data might inform optimal use of pembrolizumab in future studies enrolling subjects with TNBC.

Proteomic Analyses

In addition to expression on the tumor tissue, PD-L1 can be shed from tumor and released into the blood [93]. Enzyme-linked immunoassay can measure PD-L1 in serum and correlate this expression with response to pembrolizumab therapy and PD-L1 protein in the tumor. Blood would be a less invasive component from which to measure PD-L1 protein biomarker. In addition to this specific protein biomarker, both tissue and blood derivatives can be subjected to proteomic profiling studies using a variety of platforms that could include, but

are not limited to, immunoassay, liquid chromatography and/or mass spectrometry. This approach could identify novel protein biomarker(s) that could aid in subject selection for pembrolizumab therapy in TNBC.

Planned Genetic Analysis

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

4.2.3.5 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. For instance, exploratory pharmacogenetic (PGt) studies may be performed if significant Pharmacokinetic/Pharmacodynamic (PK/PD) relationships are observed or adverse events are identified. Genomic markers of disease may also be investigated. Such retrospective pharmacogenetic studies will be conducted with appropriate biostatistical design and analysis and compared to PK/PD results or clinical outcomes. Any significant PGt relationships to outcome would require validation in future clinical trials. 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 trials are designed to provide information about the safety and effectiveness of an investigational medicine.

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

Additional potential benefits are addressed in Section 4.1.5, which details responses to pembrolizumab in the TNBC cohort of the multi-cohort Phase Ib study, KN-012, which enrolled subjects with PD-L1-positive (in ≥1% of tumor cells or in stroma, by immunohistochemistry) tumors. Similar to pembrolizumab studies in other tumor types, the most common adverse events included fatigue (17.9%), decreased appetite (12.8%), hypothyroidism (12.8%), and arthralgia (10.3%).

The safety and efficacy data will be submitted to an external Data Monitoring Committee (DMC) for review.

5.0 METHODOLOGY

5.1 Entry Criteria

5.1.1 Diagnosis/Condition for Entry into the Trial

Female and male subjects with Stage IV/M1 mTNBC who fulfill the following inclusion/exclusion criteria 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.

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

3. Have received either one or two prior systemic treatments for metastatic breast cancer and have documented disease progression on or after their most recent therapy.

4. Have been previously treated with an anthracycline and/or taxane in the (neo)adjuvant or metastatic setting.

5. Have centrally confirmed mTNBC (determined by a newly obtained core or excisional biopsy from a metastatic, not previously irradiated, tumor lesion).

6. Have measurable disease based on RECIST 1.1 as assessed by site Investigator and local radiology review.

7. Have provided a newly obtained core or excisional biopsy from a metastatic, not previously irradiated, tumor lesion for central determination of triple-negative breast cancer status and PD-L1 biomarker analysis. Adequacy of the biopsy specimen for the above analyses must be confirmed by the central laboratory. Repeat samples may be required if adequate tumor tissue is not provided. Note: Subjects for whom fresh tumor biopsies cannot be obtained (eg inaccessible tumor site or concern for subject safety) may submit an archived tumor specimen only upon agreement from the Sponsor.

8. Have an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 assessed within 10 days prior of treatment initiation.

9. Demonstrate adequate organ function as defined in Table 2.

Table 2 Adequate Organ Function Laboratory Values

System	Laboratory Value
Hematological	
Absolute neutrophil count (ANC)	≥1,500/mcL
Platelets	≥100,000/mcL
Hemoglobin	≥9 g/dL or ≥5.6 mmol/L without qualifications [b]
Renal	
Creatinine Calculated creatinine clearance (CrCl)[a] (Glomerular filtration rate [GFR] can also be used in place of creatinine or CrCl)	≤1.5x upper limit of normal (UL)N **OR** ≥30 mL/min for subject with creatinine levels >1.5x institutional ULN
Hepatic	
Serum total bilirubin	≤1.5xULN **OR** Direct bilirubin ≤ULN for subjects with total bilirubin levels >1.5xULN
AST (serum glutamic oxaloacetic transaminase [SGOT]) and ALT (serum glutamic pyruvic transaminase [SGPT])	≤2.5xULN **OR** ≤5 X ULN for subjects with active liver metastases
Alkaline Phosphatase	If >2.5xULN, then liver fraction should be ≤2.5xULN
Albumin	≥3.0 g/dL
Lactate Dehydrogenase (LDH)	<2.5xULN
Coagulation	
International Normalized Ratio (INR) or Prothrombin Time (PT)	≤1.5xULN unless subject is receiving anticoagulant therapy as long as PT or aPTT is within therapeutic range of intended use of anticoagulants
Activated Partial Thromboplastin Time (aPTT)	≤1.5xULN unless subject is receiving anticoagulant therapy as long as PT or aPTT is within therapeutic range of intended use of anticoagulants

[a] Creatinine clearance should be calculated per institutional standard.
[b] Criteria must be met without erythropoietin dependency and without packed red blood cell (pRBC) transfusion within last 4 weeks.

10. Female subjects of childbearing potential should have a negative urine or serum pregnancy test within 72 hours prior to receiving the first dose of study medication and agree to use effective contraception, as defined in Section 5.7.2. If the urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required. Male subjects should agree to use an adequate method of contraception starting at randomization through at least 120 days after the last dose of pembrolizumab or TPC, according to local standard of care.

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

5.1.3 Subject Exclusion Criteria

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

1. Has participated or is currently participating in a study of an investigational agent/device and has received/is receiving the investigational agent/device within 4 weeks of randomization.

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

2. Has had monoclonal antibody (mAb) for direct anti-neoplastic treatment within 4 weeks of randomization.

3. Has had chemotherapy, targeted small molecule therapy, or radiation therapy within at least 2 weeks of randomization.

4. Has not recovered from adverse events (ie, downgraded to ≤ Grade 1 or to baseline) due to a previously administered therapy.

    Note: Subjects with ≤ Grade 2 neuropathy or alopecia of any grade are an exception to this criterion and may qualify for the study.

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

5. Has an active autoimmune disease that has required systemic treatment in the past 2 years (ie with use of disease modifying agents, corticosteroids or immunosuppressive drugs).

    Note: Replacement therapy (eg, thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency, etc.) is not considered a form of systemic treatment.

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

7. 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.

8. Has known **active** brain metastases and/or carcinomatous meningitis. Note: Known brain metastases are considered **active**, if <u>any</u> of the following criteria is 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.

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

    c. Steroids were used for brain metastases within 28 days of randomization

9. Has active/history of pneumonitis requiring treatment with steroids or active/history of interstitial lung disease.

10. Has an active infection requiring systemic therapy.

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

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

13. Is pregnant or breastfeeding, or expecting to conceive or father children within the projected duration of the trial, starting with the screening visit through 120 days after the last dose of trial treatment as defined in Section 5.7.2.

14. Has received prior therapy with an anti-PD-1, anti-PD-L1, or anti-PD-L2 agent or with an agent directed to another co-inhibitory T cell receptor (eg, CTLA-4, OX-40, CD137) or has previously participated in Merck MK-3475 clinical trials.

15. Has a known history of Human Immunodeficiency Virus (HIV; HIV 1/2 antibodies).

16. Has a known active Hepatitis B (eg, hepatitis B surface antigen [HBsAg] reactive) or Hepatitis C (eg, hepatitis C virus [HCV] RNA [qualitative] is detected).

17. Has received a live vaccine within 30 days of randomization.

5.2 Trial Treatment(s)

The treatments to be used in this trial are outlined below in Table 3. Medications used as treatments of physician's choice (TPC) will be handled according to local regulations and guidelines in participating countries. 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.

Table 3 Trial Treatment

Drug	Dose	Regimen/Treatment Period	Use
Capecitabine	Local standard of care	Local standard of care	TPC
Eribulin	Local standard of care	Local standard of care	TPC
Gemcitabine	Local standard of care	Local standard of care	TPC
Pembrolizumab	200 mg IV	Day 1 Q3W	Experimental
Vinorelbine	Local standard of care	Local standard of care	TPC

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

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 dose of pembrolizumab to be used in this trial is provided in Section 4.2.2. Details on preparation and administration of pembrolizumab are provided in the Pharmacy Manual.

TPC drugs will be dosed, prepared and administered according to local regulations and guidelines. The body surface area (BSA) in m^2 should be calculated per local guidelines.

5.2.1.2 Dose Modification (Interruption/Escalation/Titration/Other)

5.2.1.2.1 Pembrolizumab Dose Modifications

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

AEs associated with pembrolizumab exposure may have an immunologic etiology. These immune-related AEs (irAEs) may occur shortly after the first dose or several months after the last dose of treatment and may affect more than one body system simultaneously. Therefore, early recognition and initiation of treatment is critical to reduce complications. Based on existing clinical study data, most irAEs were reversible and could be managed with interruptions of pembrolizumab, 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, or skin biopsy may be included as part of the evaluation. Based on the severity of irAEs, withhold or permanently discontinue pembrolizumab and administer corticosteroids. Dose modification and toxicity management guidelines for irAEs associated with pembrolizumab are provided in Table 4.

In addition, subjects should receive appropriate supportive care measures as deemed necessary by the treating Investigator. Suggested supportive care measures, as described in Section 5.6.1, are also included in Table 4.

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

Table 4 Dose Modification and Toxicity Management Guidelines for Immune-related Adverse Events 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 immune-related adverse events (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 1-2mg/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 1-2mg/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- 1mg/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 1-2mg/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 discontinue1		
Hyperthyroidism	Grade 2	Continue	• Treat with non-selective beta-blockers (eg propranolol) or thionamides as appropriate	• Monitor for signs and symptoms of thyroid disorders.
	Grade 3 or 4	Withhold or Permanently discontinue1		
Hypothyroidism	Grade 2-4	Continue	• Initiate thyroid replacement hormones (eg levothyroxine or liothyronine) per standard of care	• Monitor for signs and symptoms of thyroid disorders.
Nephritis and renal dysfunction	Grade 2	Withhold	• Administer corticosteroids (prednisone 1-2mg/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 or exclude other causes
	Grade 3 or 4	Permanently discontinue		
All Other immune-related AEs	Grade 3, or intolerable/ persistent Grade 2	Withhold	• Based on severity of AE administer corticosteroids	• Ensure adequate evaluation to confirm etiology or exclude other causes
	Grade 4 or recurrent Grade 3	Permanently discontinue		

NOTES:

1. Withhold or permanently discontinue pembrolizumab is at the discretion of the Investigator or treating physician.
2. 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 5.

Table 5 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 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		

Other allowed dose interruptions for pembrolizumab

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

In case toxicity does not resolve to Grade 0-1 within 12 weeks after the last infusion, pembrolizumab should be discontinued. Subjects with a laboratory adverse event still at Grade 2 after 12 weeks post last infusion may restart pembrolizumab if asymptomatic and only after consultation with the Sponsor.

Dosing interruptions (pembrolizumab and TPC) are permitted in the case of medical/surgical events or logistical reasons not related to study therapy (eg, 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 discussed otherwise with the Sponsor. The reason for interruption of study treatment should be documented in the subject's study record.

5.2.1.2.2 Capecitabine

Refer to locally issued capecitabine package insert for subjects receiving this agent.

5.2.1.2.3 Eribulin

Refer to locally issued eribulin package insert for subjects receiving this agent.

5.2.1.2.4 Gemcitabine

Refer to locally issued gemcitabine package insert for subjects receiving this agent.

5.2.1.2.5 Vinorelbine

Refer to locally issued vinorelbine package insert for subjects receiving this agent.

5.2.2 Timing of Dose Administration

Cycle 1 Day 1 treatment with pembrolizumab or TPC should begin on the day of randomization (no later than 3 days after randomization is permitted). Trial treatments should be administered as described below and according to the details provided in the Trial Flow Charts (Section 6.0).

Pembrolizumab or TPC should be administered on an outpatient basis after all procedures/assessments have been completed.

5.2.2.1 Pembrolizumab

Pembrolizumab will be administered as a 30-minute IV infusion Q3W (treatment cycle intervals may be increased due to toxicity as described in the Dose Modification Section 5.2.1.2.1). Sites should make every effort to target infusion timing to be as close to 30 min as possible. A window of -5 min/+10 min 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 Capecitabine

Refer to locally issued capecitabine package insert for subjects receiving this agent.

5.2.2.3 Eribulin

Refer to locally issued eribulin package insert for subjects receiving this agent.

5.2.2.4 Gemcitabine

Refer to locally issued gemcitabine package insert for subjects receiving this agent.

5.2.2.5 Vinorelbine

Refer to locally issued vinorelbine package insert for subjects receiving this agent.

5.2.3 Trial Blinding/Masking

This is an open-label trial, therefore, the Sponsor, Investigator and subject will know the treatment administered. Imaging data for the primary analysis will be reviewed by central imaging vendor blinded to subject's treatment assignment. The subject-level PD-L1 biomarker results will be masked in the database to the study team and the Sponsor including clinical, statistical, statistical programming, and data management personnel. Access to the PD-L1 subject-level biomarker results will be limited to an unblinded Sponsor clinical scientist, unblinded Sponsor statistician, and unblinded Sponsor statistical programmer who will be responsible for data review but who will have no other responsibilities associated with the study.

Access to the allocation schedule and the subject-level PD-L1 results for summaries or analyses will be restricted to an unblinded external statistician, and, as needed, an external scientific programmer performing the analysis, who will have no other responsibilities associated with the study.

5.3 Randomization or Treatment Allocation

Randomization will occur centrally using an interactive voice response system / integrated web response system (IVRS/IWRS). There are 2 treatment arms. Subjects will be assigned randomly in a 1:1 ratio to pembrolizumab or TPC after stratification by PD-L1 tumor status (positive [CPS ≥1] vs negative [CPS <1]), and history of prior (neo)adjuvant treatment versus *de novo* metastatic disease at initial diagnosis. TPC should be identified and documented via IVRS prior to randomization. Subjects randomized to TPC who discontinue treatment are not allowed to cross-over to the pembrolizumab arm.

5.4 Stratification

Randomization will be stratified according to the following factors:

- PD-L1 tumor status (positive [CPS ≥1] vs negative [CPS <1])
- History of prior (neo)adjuvant therapy vs *de novo* metastatic disease at initial diagnosis

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

5.5 Concomitant Medications/Vaccinations (Allowed & Prohibited)

Medications or vaccinations specifically prohibited in the exclusion criteria are not allowed during the ongoing trial. If there is a clinical indication for any medication or vaccination specifically prohibited during the trial, discontinuation from trial therapy or vaccination may be required. The investigator should discuss any questions regarding this with the Sponsor Clinical Director. The final decision on any supportive therapy or vaccination rests with the

investigator and/or the subject's primary physician. However, the decision to continue the subject on trial therapy or vaccination schedule requires the mutual agreement of the investigator, the Sponsor and the subject.

5.5.1 Acceptable Concomitant Medications

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

All concomitant medications received within 28 days before randomization and 30 days after the last dose of study treatment should be recorded. Concomitant medications administered beyond 30 days after the last dose of trial treatment should be recorded for SAEs and ECIs as defined in Section 7.2.

5.5.2 Prohibited Concomitant Medications

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

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

    Note: Radiation therapy to a symptomatic solitary lesion or to the brain may be allowed after consultation with Sponsor (except during screening).
- Herbal supplements
- Live vaccines within 30 days prior to randomization and while participating in the trial. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, varicella, herpes zoster, yellow fever, rabies, BCG, and typhoid (oral) vaccines. Seasonal influenza vaccines for injection are generally killed virus vaccines and are allowed. However, intranasal influenza vaccines (eg Flu - Mist®) are live attenuated vaccines, and are not allowed.
- Glucocorticoids for any purpose other than to modulate symptoms from an ECI of suspected immunologic etiology. The use of physiologic doses of corticosteroids may be approved after consultation with the Sponsor.

  Note: For subjects randomized to TPC, the use of systemic glucocorticoids on trial treatment is acceptable and may be required for premedication.

  Note: Inhaled steroids are allowed for management of asthma.

Note: Use of prophylactic corticosteroids to avoid allergic reactions (eg, to IV contract dye) is permitted.

- Maalox (or medicine containing aluminum hydroxide or magnesium hydroxide) should not be administered to subjects who are randomized to capecitabine.

Subjects who, per Investigator's assessment, require any of the aforementioned medications for clinical management should be discontinued from study treatment. Subjects may receive other medications that the Investigator deems to be medically necessary.

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

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

5.6 Rescue Medications & Supportive Care

5.6.1 Supportive Care Guidelines for Subjects in Pembrolizumab Arm

Subjects should receive appropriate supportive care measures as deemed necessary by the treating Investigator. Suggested supportive care measures for the management of adverse events (AEs) with potential immunologic etiology are outlined in Section 5.2.1.2, Table 4). Where appropriate, these guidelines include the use of oral or IV 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 progression of metastatic disease or bacterial or viral infection, which might require additional supportive care. The treatment guidelines are intended to be applied when the Investigator determines the events to be related to pembrolizumab.

Note: If after the evaluation of the event, it is determined not to be related to pembrolizumab, the investigator does not need to follow the treatment guidance. Refer to Table 4 in Section 5.2.1.2 for guidelines regarding dose modification.

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

5.6.2 Supportive Care Guidelines for Immune-Related Adverse Events

See Section 5.2.1.2, Table 4.

5.6.3 Supportive Care Guidelines for Capecitabine

Refer to local product label or supportive care guidance.

5.6.4 Supportive Care Guidelines for Eribulin

Refer to local product label or supportive care guidance.

5.6.5 Supportive Care Guideline for Gemcitabine

Refer to local product label or supportive care guidance.

5.6.6 Supportive Care Guidelines for Vinorelbine

Refer to local product label or supportive care guidance.

5.7 Diet/Activity/Other Considerations

5.7.1 Diet

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

5.7.2 Contraception

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

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

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

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

OR

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

OR

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

Female and male subjects of reproductive potential must agree to avoid becoming pregnant or impregnating a partner, respectively, while receiving study drug and for 120 days (at least 6 months for subjects on gemcitabine) after the last dose of study drug by complying with one of the following:

(1) practice abstinence† from heterosexual activity;

OR

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

Acceptable methods of contraception are‡:

Single method (one of the following is acceptable):

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

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

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

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

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

Subjects should be informed that taking the study drug may involve unknown risks to the fetus (unborn baby) if pregnancy were to occur during the study. In order to participate in the study, subjects of childbearing potential must adhere to the contraception requirement (described above) from the day of study drug initiation (or 14 days prior to the initiation of study drug for oral contraception) throughout the study period up to 120 days (at least 6 months for gemcitabine) after the last dose of trial therapy. If there is any question that a subject of childbearing potential will not reliably comply with the requirements for contraception, that subject should not be entered into the study.

Male subjects should also seek advice regarding cryoconservation of sperm prior to treatment because of the possibility of infertility

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

5.7.3 Pregnancy

If a subject inadvertently becomes pregnant while on treatment with pembrolizumab or a TPC, the subject will be immediately discontinued from treatment. The site will contact the subject at least monthly and document the subject's status until the pregnancy has been completed or terminated. The outcome of the pregnancy will be reported to the Sponsor without delay and within 24 hours if the outcome is a serious adverse experience (eg, death, abortion, congenital anomaly, or other disabling or life-threatening complication to the mother or newborn). The study Investigator will make every effort to obtain permission to follow the outcome of the pregnancy and report the condition of the fetus or newborn to the Sponsor. If a male subject impregnates his female partner, the study personnel at the site must be informed immediately and the pregnancy must be reported to the Sponsor and followed as described in Section 7.2.2.

5.7.4 Nursing Women

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

5.8 Subject Withdrawal/Discontinuation Criteria

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

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

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

- The subject or legal representative (such as a parent or legal guardian) withdraws consent.
- The subject is lost to follow-up

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

- The subject or legal representative (such as a parent or legal guardian) requests to discontinue treatment

- Confirmed radiographic disease progression per the terms outlined in Section 7.1.2.7 (exception if the Sponsor approves treatment continuation). Note: For unconfirmed radiographic disease progression, please see Section 5.8.1.
- Unacceptable adverse experiences as described in Section 7.2
- Any progression or recurrence of any malignancy, or any occurrence of another malignancy that requires active treatment
- Intercurrent illness other than another malignancy as noted above that prevents further administration of treatment
- Recurrent Grade 2 pneumonitis
- Investigator's decision to discontinue treatment
- The subject has a confirmed positive serum pregnancy test
- Noncompliance with trial treatment or procedure requirements
- Completed 35 treatments with pembrolizumab. Note: Subjects who stop pembrolizumab after 35 treatments may be eligible for up to 17 additional study treatments if they progress after stopping study treatment provided they meet the requirements detailed in Section 7.1.5.2.1.
- Administrative reasons

Chemotherapy may be discontinued when a subject has received the maximum number of cycles permitted according to local regulations and guidelines in participating countries.

The End of Treatment and Follow-up visit procedures are listed in Section 6.0 and Section 7.1.5.3. After the end of treatment, each subject will be followed for a minimum of 30 days for AEs and ECI monitoring. Serious adverse events will be collected for 90 days after the end of treatment as described in Section 7.2.3.1). Subjects who discontinue for reasons other than progressive disease will have post-treatment follow-up for disease status until disease progression, initiating a non-study cancer treatment, withdrawing consent, becoming lost to follow-up or death. After documented disease progression each subject will be followed by telephone for overall survival until death, withdrawal of consent, or the end of the study, whichever occurs first.

5.8.1 Treatment After First Radiologic Evidence of Disease Progression

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

After the site has assessed the 1st radiographic evidence of PD by RECIST 1.1, all images must be immediately submitted to the central imaging vendor for verification of Progressive Disease (PD). The central imaging vendor will notify the site and the Sponsor of the results

of this rapid review. Subjects should remain on treatment until central imaging assessment of site-assessed 1st radiologic evidence of PD is performed. If central imaging vendor verifies site-assessed 1st radiologic evidence of PD in either treatment arm, tumor assessment may be repeated by the site ≥4 weeks later in order for the site to confirm PD by irRECIST with the option of continuing treatment per below while awaiting radiologic confirmation of disease progression.

The decision to continue study treatment after site-assessed 1st radiologic evidence of PD is verified by the central imaging vendor is at the Investigator's discretion based on the clinical status of the subject as described in Table 6 below. Subjects may receive study treatment while waiting for confirmation of PD by the site, if they are clinically stable as defined by the following criteria:

- Absence of signs and symptoms (including worsening of laboratory values) indicating disease progression
- No decline in ECOG performance status
- Absence of rapid progression of disease
- Absence of progressive tumor at critical anatomical sites (eg, cord compression) requiring urgent alternative medical intervention

Table 6 Imaging and Treatment After Site-Assessed First Radiologic Evidence of Progressive Disease has Been Verified by the Central Imaging Vendor. Table Represents irRECIST

	Clinically Stable		**Clinically Unstable**	
	Imaging	**Treatment**	**Imaging**	**Treatment**
1st radiologic evidence of PD by RECIST 1.1 which has been verified by the central imaging vendor	Repeat imaging at ≥4 weeks at site to confirm PD	May continue study treatment at the local site Investigator's discretion while awaiting confirmatory tumor imaging by site by irRECIST.	Repeat imaging at ≥ 4 weeks to confirm PD per physician discretion only	Discontinue treatment
Repeat tumor imaging confirms PD by irRECIST at the local site	No additional imaging required	Discontinue treatment (exception is possible upon consultation with sponsor)	No additional imaging required	N/A

	Clinically Stable		Clinically Unstable	
	Imaging	**Treatment**	**Imaging**	**Treatment**
Repeat tumor imaging shows SD, PR or CR by irRECIST by the local site	Continue regularly scheduled imaging assessments	Continue study treatment at the local site Investigator's discretion	Continue regularly scheduled imaging assessments	May restart study treatment if condition has improved and/or clinically stable per Investigator's discretion. Next tumor imaging should occur according to the every 9 week (63 ± 7 days) imaging schedule for the first year and 12 weeks (84 ± 7 days) after the first year

This allowance to continue treatment despite centrally verified 1st radiologic evidence of PD takes into account the observation that some subjects may have a transient tumor flare in the first few months after the start of immunotherapy before experiencing disease response. Subjects that are deemed clinically unstable are not required to have repeat imaging for confirmation of progressive disease by the local site.

It must be emphasized that clinically stable subjects may remain on treatment after RECIST 1.1 defined disease progression is verified by blinded central imaging vendor for both the experimental and control arms of the study, and that the schedule of assessments be adhered to. If study therapy is discontinued for toxicity but the subject is otherwise stable, the subject should continue tumor imaging as indicated in the flow chart until RECIST 1.1 defined progression has been established by a blinded central imaging vendor.

Note: If a subject with confirmed radiographic progression (ie 2 tumor images at least 28 days apart demonstrating progressive disease) is clinically stable or clinically improved, and there is no further increase in the tumor dimensions at the confirmatory tumor image (as assessed by the site investigator/local radiology review), an exception may be considered to continue treatment upon consultation with the Sponsor.

5.8.2 Discontinuation of Study Therapy After Complete Response

Discontinuation of treatment may be considered for subjects who have attained a confirmed CR **and** have been treated for at least 8 cycles with pembrolizumab **and** had at least 2 cycles with pembrolizumab beyond the date when the initial CR was declared. Subjects who then experience radiographic disease progression may be eligible for up to 17 additional treatments with pembrolizumab (Second Course Phase or Re-treatment Phase) at the discretion of the Investigator if:

- No cancer treatment was administered since the last dose of pembrolizumab

- The subject meets the safety parameters listed in the Inclusion/Exclusion criteria
- The trial is ongoing

Subjects will resume therapy at the same dose and schedule at the time of initial discontinuation. Additional details are provided in Section 7.1.5.2.1. Response or progression in this Second Course Phase will not count towards the ORR and PFS of the primary endpoint in this trial.

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 enrolled in a pembrolizumab extension study.

5.11 Clinical Criteria for Early Trial Termination

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

- The trial may be stopped early for futility or safety at the recommendation of the external Data Monitoring Committee (eDMC).
- Quality or quantity of data recording is inaccurate or incomplete as assessed by the Sponsor
- Poor adherence to protocol and regulatory requirements
- Incidence or severity of adverse drug reaction in this or other studies indicates a potential health hazard to subjects
- Plans to modify or discontinue the development of the study medication

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

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

6.0 TRIAL FLOW CHART

6.1 Initial Treatment Phase

6.1.1 Pembrolizumab Treatment Arm

Trial Period:	Screening Phase		Treatment Cycles							End of Treatment	Post-Treatment		
Treatment Cycle/Title:	Screening (Visit 1)		1	2	3	4	5	6	7 and Beyond	Discon[c]	Safety Follow-up	Follow-up Visits	Survival Follow-up[a]
Scheduling Window (Days)	-56 to -1	-28 to -1	+ 3	± 3	± 3	± 3	± 3	± 3	± 3	At time of discon	30 days post discon (±3 days)	Post discon (±7 days)	Every 12 weeks (±7 days)
Administrative Procedures[b]													
Informed Consent	X												
Informed Consent for Future Biomedical Research	X												
Inclusion/Exclusion Criteria		X											
Subject Identification Card	X												
Demographics and Medical History[d]		X											
Prior and Concomitant Medication Review		X	X	X	X	X	X	X	X	X	X	X[z]	
Trial Treatment Administration (Pembrolizumab)			X	X	X	X	X	X	X				
Post-study Anticancer Therapy Status												X	X
Survival Status[a]			<- - - -

Trial Period:	Screening Phase		Treatment Cycles							End of Treatment	Post-Treatment		
Treatment Cycle/Title:	Screening (Visit 1)		1	2	3	4	5	6	7 and Beyond	Discon[c]	Safety Follow-up	Follow-up Visits	Survival Follow-up[a]
Scheduling Window (Days)	-56 to -1	-28 to -1	+ 3	± 3	± 3	± 3	± 3	± 3	± 3	At time of discon	30 days post discon (±3 days)	Post discon (±7 days)	Every 12 weeks (±7 days)
Vital Signs and Weight[g]		X	X	X	X	X	X	X	X	X			
ECOG Performance Status		X[h]	X	X	X	X	X	X	X	X			
Menopausal Status[i]		X											
Laboratory Procedures/Assessments: LOCAL laboratory[b, j]													
Pregnancy Test [k]		X											
PT/INR and aPTT[l]		X											
CBC with Differential		X		X	X	X	X	X	X	X	X		
Chemistry Panel		X		X	X	X	X	X	X	X	X		
Urinalysis		X		X		X		X	X[x]		X		
T3, FT4 and TSH[m, v]		X		X		X		X	X[x]		X		
Serum Vitamin D[v]		X											
Tumor markers (CA15-3, CEA and CA27.29)[n, v]		X	X[n]							X		X	
Laboratory Procedures/Assessments: CENTRAL laboratory[b]													
Blood for Genetics[o]			X										
Correlative Blood Samples (DNA and RNA)			X	X	X					X			
Blood for Exploratory Biomarkers (Plasma, Serum)			X										
Efficacy Measurements[b]													
Tumor Imaging[w]		X	X[x]							X		X	
Brain Imaging-if applicable[p]		X	X[p]							X		X	
Bone Imaging-if applicable[q]		X	X[q]									X	

Trial Period:	Screening Phase		Treatment Cycles							End of Treatment	Post-Treatment		
Treatment Cycle/Title:	Screening (Visit 1)		1	2	3	4	5	6	7 and Beyond	Discon[c]	Safety Follow-up	Follow-up Visits	Survival Follow-up[a]
Scheduling Window (Days)	-56 to -1	-28 to -1	+ 3	± 3	± 3	± 3	± 3	± 3	± 3	At time of discon	30 days post discon (±3 days)	Post discon (±7 days)	Every 12 weeks (±7 days)
Tissue Collection[b]													
Screening tissue for central confirmation of TNBC, PD-L1 status and biomarker analysis[r]	X												
Optional tissue for biomarker analysis[s]				X						X			
Optional archival tissue for biomarker /PD-L1 analysis[t]	X												
Subject Reported Outcomes [b, u]													
EQ-5D			X	X	X			X	X[y]	X	X		
EORTC QLQ-C30			X	X	X			X	X[y]	X	X		
EORTC QLQ-BR23			X	X	X			X	X[y]	X	X		

a. After documented local site assessed disease progression, or the start of new anticancer treatment; contacts are approximately every 12 weeks by telephone. Updated survival status may be requested by the Sponsor at any time during the course of the study. Upon Sponsor notification, all participants 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 participants that have a death event previously recorded).
b. Review all detailed instructions on assessments/ procedures in Section 7.0.
c. Subjects who discontinue trial treatment for any reason other than disease progression will move to the post-treatment follow up phase. If a subject is discontinued from trial treatment with documented PD, imaging is not performed. The subject will then enter survival follow up where subject will be contacted via a phone call every 12 weeks from the last contact date to assess for survival status.
d. Medical history includes all active conditions and any condition diagnosed within past 10 years considered to be clinically significant and all autoimmune disorders, regardless of onset date.
e. Guidance on monitoring AEs and ECIs can be found in Section 7.1.2.1.
f. Additional ECGs may be performed as clinically necessary.
g. Vital signs will include systolic and diastolic blood pressure, body temperature, pulse rate, body weight, and height (only at screening). Vital signs should be performed prior to treatment administration.
h. Screening ECOG Performance Status (PS) should be performed within 10 days prior to randomization.
i. When indicated, serum FSH and estradiol levels must be assessed and recorded in the eCRFs. See Section 7.1.2.6.
j. Screening laboratory tests are to be performed within 10 days prior to randomization. After Cycle 1, lab samples can be collected up to 72 hours prior to the scheduled dose. See Section 7.1.3 for details regarding laboratory tests.
k. For women of reproductive potential, a urine or serum pregnancy test should be performed within 72 hours prior to the first dose of trial treatment. If the urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required. Pregnancy tests (serum and/or urine tests) during the study should be completed if deemed necessary by PI or required by local guidelines.

Trial Period:	Screening Phase		Treatment Cycles							End of Treatment	Post-Treatment		
Treatment Cycle/Title:	Screening (Visit 1)		1	2	3	4	5	6	7 and Beyond	Discon[c]	Safety Follow-up	Follow-up Visits	Survival Follow-up[a]
Scheduling Window (Days)	-56 to -1	-28 to -1	+ 3	± 3	± 3	± 3	± 3	± 3	± 3	At time of discon	30 days post discon (±3 days)	Post discon (±7 days)	Every 12 weeks (±7 days)

l. Any subject receiving anticoagulant therapy should have coagulation factors monitored closely throughout the trial.
m. T3 or FT3 can be assayed based on local standards.
n. Tumor markers (CA15-3, CEA, and CA27.29) will follow the same visit schedule as the tumor imaging based on a calendar schedule and not treatment cycles. See footnote x for details.
o. Blood for genetics are mandatory samples unless there is either a documented law or regulation prohibiting collection, or if the IRB/IEC does not approve the collection of the sample for these purposes.
p. During screening, brain imaging should be performed in subjects with new or worsening neurological symptoms and those with known brain metastases (such subjects also need records of brain imaging performed at least 4 weeks earlier). While on study, brain imaging follows a calendar schedule (every 9 weeks [Q9W] for the first year, then Q12W) and will be performed in subjects with known brain metastases and subjects with worsening and/or new neurological symptoms.
q. Bone scans will be performed at screening for subject with known bone metastases and/or new bone pain and musculoskeletal complaints. On treatment performed as needed for evaluation of worsening and/or new bone pain and musculoskeletal complaints or if the site believes they have attained a Complete Response. If a subject has no known metastatic disease in the bone or active symptoms, a bone scan at baseline is not needed. A bone scan can be obtained at follow up if there are new symptoms of bone pain.
r. All subjects must have central confirmation of TNBC status prior to randomization. A fresh core or excisional tumor biopsy **from a metastatic, not previously irradiated lesion** will be used for confirmation of TNBC status, PD-L1 status and biomarker analysis. If new biopsy cannot be obtained due to site inaccessibility or a medical contraindication an archival or sample or slides may be submitted **AFTER** sponsor approval. Newly obtained tissue may be obtained up to 56 days prior to treatment initiation. Any tissue prior to the 56-day window may be considered with Sponsor consultation.
s. For subjects on the pembrolizumab arm, 2 optional tissue biopsies may be obtained on or after Cycle 2, and/or at disease progression. There are consent check boxes in the main consent that must be completed for every subject on the pembrolizumab arm.
t. When available, archived tumor specimens from prior biopsies will be collected for determination of PD-L1 tumor status and comparison of biomarker expression in archived vs. newly obtained tumor specimens.
u. It is strongly recommended that electronic patient-reported outcomes (ePROs) are administered prior to drug administration, adverse event evaluation and disease status notification.
v. T3, FT4 and TSH, serum vitamin D, and tumor markers (CA15-3, CEA and CA27.29) can be done centrally if a site is unable to complete locally.
w. Tumor imaging follows a calendar schedule; it is independent of cycles. To meet screening criteria, tumor imaging must be performed within 28 days prior to date of randomization. During treatment, tumor imaging is performed Q9W (+/- 7 days) for the first year, then Q12W (+/- 7 days) thereafter. Imaging should continue until site-assessed 1st radiologic evidence of disease progression (PD) is verified by the central imaging vendor (unless the site PI determines the subject would benefit from continued treatment and then follows the subject per irRECIST), the start of new anti-cancer treatment, withdrawal of consent, death, or the end of the study, whichever occurs first.
x. Urinalysis, T3, FT4, and TSH laboratory assessments after Cycle 6 will be repeated on Treatment Day 1 every 2 Cycles (ie, Cycles 8, 10, 12, etc.).
y. Subject Reported Outcomes (EQ-5D, EORTC QLQ-C30, and EORTC QLQ-BR23) questionnaires will be administered on Treatment Day 1 every third cycle after Cycle 3 until the end of year 1 (ie, Cycles 6, 9, 12, etc.) and every fourth cycle during year 2 until PD.
z. Concomitant medication review during Follow-Up Visits is for new anti-cancer treatment and medications administered to treat any AE or ECI reported during this period (as specified in Section 7.1.2.1).

6.1.2 Standard Treatment Arm – Gemcitabine or Eribulin

Trial Period:	Screening Phase		Treatment Cycles														End of Treatment	Post-Treatment		
Treatment Cycle/Title:	Screening (Visit 1)		1		2		3		4		5		6		7 and Beyond		Discon[c]	Safety Follow-up	Follow-up Visits	Survival Follow-up[a]
Treatment Day			1	8	1	8	1	8	1	8	1	8	1	8	1	8				
Scheduling Window (Days):	-56 to -1	-28 to -1	+ 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	At time of discon	30 days post discon (±3 days)	Post discon (±7 days)	Every 12 weeks (±7 days)
Administrative Procedures[b]																				
Informed Consent	X																			
Informed Consent for Future Biomedical Research	X																			
Inclusion/Exclusion Criteria		X																		
Subject Identification Card	X																			
Demographics and Medical History[d]		X																		
Prior and Concomitant Medication Review		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X[z]	
Gemcitabine or eribulin Administration[e]			X	X	X	X	X	X	X	X	X	X	X	X	X	X				
Post-study Anticancer Therapy Status																			X	X
Survival Status[a]			<- - - -

Trial Period:	Screening Phase		Treatment Cycles														End of Treatment	Post-Treatment		
Treatment Cycle/Title:	Screening (Visit 1)		1		2		3		4		5		6		7 and Beyond		Discon[c]	Safety Follow-up	Follow-up Visits	Survival Follow-up[a]
Treatment Day			1	8	1	8	1	8	1	8	1	8	1	8	1	8				
Scheduling Window (Days):	-56 to -1	-28 to -1	+ 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	At time of discon	30 days post discon (±3 days)	Post discon (±7 days)	Every 12 weeks (±7 days)
Full Physical Examination		X															X			
Directed Physical Examination			X	X	X	X	X	X	X	X	X	X	X	X	X	X				
Vital Signs and Weight[h]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X			
ECOG Performance Status		X[i]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X			
Menopausal Status[j]		X																		
Laboratory Procedures/Assessments: LOCAL laboratory[b, k]																				
Pregnancy Test[l]		X																		
PT/INR and aPTT[m]		X																		
CBC with Differential		X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Chemistry Panel		X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Urinalysis		X			X				X				X		X[x]			X		
T3, FT4 and TSH[n, v]		X			X				X				X		X[x]			X		
Serum Vitamin D [v]		X																		
Tumor markers (CA15-3, CEA and CA27.29)[o, v,]		X	X[o]														X		X	
Laboratory Procedures/Assessments: CENTRAL laboratory[b]																				
Blood for Genetics[p]			X																	

Trial Period:	Screening Phase		Treatment Cycles														End of Treatment	Post-Treatment		
Treatment Cycle/Title:	Screening (Visit 1)		1		2		3		4		5		6		7 and Beyond		Discon[c]	Safety Follow-up	Follow-up Visits	Survival Follow-up[a]
Treatment Day			1	8	1	8	1	8	1	8	1	8	1	8	1	8				
Scheduling Window (Days):	-56 to -1	-28 to -1	+ 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	At time of discon	30 days post discon (±3 days)	Post discon (±7 days)	Every 12 weeks (±7 days)
Correlative Blood Samples (DNA and RNA)			X		X		X										X			
Blood for Exploratory Biomarkers (Plasma, Serum)			X																	
Efficacy Measurements[b]																				
Tumor Imaging[w]		X	X[w]														X		X	
Brain Imaging-if applicable[q]		X	X[q]														X			
Bone Imaging-if applicable[r]		X	X[r]																	
Tumor Tissue Collection[b]																				
Screening tissue for central confirmation of TNBC, PD-L1 status and biomarker analysis[s]	X																			
Optional archival tissue for biomarker/PD-L1 analysis[t]	X																			
Subject Reported Outcomes[b, u]																				
EQ-5D			X		X		X						X		X[y]		X	X		
EORTC QLQ-C30			X		X		X						X		X[y]		X	X		
EORTC QLQ-BR23			X		X		X						X		X[y]		X	X		

Trial Period:	Screening Phase		Treatment Cycles														End of Treatment	Post-Treatment		
Treatment Cycle/Title:	Screening (Visit 1)		1		2		3		4		5		6		7 and Beyond		Discon[c]	Safety Follow-up	Follow-up Visits	Survival Follow-up[a]
Treatment Day			1	8	1	8	1	8	1	8	1	8	1	8	1	8				
Scheduling Window (Days):	-56 to -1	-28 to -1	+ 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	At time of discon	30 days post discon (±3 days)	Post discon (±7 days)	Every 12 weeks (±7 days)

a. After documented local site assessed disease progression, or the start of new anticancer treatment; contacts are approximately every 12 weeks by telephone. Updated survival status may be requested by the Sponsor at any time during the course of the study. Upon Sponsor notification, all participants 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 participants that have a death event previously recorded).

b. Review all detailed instructions on assessments/ procedures in Section 7.0.

c. Subjects who discontinue trial treatment for any reason other than disease progression will move to the post-treatment follow up phase. If a subject is discontinued from study treatment with documented PD, imaging is not performed. The subject will then enter survival follow up where subject will be contacted via a phone call every 12 weeks from the last contact date to assess for survival status.

d. Medical history includes all active conditions and any condition diagnosed within past 10 years considered to be clinically significant and all autoimmune disorders, regardless of onset date.

e. If country guidelines specify an additional dosing day (ex. Day 15), the assessments should mirror Day 8 in the flow chart.

f. Guidance on monitoring AEs and ECIs can be found in Section 7.1.2.1.

g. Additional ECGs may be performed as clinically necessary.

h. Vital signs will include systolic and diastolic blood pressure, body temperature, pulse rate, body weight, and height (only at screening). Vital signs should be performed prior to treatment administration.

i. Screening ECOG should be performed within 10 days prior to randomization.

j. When indicated, serum FSH and estradiol levels must be assessed and recorded in the eCRFs. See Section 7.1.2.6.

k. Screening laboratory tests are to be performed within 10 days prior to randomization. After Cycle 1, lab samples can be collected up to 72 hours prior to the scheduled dose. See Section 7.1.3 for details regarding laboratory tests.

l. For women of reproductive potential, a urine or serum pregnancy test should be performed within 72 hours prior to the first dose of trial treatment. . If the urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required. Pregnancy tests (serum and/or urine tests) during the study should be completed if deemed necessary by PI or required by local guidelines.

m. Any subject receiving anticoagulant therapy should have coagulation factors monitored closely throughout the trial.

n. T3 or FT3 can be assayed based on local standards.

o. Tumor markers (CA15-3, CEA and CA27.29) will follow the same visit schedule as the tumor imaging based on a calendar schedule and not treatment cycles. See footnote w for details.

p. Blood for genetics are mandatory samples unless there is either a documented law or regulation prohibiting collection, or if the IRB/IEC does not approve the collection of the sample for these purposes.

q. During screening, brain imaging should be performed in subjects with new or worsening neurological symptoms and those with known brain metastases (such subjects also

Trial Period:	Screening Phase		Treatment Cycles														End of Treatment	Post-Treatment		
Treatment Cycle/Title:	Screening (Visit 1)		1		2		3		4		5		6		7 and Beyond		Discon[c]	Safety Follow-up	Follow-up Visits	Survival Follow-up[a]
Treatment Day			1	8	1	8	1	8	1	8	1	8	1	8	1	8				
Scheduling Window (Days):	-56 to -1	-28 to -1	+ 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	At time of discon	30 days post discon (±3 days)	Post discon (±7 days)	Every 12 weeks (±7 days)

need records of brain imaging performed at least 4 weeks earlier). While on study, brain imaging follows a calendar schedule (Q9W for the first year, then Q12W) and will be performed in subjects with known brain metastases and subjects with worsening and/or new neurological symptoms.

r. Bone scans will be performed at screening for subject with known bone metastases and/or new bone pain and musculoskeletal complaints. On treatment performed as needed for evaluation of worsening and/or new bone pain and musculoskeletal complaints or if the site believes they have attained a Complete Response. If a subject has no known metastatic disease in the bone or active symptoms, a bone scan at baseline is not needed. A bone scan can be obtained at follow up if there are new symptoms of bone pain.

s. All subjects must have central confirmation of TNBC status prior to randomization. A fresh core or excisional tumor biopsy **from a metastatic, not previously irradiated lesion** will be used for confirmation of TNBC status, PD-L1 status and biomarker analysis. If new biopsy cannot be obtained due to site inaccessibility or a medical contraindication, an archival or sample or slides may be submitted **AFTER** sponsor approval. Newly obtained tissue may be obtained up to 56 days prior to treatment initiation. Any tissue prior to the 56-day window may be considered with Sponsor consultation.

t. When available, archived tumor specimens from prior biopsies will be collected for determination of PD-L1 tumor status and comparison of biomarker expression in archived vs. newly obtained tumor specimens.

u. It is strongly recommended that ePROs are administered prior to drug administration, AE evaluation and disease status notification.

v. T3, FT4 and TSH, serum vitamin D, and tumor markers (CA15-3, CEA and CA27.29) can be done centrally if a site is unable to complete locally.

w. Tumor imaging follows a calendar schedule; it is independent of cycles. To meet screening criteria, tumor imaging must be performed within 28 days prior to date of randomization. During treatment, tumor imaging is performed Q9W (+/- 7 days) for the first year then Q12W (+/- 7 days) thereafter. Imaging should continue until site-assessed 1st radiologic evidence of PD is verified by the central imaging vendor (unless the site PI determines the subject would benefit from continued treatment and then follows the subject per irRECIST), the start of new anti-cancer treatment, withdrawal of consent, death, or the end of the study, whichever occurs first.

x. Urinalysis, T3, FT4, and TSH laboratory assessments after Cycle 6 will be repeated on Treatment Day 1 every 2 Cycles (ie, Cycles 8, 10, 12, etc.).

y. Subject Reported Outcomes (EQ-5D, EORTC QLQ-C30, and EORTC QLQ-BR23) questionnaires will be administered on Treatment Day 1 every third cycle after Cycle 3 until the end of year 1 (ie, Cycles 6, 9, 12, etc.) and every fourth cycle during year 2 until PD.

z. Concomitant Medication Review during Follow-Up Visits is for new anti-cancer treatment and medications administered to treat any AE or ECI reported during this period (as specified in Section 7.1.2.1).

6.1.3 Standard Treatment Arm – Capecitabine

Trial Period:	Screening Phase		Treatment Cycles							End of Treatment	Post-Treatment		
Treatment Cycle/Title:	Screening (Visit 1)		1	2	3	4	5	6	7 and beyond	Discon[c]	Safety Follow-up	Follow Up Visits	Survival Follow-up[a]
Scheduling Window (Days):	-56 to -1	-28 to -1	+ 3	± 3	± 3	± 3	± 3	± 3	± 3	At time of discon	30 days post discon (±3 days)	Post discon (±7 days)	Every 12 weeks (±7 days)
Administrative Procedures[b]													
Informed Consent	X												
Informed Consent for Future Biomedical Research	X												
Inclusion/Exclusion Criteria		X											
Subject Identification Card	X												
Demographics and Medical History[d]		X											
Prior and Concomitant Medication Review		X	X	X	X	X	X	X	X	X	X	X[z]	
Capecitabine Administration[e]			X	X	X	X	X	X	X				
Post-study Anticancer Therapy Status												X	X
Survival Status[a]			←- - - -

Trial Period:	Screening Phase		Treatment Cycles							End of Treatment	Post-Treatment		
Treatment Cycle/Title:	Screening (Visit 1)		1	2	3	4	5	6	7 and beyond	Discon[c]	Safety Follow-up	Follow Up Visits	Survival Follow-up[a]
Scheduling Window (Days):	-56 to -1	-28 to -1	+ 3	± 3	± 3	± 3	± 3	± 3	± 3	At time of discon	30 days post discon (±3 days)	Post discon (±7 days)	Every 12 weeks (±7 days)
Vital Signs and Weight[h]		X	X	X	X	X	X	X	X	X			
ECOG Performance Status[i]		X[i]	X	X	X	X	X	X	X	X			
Menopausal Status[j]		X											
Laboratory Procedures/Assessments: LOCAL laboratory[b, k h]													
Pregnancy Test Serum[l]		X											
PT/INR and aPTT[m]		X											
CBC with Differential		X		X	X	X	X	X	X	X	X		
Chemistry Panel		X		X	X	X	X	X	X	X	X		
Urinalysis		X		X		X		X	X[x]		X		
T3, FT4 and TSH[n, v]		X		X		X		X	X[x]		X		
Serum Vitamin D[v]		X											
Tumor markers (CA15-3, CEA and CA27.29)[o, v, w]		X	X[o]							X		X	
Laboratory Procedures/Assessments: analysis performed by CENTRAL laboratory[b]													
Blood for Genetics[p]			X										
Correlative Blood Samples (DNA and RNA)			X	X	X					X			
Blood for Exploratory Biomarkers (Plasma, Serum)			X										

Trial Period:	Screening Phase		Treatment Cycles							End of Treatment	Post-Treatment		
Treatment Cycle/Title:	Screening (Visit 1)		1	2	3	4	5	6	7 and beyond	Discon[c]	Safety Follow-up	Follow Up Visits	Survival Follow-up[a]
Scheduling Window (Days):	-56 to -1	-28 to -1	+ 3	± 3	± 3	± 3	± 3	± 3	± 3	At time of discon	30 days post discon (±3 days)	Post discon (±7 days)	Every 12 weeks (±7 days)
Efficacy Measurements [b]													
Tumor Imaging[w]		X	X[w]							X		X	
Brain Imaging-if applicableg[q]		X	X[q]							X		X	
Bone Imaging-if applicable[r]		X	X[r]										
Tumor Tissue Collection[b]													
Screening tissue for central confirmation of TNBC, PD-L1 status and biomarker analysis[s]	X												
Optional archival tissue for biomarker/PD-L1 analysis [t]	X												
Subject Reported Outcomes[b, u]													
EQ-5D			X	X	X			X	X[y]	X	X		
EORTC QLQ-C30			X	X	X			X	X[y]	X	X		
EORTC QLQ-BR23			X	X	X			X	X[y]	X	X		

a. After documented local site assessed disease progression, or the start of new anticancer treatment; contacts are approximately every 12 weeks by telephone. Updated survival status may be requested by the Sponsor at any time during the course of the study. Upon Sponsor notification, all participants 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 participants that have a death event previously recorded).

b. Review all detailed instructions on assessments/ procedures in Section 7.0.

c. Subjects who discontinue trial treatment for any reason other than disease progression will move to the post-treatment follow up phase. If a subject is discontinued from study treatment with documented PD, imaging is not performed. The subject will then enter survival follow up where subject will be contacted via a phone call every 12 weeks from the last contact date to assess for survival status.

d. Medical history includes all active conditions and any condition diagnosed within past 10 years considered to be clinically significant and all autoimmune disorders, regardless of onset date.

e. If a country guidelines specify an additional dosing day (ex. Day 15), the assessments should mirror Day 8 in the flow chart.

Trial Period:	Screening Phase		Treatment Cycles							End of Treatment	Post-Treatment		
Treatment Cycle/Title:	Screening (Visit 1)		1	2	3	4	5	6	7 and beyond	Discon[c]	Safety Follow-up	Follow Up Visits	Survival Follow-up[a]
Scheduling Window (Days):	-56 to -1	-28 to -1	+ 3	± 3	± 3	± 3	± 3	± 3	± 3	At time of discon	30 days post discon (±3 days)	Post discon (±7 days)	Every 12 weeks (±7 days)

f. Guidance on monitoring AEs and ECIs can be found in Section 7.1.2.1.
g. Additional ECGs may be performed as clinically necessary.
h. Vital signs will include systolic and diastolic blood pressure, body temperature, pulse rate, body weight, and height (only at screening). Vital signs should be performed prior to treatment administration.
i. Screening ECOG PS should be performed within 10 day prior to randomization.
j. When indicated, serum FSH and estradiol levels must be assessed and recorded in the eCRFs. See Section 7.1.2.6.
k. After Cycle 1, lab samples can be collected up to 72 hours prior to the scheduled dose. See Section 7.1.3 for details regarding laboratory tests.
l. For women of reproductive potential, a urine or serum pregnancy test should be performed within 72 hours prior to the first dose of trial treatment. . If the urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required. Pregnancy tests (serum and/or urine tests) during the study should be completed if deemed necessary by PI or required by local guidelines.
m. Any subject receiving anticoagulant therapy should have coagulation factors monitored closely throughout the trial.
n. T3 or FT3 can be assayed based on local standards.
o. Tumor markers (CA15-3, CEA and CA27.29) will follow the same visit schedule as the tumor imaging based on a calendar schedule and not treatment cycles. See footnote w for details.
p. Blood for genetics are mandatory samples unless there is either a documented law or regulation prohibiting collection, or if the IRB/IEC does not approve the collection of the sample for these purposes.
q. During screening, brain imaging should be performed in subjects with new or worsening neurological symptoms and those with known brain metastases (such subjects also need records of brain imaging performed at least 4 weeks earlier). While on study, brain imaging follows a calendar schedule (Q9W for the first year, then Q12W) and will be performed in subjects with known brain metastases and subjects with worsening and/or new neurological symptoms.
r. Bone scans will be performed at screening for subject with known bone metastases and/or new bone pain and musculoskeletal complaints. On treatment performed as needed for evaluation of worsening and/or new bone pain and musculoskeletal complaints or if the site believes they have attained a Complete Response. If a subject has no known metastatic disease in the bone or active symptoms, a bone scan at baseline is not needed. A bone scan can be obtained at follow up if there are new symptoms of bone.
s. All subjects must have central confirmation of TNBC status prior to randomization. A fresh core or excisional tumor biops**y from a metastatic, not previously irradiated lesion** will be used for confirmation of TNBC status, PD-L1 status and biomarker analysis. If new biopsy cannot be obtained due to site inaccessibility or a medical contraindication, an archival or sample or slides may be submitted **AFTER** sponsor approval. Newly obtained tissue may be obtained up to 56 days prior to treatment initiation. Any tissue prior to the 56-day window may be considered with Sponsor consultation.
t. When available, archived tumor specimens from prior biopsies will be collected for determination of PD-L1 tumor status and comparison of biomarker expression in archived vs. newly obtained tumor specimens.
u. It is strongly recommended that ePROs are administered prior to drug administration, AE evaluation and disease status notification.
v. T3, FT4 and TSH, serum vitamin D, and tumor markers (CA15-3, CEA and CA27.29) can be done centrally if a site is unable to complete locally.

Trial Period:	Screening Phase		Treatment Cycles							End of Treatment	Post-Treatment		
Treatment Cycle/Title:	Screening (Visit 1)		1	2	3	4	5	6	7 and beyond	Discon[c]	Safety Follow-up	Follow Up Visits	Survival Follow-up[a]
Scheduling Window (Days):	-56 to -1	-28 to -1	+ 3	± 3	± 3	± 3	± 3	± 3	± 3	At time of discon	30 days post discon (±3 days)	Post discon (±7 days)	Every 12 weeks (±7 days)

w. Tumor imaging follows a calendar schedule; it is independent of cycles. To meet screening criteria, tumor imaging must be performed within 28 days prior to date of randomization. During treatment, tumor imaging is performed Q9W (+/- 7 days) for the first year, then Q12W (+/- 7 days) thereafter. Imaging should continue until site-assessed 1st radiologic evidence of disease progression (PD) is verified by the central imaging vendor (unless the site PI determines the subject would benefit from continued treatment and then follows the subject per irRECIST), the start of new anti-cancer treatment, withdrawal of consent, death, or the end of the study, whichever occurs first.

x. Urinalysis, T3, FT4, and TSH laboratory assessments after Cycle 6 will be repeated on Treatment Day 1 every 2 Cycles (ie, Cycles 8, 10, 12, etc.).

y. Subject Reported Outcomes (EQ-5D, EORTC QLQ-C30, and EORTC QLQ-BR23) questionnaires will be administered on Treatment Day 1 every third cycle after Cycle 3 until the end of year 1 (ie, Cycles 6, 9, 12, etc.) and every fourth cycle during year 2 until PD.

z. Concomitant Medication Review during Follow-Up Visits is for new anti-cancer treatment and medications administered to treat any AE or ECI reported during this period (as specified in Section 7.1.2.1).

6.1.4 Standard Treatment Arm – Vinorelbine

Trial Period:	Screening Phase		Treatment Cycles																				End of Treatment		Post-Treatment	
Treatment Cycle/Title:	Screening (Visit 1)		1		2			3			4			5			6			7 and Beyond			Discon[c]	Safety Follow-up	Follow-up Visits	Survival Follow-up[a]
Treatment Visit (Admin weekly)			1	2,3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21				
Scheduling Window (Days):	-56 to -1	-28 to -1	+ 3 d	± 3																			At time of discon	30 days post discon (±3 days)	Post discon (±7 days)	Every 12 weeks (±7 days)
Administrative Procedures[b]																										
Informed Consent	X																									
Informed Consent for Future Biomedical Research	X																									
Inclusion/Exclusion Criteria		X																								
Subject Identification Card	X																									
Demographics and Medical History[d]		X																								
Prior and Concomitant Medication Review		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X[z]	
Vinorelbine Administration[e]			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X				
Post-study Anticancer Therapy Status																									X	X
Survival Status[a]			←---------- →																							X

Trial Period:	Screening Phase		Treatment Cycles																				End of Treatment		Post-Treatment	
Treatment Cycle/Title:	Screening (Visit 1)		1		2			3			4			5			6			7 and Beyond			Discon[c]	Safety Follow-up	Follow-up Visits	Survival Follow-up[a]
Treatment Visit (Admin weekly)			1	2,3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21				
Scheduling Window (Days):	-56 to -1	-28 to -1	+3 d	± 3																			At time of discon	30 days post discon (±3 days)	Post discon (±7 days)	Every 12 weeks (±7 days)
Clinical Procedures/Assessments[b]																										
Review Adverse Events[f]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
12-Lead ECG (Local)[g]		X																								
Full Physical Examination		X																					X			
Directed Physical Examination			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X				
Vital Signs and Weight[h]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X			
ECOG Performance Status[i]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X			
Menopausal Status[j]		X																								
Laboratory Procedures/Assessments: LOCAL laboratory[b, k]																										
Pregnancy Test – Serum[l]		X																								
PT/INR and aPTT[m]		X																								
CBC with Differential		X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Chemistry Panel		X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Urinalysis		X			X						X						X			X[x]	X[x]	X[x]		X		
T3, FT4 and TSH[n, v]		X			X						X						X			X[x]	X[x]	X[x]		X		
Serum Vitamin D[v]		X																								
Tumor markers (CA15-3, CEA and CA27.29)[o, v]		X	X[o]																				X		X	

Trial Period:	Screening Phase		Treatment Cycles																				End of Treatment		Post-Treatment	
Treatment Cycle/Title:	Screening (Visit 1)		1		2			3			4			5			6			7 and Beyond			Discon[c]	Safety Follow-up	Follow-up Visits	Survival Follow-up[a]
Treatment Visit (Admin weekly)			1	2,3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21				
Scheduling Window (Days):	-56 to -1	-28 to -1	+3 d	± 3																			At time of discon	30 days post discon (±3 days)	Post discon (±7 days)	Every 12 weeks (±7 days)
Laboratory Procedures/Assessments: CENTRAL laboratory[b]																										
Blood for Genetics[p]			X																							
Correlative Blood Samples (DNA and RNA)			X		X			X															X			
Blood for Exploratory Biomarkers (Plasma, Serum)			X																							
Efficacy Measurements[b]																										
Tumor Imaging[w]		X	X[w]																				X		X	
Brain Imaging–if applicable[q]		X	X[q]																				X		X	
Bone Imaging-if applicable[r]		X	X[r]																							
Tumor Tissue Collection[b]																										
Screening tissue for central confirmation of TNBC, PD-L1 status and biomarker analysis[s]	X																									
Optional archival tissue for biomarker/PD-L1 analysis[t]	X																									
Subject Reported Outcome[b, u]																										
EQ-5D			X		X			X									X			X[y]	X[y]	X[y]	X	X		

Trial Period:	Screening Phase		Treatment Cycles																				End of Treatment		Post-Treatment	
Treatment Cycle/Title:	Screening (Visit 1)		1		2			3			4			5			6			7 and Beyond			Discon[c]	Safety Follow-up	Follow-up Visits	Survival Follow-up[a]
Treatment Visit (Admin weekly)			1	2,3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21				
Scheduling Window (Days):	-56 to -1	-28 to -1	+3 d	± 3																			At time of discon	30 days post discon (±3 days)	Post discon (±7 days)	Every 12 weeks (±7 days)
EORTC QLQ-C30			X		X			X									X			X[y]	X[y]	X[y]	X	X		
EORTC QLQ-BR23			X		X			X									X			X[y]	X[y]	X[y]	X	X		

a. After documented local site assessed disease progression, or the start of new anticancer treatment; contacts are approximately every 12 weeks by telephone. Updated survival status may be requested by the Sponsor at any time during the course of the study. Upon Sponsor notification, all participants 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 participants that have a death event previously recorded).

b. Review all detailed instructions on assessments/ procedures in Section 7.0.

c. Subjects who discontinue trial treatment for any reason other than disease progression will move to the post-treatment follow up phase. If a subject is discontinued from study treatment with documented PD, imaging is not performed. The subject will then enter survival follow up where subject will be contacted via a phone call every 12 weeks from the last contact date to assess for survival status.

d. Medical history includes all active conditions and any condition diagnosed within past 10 years considered to be clinically significant and all autoimmune disorders, regardless of onset date.

e. If country guidelines specify an additional dosing day (ex. Day 15), the assessments should mirror Day 8 in the flow chart.

f. Guidance on monitoring AEs and ECIs can be found in Section 7.1.2.1.

g. Additional ECGs may be performed as clinically necessary.

h. Vital signs will include systolic and diastolic blood pressure, body temperature, pulse rate, body weight, and height (only at screening). Vital signs should be performed prior to treatment administration.

i. Screening ECOG should be performed within 10 days prior to randomization.

j. When indicated, serum FSH and estradiol levels must be assessed and recorded in the eCRFs. See Section 7.1.2.6.

k. Screening laboratory tests are to be performed within 10 days prior to randomization. After Cycle 1, lab samples can be collected up to 72 hours prior to the scheduled dose. See Section 7.1.3 for details regarding laboratory tests.

l. For women of reproductive potential, a urine or serum pregnancy test should be performed within 72 hours prior to the first dose of trial treatment. If the urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required. Pregnancy tests (serum and/or urine tests) during the study should be completed if deemed necessary by PI or required by local guidelines.

m. Any subject receiving anticoagulant therapy should have coagulation factors monitored closely throughout the trial.

n. T3 or FT3 can be assayed based on local standards.

o. Tumor markers (CA15-3, CEA and CA27.29) will follow the same visit schedule as the tumor imaging based on a calendar schedule and not treatment cycles. See footnote w for details.

Trial Period:	Screening Phase		Treatment Cycles																			End of Treatment		Post-Treatment	
Treatment Cycle/Title:	Screening (Visit 1)		1		2			3			4			5			6			7 and Beyond			Discon[c]	Safety Follow-up	Follow-up Visits	Survival Follow-up[a]
Treatment Visit (Admin weekly)			1	2,3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21				
Scheduling Window (Days):	-56 to -1	-28 to -1	+ 3 d	± 3																			At time of discon	30 days post discon (±3 days)	Post discon (±7 days)	Every 12 weeks (±7 days)

p. Blood for genetics are mandatory samples unless there is either a documented law or regulation prohibiting collection, or if the IRB/IEC does not approve the collection of the sample for these purposes.

q. During screening, brain imaging should be performed in subjects with new or worsening neurological symptoms and those with known brain metastases (such subjects also need records of brain imaging performed at least 4 weeks earlier). While on study, brain imaging follows a calendar schedule (Q9W for the first year, then Q12W) and will be performed in subjects with known brain metastases and subjects with worsening and/or new neurological symptoms.

r. Bone scans will be performed at screening for subject with known bone metastases and/or new bone pain and musculoskeletal complaints. On treatment performed as needed for evaluation of worsening and/or new bone pain and musculoskeletal complaints or if the site believes they have attained a Complete Response. If a subject has no known metastatic disease in the bone or active symptoms, a bone scan at baseline is not needed. A bone scan can be obtained at follow up if there are new symptoms of bone metastasis.

s. All subjects must have central confirmation of TNBC status prior to randomization. A fresh core or excisional tumor biop**sy from a metastatic, not previously irradiated lesion** will be used for confirmation of TNBC status, PD-L1 status and biomarker analysis. If new biopsy cannot be obtained due to site inaccessibility or a medical contraindication an archival or sample or slides may be submitted **AFTER** sponsor approval. Newly obtained tissue may be obtained up to 56 days prior to treatment window may be considered with Sponsor consultation. Any tissue prior to the 56-day window may be considered with Sponsor consultation.

t. When available, archived tumor specimens form prior biopsies will be collected for determination of PD-L1 status and comparison of biomarker expression in archived vs. newly obtained tumor specimens.

u. It is strongly recommended that ePROs are administered prior to drug administration, AE evaluation and disease status notification.

v. T3, FT4 and TSH, serum vitamin D, and tumor markers (CA15-3, CEA and CA27.29) can be done centrally if a site is unable to complete locally.

w. Tumor imaging follows a calendar schedule; it is independent of cycles. To meet screening criteria, tumor imaging must be performed within 28 days prior to date of randomization. During treatment, tumor imaging is performed Q9W (+/- 7 days) for first year then Q12W (+/- 7 days) thereafter. Imaging should continue until site-assessed 1st radiologic evidence of disease progression (PD) is verified by the central imaging vendor (unless the site PI determines the subject would benefit from continued treatment and then follows the subject per irRECIST), the start of new anti-cancer treatment, withdrawal of consent, death, or the end of the study, whichever occurs first.

x. Urinalysis, T3, FT4, and TSH laboratory assessments after Cycle 6 will be repeated on Treatment Day 1 every 2 Cycles (ie, Cycles 8, 10, 12, etc.).

y. Subject Reported Outcomes (EQ-5D, EORTC QLQ-C30, EORTC QLQ-BR23) questionnaires will be administered on Treatment Day 1 every third cycle after Cycle 3 until the end of year 1 (ie, Cycles 6, 9, 12, etc.) and every fourth cycle during year 2 until PD.

z. Concomitant medication review during Follow-Up Visits is for new anti-cancer treatment and medications administered to treat any AE or ECI reported during this period (as specified in Section 7.1.2.1).

6.2 Second Course Phase (Retreatment) for Pembrolizumab Arm Only

Trial Period:	Treatment Cycles								End of Treatment	Post-Treatment		
Treatment Cycle/Title:	Verified prior to treatment	1	2	3	4	5	6	7 and Beyond	Discon[c]	Safety Follow-up	Follow-up Visits	Survival Follow-up[a]
Scheduling Window (Days):		+ 3	± 3	± 3	± 3	± 3	± 3		At time of discon	30 days post discon (±3 days)	Post discon (±7 days)	Every 12 weeks (±7 days)
Administrative Procedures[b]												
Eligibility Criteria	X											
Concomitant Medication & Medical History	X		X	X	X	X	X	X	X	X	X[r]	
Pembrolizumab Administration		X	X	X	X	X	X	X				
Post-study Anticancer Therapy Status											X	X
Survival Status[a]		<- - - -

Trial Period:	Treatment Cycles								End of Treatment	Post-Treatment		
Treatment Cycle/Title:	Verified prior to treatment	1	2	3	4	5	6	7 and Beyond	Discon[c]	Safety Follow-up	Follow-up Visits	Survival Follow-up[a]
Scheduling Window (Days):		+ 3	± 3	± 3	± 3	± 3	± 3		At time of discon	30 days post discon (±3 days)	Post discon (±7 days)	Every 12 weeks (±7 days)
T3, FT4 and TSH[i, n]			X		X		X	X[p]		X		
Tumor markers (CA15-3, CEA and CA27.29)[j, n, o]	X[j]								X		X	
Efficacy Measurements[b]												
Tumor Imaging[k, o]	X	X[o]							X		X	
Brain Imaging-if applicable[l]	X	X[l]										
Bone Imaging-if applicable[m]	X	X[m]										

a. After documented local site assessed disease progression, or the start of new anticancer treatment; contacts are approximately every 12 weeks by telephone. Updated survival status may be requested by the Sponsor at any time during the course of the study. Upon Sponsor notification, all participants 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 participants that have a death event previously recorded).

b. Review all detailed instructions on assessment/procedures in Section 7.0.

c. Subjects who discontinue trial treatment for any reason other than disease progression will move to the post-treatment follow up phase. If a subject is discontinued from study treatment with documented PD, imaging is not performed. The subject will then enter survival follow up where subject will be contacted via a phone call every 12 weeks from the last contact date to assess for survival status.

d. Guidance on recording AEs and ECIs can be found in Section 7.1.2.1.

e. Vital signs will include systolic and diastolic blood pressure, body temperature, pulse rate, and body weight. Vital signs should be performed prior to treatment administration.

f. After Cycle 1, lab samples can be collected up to 72 hours prior to the scheduled dose. See Section 7.1.3 for details regarding laboratory tests.

g. For women of reproductive potential, a urine or serum pregnancy test should be performed within 72 hours prior to the first dose of trial retreatment. . If the urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required. Pregnancy tests (serum and/or urine tests) during the study should be completed if deemed necessary by PI or required by local guidelines.

h. Any subject receiving anticoagulant therapy should have coagulation factors monitored closely throughout the trial.

i. T3 or FT3 can be assayed based on local standards.

j. Tumor markers (CA15-3, CEA and CA27.29) will follow the same visit schedule as the tumor imaging based on a calendar schedule and not treatment cycles. See footnote o for details.

k. Tumor imaging must be performed within 28 days prior to restarting treatment.

l. Brain imaging should be performed within 28 days prior to restarting treatment in subjects with new or worsening neurological symptoms and those with known brain metastases. During a subject's first year on trial, brain imaging follows a Q9W calendar schedule. After the first year, brain imaging is Q12W.

m. Bone scans should be performed within 28 days prior to restarting treatment in subjects with known bone metastases and/or new bone pain and musculoskeletal complaints.

Trial Period:	Treatment Cycles								End of Treatment	Post-Treatment		
Treatment Cycle/Title:	Verified prior to treatment	1	2	3	4	5	6	7 and Beyond	Discon[c]	Safety Follow-up	Follow-up Visits	Survival Follow-up[a]
Scheduling Window (Days):		+ 3	± 3	± 3	± 3	± 3	± 3		At time of discon	30 days post discon (±3 days)	Post discon (±7 days)	Every 12 weeks (±7 days)

Bone scans should be performed on treatment for evaluation of worsening and/or new bone pain and musculoskeletal complaints or if the site believes they have attained a Complete Responses. If a subject has no known metastatic disease in the bone or active symptoms, bone scans are not needed. A bone scan can be obtained at follow up with there are new symptoms of bone pain.

n. T3, FT4 and TSH, serum vitamin D, and tumor markers (CA15-3, CEA and CA27.29) can be done centrally if a site is unable to complete locally.

o. Imaging follows a Q9W calendar schedule, it is independent of cycles.

p. Urinalysis, T3, FT4, and TSH laboratory assessments after Cycle 6 will be repeated on Treatment Day 1 every 2 Cycles (ie, Cycles 8, 10, 12, etc.).

q. Subject Reported Outcomes (EQ-5D, EORTC QLQ-C30, EORTC QLQ-BR23) questionnaires will be administered on Treatment Day 1 every third cycle after Cycle 3 until the end of year 1 (ie, Cycles 6, 9, 12, etc.) and every fourth cycle during year 2 until PD.

r. Concomitant medication review during Follow-Up Visits is for new anti-cancer treatment and medications administered to treat any AE or ECI reported during this period (as specified in Section 7.1.2.1).

7.0 TRIAL PROCEDURES

7.1 Trial Procedures

The Trial Flow Chart - Section 6.0 summarizes the trial procedures to be performed at each visit. Individual trial procedures are described in detail below. It may be necessary to perform these procedures at unscheduled time points if deemed clinically necessary by the investigator.

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

7.1.1 Administrative Procedures

7.1.1.1 Informed Consent

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

7.1.1.2 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.

7.1.1.2.1 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.

7.1.1.3 Inclusion/Exclusion Criteria

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

7.1.1.4 Subject Identification Card

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

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

7.1.1.5 Medical History

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

7.1.1.5.1 Disease Details

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

7.1.1.6 Prior and Concomitant Medications Review

The Investigator or qualified designee will review prior medication use as specified in the Trial Flow Chart (Section 6.0), including any protocol-specified washout requirement, and record prior medication taken by the subject within 28 days before randomization. Prior treatment for breast cancer will be recorded separately and not listed as a prior medication.

7.1.1.6.1 Prior Treatment Details for Breast Cancer Diagnosis

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

7.1.1.6.2 Concomitant Medications

The Investigator or qualified designee will record medications, if any, taken by the subject during the trial through the Safety Follow-up visit, as specified in the Trial Flow Chart (Section 6.0). In addition, new medications started during the Second Course Phase through the Second Course Safety Follow-up visit should be recorded. All medications related to reportable AEs, SAEs, and ECIs should be recorded as defined in Section 7.2.

7.1.1.6.3 Subsequent Anti-cancer Therapy Status

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

7.1.1.7 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 allocation. Each subject will be assigned only one screening number. Screening numbers must not be re-used for different subjects.

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

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

7.1.1.8 Assignment of Randomization Number

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

Investigators must choose a TPC drug (capecitabine, eribulin, gemcitabine or vinorelbine) prior to randomization and document the selection in the IVRS and trial database (See Data Entry Guidelines).

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

Any interruptions greater than 12 weeks between doses (pembrolizumab or TPC arms) for non drug-related or administrative reasons require consultation between the investigator and the Sponsor and written documentation of the collaborative decision on subject management.

Administration of trial medication will be witnessed by the Investigator and/or trial staff. The total volume of pembrolizumab or comparator infused will be compared to the total volume prepared to determine compliance with each dose of pembrolizumab or comparator administered.

The instructions for preparing and administering pembrolizumab will be provided in the Pharmacy Manual. TPC agents will be prepared and administered as per local product label.

Please refer to Section 5.2 for instructions on pembrolizumab and TPC.

7.1.1.10 Survival

After the start of new anti-cancer treatment or documented disease progression by the central imaging vendor, the subject should be contacted by telephone every 12 weeks from the last contact date for survival status assessment.

7.1.2 Clinical Procedures/Assessments

7.1.2.1 Adverse Event Monitoring

The Investigator or qualified designee will assess each subject to evaluate potential new or worsening AEs at each visit and as specified in the Trial Flow Chart (Section 6.0), or more frequently if clinically indicated. AEs will be graded and recorded throughout the study and during the follow-up period according to NCI CTCAE Version 4.0 (Section 7.2). Toxicities will be characterized in terms regarding seriousness, causality, toxicity grading, and action taken with regard to trial treatment.

Please refer to Section 7.2 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 standard procedures once at screening. Clinically significant abnormal findings should be recorded as medical history. Additional time points may be performed as clinically necessary.

7.1.2.3 Physical Exam

7.1.2.3.1 Full Physical Exam

The Investigator or clinical designee will perform a complete physician exam during the screening period. Clinically significant abnormal findings should be recorded as medical history. After the screening period, a full physical exam should be performed as specified in the Trial Flow Chart (Section 6.0). After randomization new clinically significant abnormal findings should be recorded as AEs.

7.1.2.3.2 Directed Physical Exam

The Investigator or clinical designee will perform directed physical exams at each visit while on trial treatment, 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 trial treatment and at treatment discontinuation, as specified in the Trial Flow Chart (Section 6.0). Vital signs should include temperature, pulse, respiratory rate, weight and blood pressure. Height will be measured at screening only. Vitals should be taken prior to treatment administration.

7.1.2.5 Eastern Cooperative Oncology Group Performance Status

The Investigator or qualified designee will assess ECOG status (Section 12.5) at screening, at each treatment cycle and at discontinuation of trial treatment, as specified in the Trial Flow Chart (Section 6.0).

7.1.2.6 Menopausal Status

The menopausal status (pre- or post-menopausal) for all female subjects less than age 60 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.

<u>Pre-menopausal</u>

- ≤12 months since LMP

  OR

- Biochemical evidence of pre-menopausal status, according to serum FSH and estradiol levels and local institutional guidelines

Post-menopausal

- Subject has undergone prior bilateral ovariectomy/oophorectomy

OR

- >12 months since LMP and no hysterectomy, hormone replacement, estrogen receptor antagonist, chemotherapy or ovarian suppression at any time since LMP

OR

- Biochemical evidence of post-menopausal status, according to serum FSH and estradiol levels and local institutional guidelines.

7.1.2.7 Tumor Imaging and Assessment of Disease

The process for image collection and transmission to the central imaging vendor can be found in the Site Imaging Manual. Tumor imaging may be performed by computed tomography (CT) (preferred) or magnetic resonance imaging (MRI), but the same imaging technique should be used in a subject throughout the trial. A CT is the more commonly used modality and is preferred for the majority of subjects. An MRI can be utilized if clinically appropriate.

During screening, brain imaging should be performed in subjects with known brain metastases (such subject also need records of brain imaging performed at least 4 weeks earlier) and subjects with worsening and/or new neurological symptoms. Subjects with previously treated brain metastases may participate provided they have stable brain metastases, ie, without evidence of progression by imaging (confirmed by MRI if MRI was used at prior imaging, or confirmed by CT imaging if CT was used at prior imaging) for at least 4 weeks prior to the first dose of trial treatment. Any neurologic symptoms must have returned to baseline and subjects must have no evidence of new or enlarging brain metastases, and have not used steroids for brain metastases for at least 28 days prior to trial initiation as per local site assessment. This exception does not include carcinomatous meningitis, as subjects with carcinomatous meningitis are excluded regardless of clinical stability.

While on study, brain imaging should be performed in subjects with known brain metastases and subjects with worsening and/or new neurological symptoms. If MRI is medically contraindicated, CT imaging will be accepted. Brain imaging would be done Q9W for first year, then Q12W, as specified in the Trial Flow Chart (Section 6.0).

If applicable, bone scans will be performed as specified in the Trial Flow Chart (Section 6.0). Bone scans at screening for any subject with known bone metastases and/or new bone pain and musculoskeletal complaints. During the study, bone scans will be performed as needed for evaluation of worsening and/or new bone pain and musculoskeletal complaints or if the site believes they have attained a Complete Response. If a subject has no known metastatic disease in the bone or active symptoms, a bone scan at baseline is not needed. A bone scan can be obtained at follow up if there are new symptoms of bone pain.

All scheduled images for all study subjects from the sites will be submitted to the central imaging vendor (CIV). In addition, all unscheduled images that the site considers contributes to progression or response will be submitted to the CIV. The central imaging vendor will receive all images from the sites and verify progressive disease following site-assessed 1st radiologic evidence of progressive disease using RECIST 1.1. The verification of radiologic PD will be expedited by the CIV. The CIV verification of radiologic PD will be communicated to the site (Section 7.1.2.7.3) and sponsor within 3- 5 business days after receipt of all required imaging and resolution of all queries in real-time. Expedited verification of radiologic progression as determined by central imaging vendor review (following site-assessed 1st radiologic evidence of progressive disease) will be communicated to the site (Section 7.1.2.7.3). The CIV will perform a retrospective analysis of subject eligibility (per RECIST 1.1) and treatment response by (using RECIST 1.1 and irRECIST) and these will be provided to the sponsor. Sponsor will also receive tumor imaging for a retrospective analysis of subject eligibility and treatment response to be performed by the central vendor using RECIST 1.1 and irRECIST. Figure 2 shows the process for tumor assessment by site and central imaging vendor for a clinically stable subject.

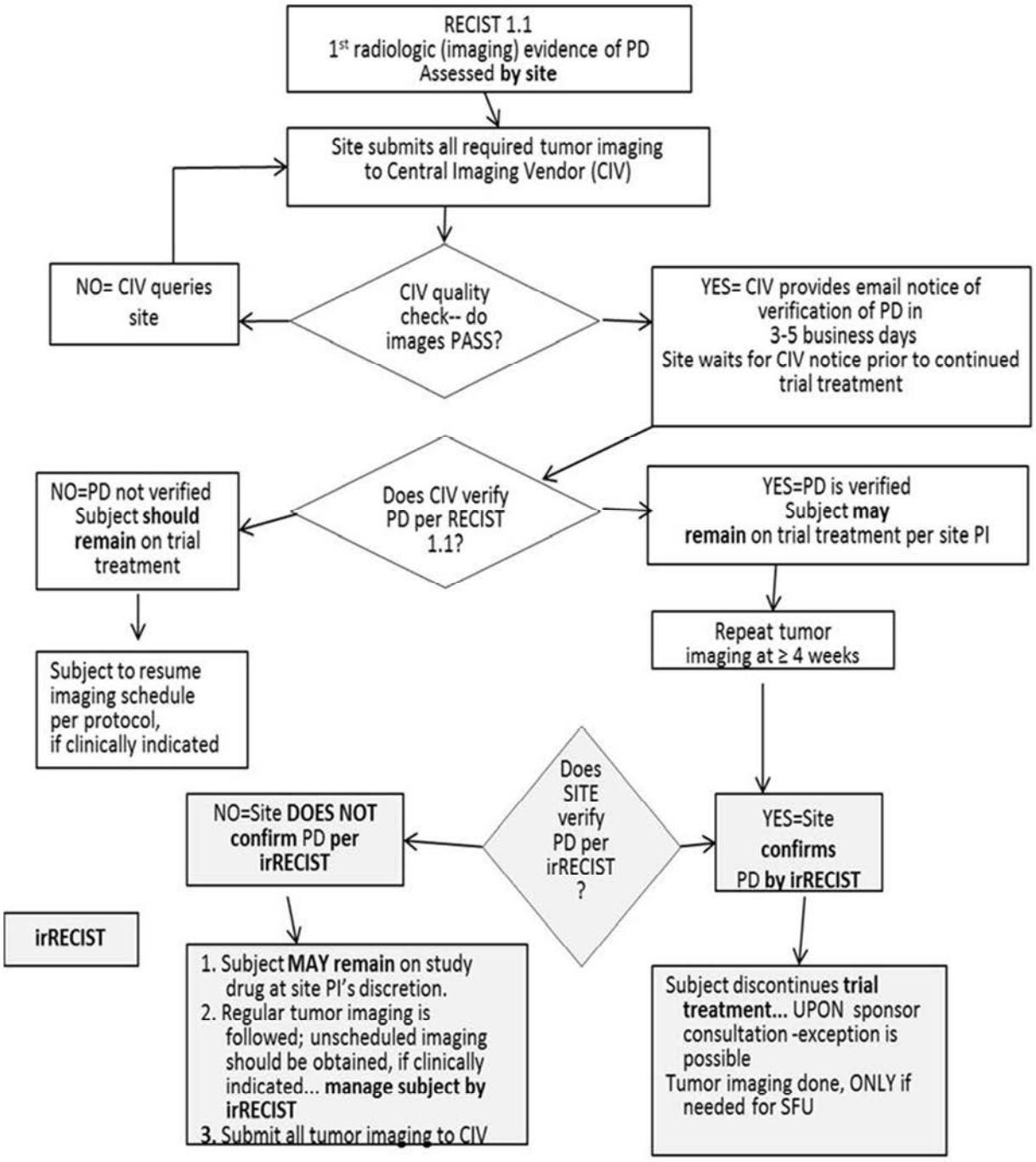
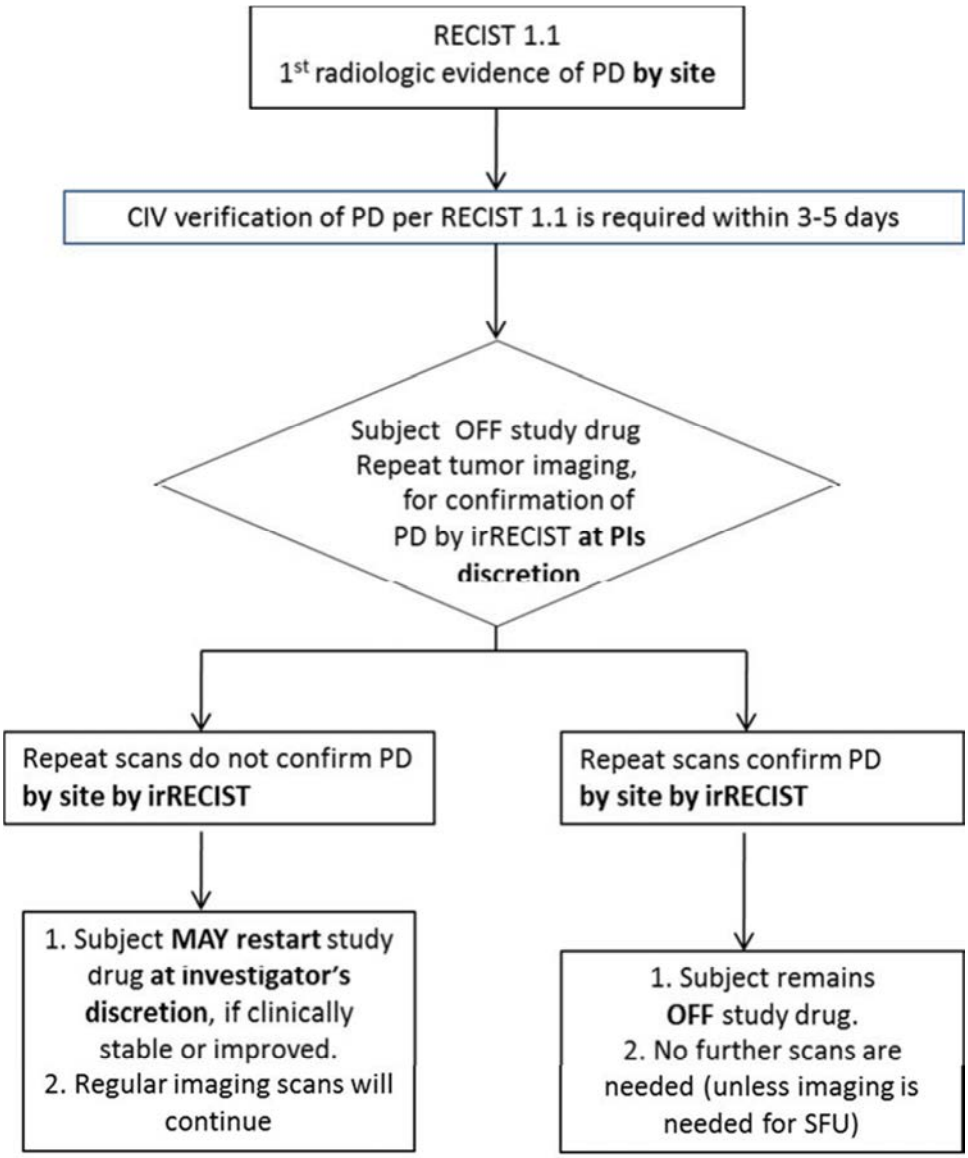


Figure 2 Imaging and Treatment for Clinically Stable Subjects After First Radiologic Evidence of Progressive Disease Assessed by the Site

Figure 3 shows the process for tumor assessment by site and central imaging vendor for a clinically unstable subject.



* Site must send all required imaging to CIV and resolve all imaging queries; then the 3 -5 business day TAT for notification begins. Any unscheduled imaging that supports a site based assessment of PD should also be sent to CIV.

Figure 3 Imaging Process for a Clinically Unstable Subject

7.1.2.7.1 Baseline Tumor Imaging

To meet screening criteria, tumor imaging must be performed within 28 days prior to date of randomization. Eligible subjects must have measurable disease based on RECIST 1.1 as assessed by site Investigator and local radiology review. Tumor imaging performed as part of routine clinical management are acceptable for use as the screening tumor imaging if they are of diagnostic quality, meet the requirements specified in the Site Imaging Manual (SIM), and were performed within 28 days prior to randomization.

Brain imaging at baseline should be performed in subjects with known brain metastases (such subjects also need records of brain imaging performed at least 4 weeks earlier) and those with worsening and/or new neurological symptoms.

If a subject has a known history of bone metastases or has new bone pain during screening, a bone scan should be obtained prior to study entry. If a subject has no known metastatic disease in the bone or active symptoms, a bone scan at baseline is not needed. Additionally, plain X-ray evaluation should be obtained for symptomatic skeletal sites with negative bone scan evaluations.

7.1.2.7.2 Tumor Imaging During the Trial

All subjects should have imaging assessments performed as specified in the Trial Flow Chart (Section 6.0). Subjects should have tumor imaging at 9 weeks (± 7 days) from date of randomization up to 1 year (more frequently if clinically indicated). All subjects who remain on treatment for a year will subsequently 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 continue to be performed until site-assessed 1st radiologic evidence of disease progression (PD) is verified by the central imaging vendor (unless the site PI determines the subject would benefit from continued treatment and then follows the subject per irRECIST), the start of new anti-cancer treatment, withdrawal of consent, death, or the end of the study, whichever occurs first. All supplemental imaging must be submitted to the central imaging vendor.

Bone scans will also be utilized to assess osseous metastases. If a subject has a known history of bone metastases or has new bone pain during screening, a bone scan should be obtained prior to study entry. A bone scan at follow up is required only if they develop new or worsening symptoms or if the site believes they have attained a Complete Response. If a subject has no known metastatic disease in the bone or active symptoms, a bone scan at baseline is not needed. A bone scan can be obtained at follow up if there are new symptoms of bone pain. Additionally, plain X-ray evaluation will be obtained for symptomatic sites with negative bone scan evaluations.

Brain imaging during the trial should be performed as specified in the Trial Flow Chart (Section 6.0) in subjects with known brain metastases (Q9W for first year, then Q12W) and those with worsening and/or new neurological symptoms.

Per RECIST 1.1, response (partial response (PR) or CR should be confirmed by a repeat tumor imaging not less than 4 weeks from the date the response was first documented. The tumor image for confirmation of response may be performed at the earliest 4 weeks after the first indication of response, or at the next scheduled tumor imaging (eg 9 weeks later) whichever is clinically indicated.

After central verification of PD by RECIST 1.1 in support of the PFS analysis, if the site PI determines the subject is clinically stable and will benefit from continued treatment, the subject will then be managed by irRECIST. Per irRECIST, that initial PD by RECIST 1.1 must be in clinically stable subjects, disease progression may be confirmed by the site Investigator/ local radiology review at least 4 weeks after verification of 1st site-assessed 1st radiologic evidence of PD. Subjects who have unconfirmed disease progression (PD) may continue on treatment until progression PD is confirmed provided they have met the conditions detailed in Section 7.1.2.7.4.

7.1.2.7.3 End of Treatment and Follow-up Tumor Imaging

In subjects who discontinue study therapy, tumor imaging should be performed at the time of treatment discontinuation (ie, date of discontinuation ± 4 week window). If previous tumor imaging was obtained within 4 weeks prior to the date of discontinuation, then tumor imaging at treatment discontinuation is not required. In subjects who discontinue trial treatment due to documented disease progression, this is the final required tumor imaging.

In subjects who discontinue trial treatment without centrally verified disease progression, every effort should be made to continue monitoring their disease status by tumor imaging using the same imaging schedule used while on treatment (Q9W in Year 1 or 12 weeks after Year 1) to monitor disease status until the start of a new anticancer treatment, disease progression, death, or the end of the trial, whichever occurs first.

7.1.2.7.4 RECIST 1.1

RECIST 1.1 will be applied by the central imaging vendor within 3- 5 business days in real-time after receipt of all imaging and resolution of any queries to verify site-assessed 1st radiologic evidence of PD retrospectively as the primary measure for assessment of tumor response and retrospectively to determine subject eligibility. All scheduled images for all study subjects from the sites will be submitted to the central imaging vendor (CIV). In addition, all unscheduled images that the site considers contributes to progression or response will be submitted to the CIV. All tumor images should be submitted to the central vendor.

7.1.2.7.5 irRECIST

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 antitumor 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. Immune-related RECIST (irRECIST) is RECIST 1.1 adapted to account for the unique tumor response seen with immuno-therapeutics as described in section 7.1.2.6. irRECIST will be used by local site investigators to assess tumor response and progression, and make treatment decisions.

Therefore, RECIST 1.1 will be used with the following adaptations:

In subjects who have initial evidence of radiological PD by RECIST 1.1 as verified by central imaging vendor, it is at the discretion of the PI whether to continue a subject on study treatment until repeat imaging is obtained. Subjects may receive study treatment and tumor assessment should be repeated ≥ 4 weeks later in order to confirm PD by irRECIST per site assessment. Clinical stability is defined as the following:

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

In determining whether or not the tumor burden has increased or decreased per irRECIST, the local site Investigator should consider all target and non-target lesions as well as any incremental new lesion(s). An adaptation of irRECIST has been employed and is outlined below [102].

Scenarios where PD is confirmed at repeat imaging if ANY of the following occur by irRECIST:

- Tumor burden remains ≥ 20% and at least 5 mm absolute increase compared to nadir
- Non-target disease resulting in initial PD is worse (qualitative assessment)
- New lesion resulting in initial PD is worse (qualitative assessment)
- Additional new lesion(s) since last evaluation
- Additional new non-target progression since last evaluation

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

Scenarios where PD is not confirmed at repeat imaging if ALL of the following occur by irRECIST:

- Tumor burden is < 20 % or < 5 mm absolute increase compared to nadir
- Non-target disease resulting in initial PD is stable or improved (qualitative assessment)
- New lesion resulting in initial PD is stable or improved (qualitative assessment)

- No incremental new lesion(s) since last evaluation
- No incremental new non-target progression since last evaluation

If repeat imaging does not confirm PD by irRECIST and the subject continues to be clinically stable, treatment may continue and follow the regular imaging schedule.

When feasible, subjects should not be discontinued until progression is confirmed by the local site Investigator/radiology assessment. This allowance to continue treatment despite initial radiologic progressive disease (PD) takes into account the observation that some subjects can have a transient tumor flare in the first few months after the start of immunotherapy, and then experience subsequent disease response. Subjects that are deemed clinically unstable are not required to have repeat tumor imaging for confirmation of PD.

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

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

For a clinically stable subject with site-assessed 1st radiologic evidence of progressive disease by RECIST 1.1 that has been verified by central imaging vendor (ie, unconfirmed progression of disease), it is at the discretion of the site Investigator to continue treating the subject with the assigned treatment per protocol until progression of disease is confirmed at least 28 days from the date of the tumor image first suggesting PD which was ultimately verified by CIV per RECIST 1.1. If progression by irRECIST is not confirmed by the subsequent tumor imaging, the subject should continue to receive study therapy and have tumor imaging performed every 9 weeks (63 ± 7 days) during the first year and every 12 weeks (84± 7 days) after the first year, or sooner if clinically indicated, to monitor disease status. If radiologic progression is confirmed by subsequent tumor image, then the subject will be discontinued from trial treatment.

NOTE: If a subject with confirmed radiographic progression (ie 2 tumor images at least 28 days apart demonstrating progressive disease) per irRECIST, but the subject is achieving a clinically meaningful benefit, and there is no further increase in the tumor burden at the confirmatory tumor imaging, an exception to continue treatment may be considered following consultation with the Sponsor. In this case, if treatment is continued, tumor imaging should continue to be performed following the intervals as outlined in section 7.1.2.7. Study Flowchart and be submitted to the CIV. Subjects exhibiting toxicity from trial therapy as outlined in Sections 5.2.1 and Section 7.2 may NOT continue to receive trial therapy.

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

The same imaging technique, acquisition, and processing parameters should be used in a subject throughout the trial. Additional information is included in the Site Imaging Manual.

7.1.2.8 Tumor Tissue Collection and Correlative Blood Sampling

7.1.2.8.1 Tumor Tissue Collection

All subjects must have central confirmation of triple-negative breast cancer status prior to randomization (Section 5.1.2). A newly obtained core or excisional tumor biopsy (fine needle aspirate [FNA] not adequate) **from a metastatic lesion** (or archival biopsy, if new biopsy cannot be obtained due to site inaccessibility or a medical contraindication and sponsor agreement is obtained) will be used for confirmation of triple-negative breast tumor status. 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 guide-lines:

a. Estrogen receptor (ER) negative status is defined as <1% tumor cells positive for ER by IHC, irrespective of staining intensity

b. Progesterone receptor negative status is defined as <1% tumor cells positive for Progesterone receptor 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*/CEP17 ratio <2.0 with an average HER2 copy number <4.0 signals/cell

A newly obtained core or excisional tumor biopsy (fine needle aspirate is not adequate) from a metastatic lesion will also be used for central determination of PD-L1 tumor status.

When available, archived tumor specimens from prior biopsies will also be collected for determination of PD-L1 tumor status and comparison of biomarker expression in archived vs newly obtained tumor specimens.

Newly obtained tumor tissue should be submitted in formalin (preferred) or as formalin-fixed paraffin embedded 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 7 days from site slide sectioning date otherwise a new specimen will be requested.

The same new tissue sample may be used for both mTNBC status and PD-L1 status. Newly obtained tumor tissue may be obtained up to 56 days prior to treatment initiation. Tumor tissue obtained recently, but prior to the 56-day window, may be considered with Sponsor consultation.

Only in the pembrolizumab arm, an optional core or excisional biopsies may be obtained while on treatment, on or after cycle 2, and/or at disease progression, as specified in the Trial Flow Charts (Section 6.0).

Note: For all tumor tissue collected, a fine needle aspirate, frozen sample, plastic embedded sample, cell block, clot, bone, bone marrow, cytologic specimen, decalcified, or formalin fixed sample that was frozen at any point will not be acceptable for analysis.

Detailed instructions for tissue collection, processing and shipments are provided in the vendor's manual.

7.1.2.8.2 Blood for Correlative Studies

Blood for correlative biomarker studies (RNA and DNA) should be collected pre-dose at Cycle 1, 2, 3, and at treatment discontinuation.

Detailed instructions for specific time points per sample, tissue collection, processing and shipment are provided in the vendor's manual.

7.1.2.9 Patient-Reported Outcomes

The eEuroQol (EQ)-5D, eEORTC QLQ-C30 and eEORTC QLQ-BR23 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 drug administration, adverse event evaluation and disease status notification. The ePROs are completed in the following order: eEuroQol (EQ)-5D first, then eEORTC QLQ-C30, and lastly the eEORTC QLQ-BR23 at the time points specified in the Trial Flow Charts and briefly summarized below.

7.1.2.9.1 The Patient-Reported Outcomes

The Patient Reported Outcomes (PROs) are assessed as follows (as specified in the Trial Flow Charts (Section 6.0):

- If a TPC treatment has more than one dose per cycle, the ePROs will only be administered on the first treatment day of the cycle.
- At cycles 1, 2, and 3
- Every 3rd cycle after Cycle 3 until the end of Year 1 (ie, Cycles 6, 9, 12, etc.)

- Every 4th cycle during Year 2 until PD
- At the Treatment Discontinuation Visit*
- At the 30-day Safety Follow-up Visit*

*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, PROs do not need to be repeated.

7.1.3 Laboratory Procedures/Assessments

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

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

Laboratory tests for hematology, chemistry and urinalysis are specified in Table 7

Table 7 Laboratory Tests

Hematology	Chemistry	Urinalysis	Other
Hematocrit	Albumin	Blood	Serum β-human chorionic gonadotropin (β-hCG)[a]
Hemoglobin	Alkaline phosphatase	Glucose	PT (INR)
Platelet count	Alanine aminotransferase (ALT)	Protein	aPTT[d]
White blood cell (total and differential)	Aspartate aminotransferase (AST)	Specific gravity	Total triiodothyronine (T3) or Free T3[e]
Red blood Cell Count	Bicarbonate[b]	Microscopic exam, if abnormal results are noted	Free thyroxine (T4)
Absolute neutrophil count[g]	Calcium		Thyroid stimulating hormone (TSH)
Absolute lymphocyte count[g]	Chloride		Blood for future biomedical research (FBR)
	Creatinine		Blood for correlative studies
	Glucose		PK (for subjects on the pembrolizumab arm only)
	Phosphorus		Anti-pembrolizumab Antibodies (for subjects on the pembrolizumab arm only)
	Magnesium (only subjects on Eribulin)		FSH, estradiol[f]
	Potassium		Vitamin D levels

Hematology	Chemistry	Urinalysis	Other
	Sodium		Tumor markers (CA15-3, CEA, and CA27.29)
	Total bilirubin		
	Direct bilirubin, if total bilirubin is elevated above the upper limit of normal		
	Total protein		
	Blood urea nitrogen		
	Lactate dehydrogenase (LDH)		
	Carbon dioxide (CO_2 or bicarbonate)[b]		
	Uric acid		
	Urea[c]		

a. Perform on women of childbearing potential only.
b. If considered standard of care in your region.
c. Blood urea nitrogen is preferred; if not available urea may be tested.
d. 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 trial.
e. Total T3 is preferred; if not available free T3 may be tested.
f. Blood for menopausal status is only required for some subjects as described in Section 7.1.3.6
g. Either absolute or % is acceptable as per institutional standard

Laboratory tests will be performed as specified in the Trial Flow Chart (Section 6.0). Laboratory tests for screening should be performed within 10 days prior to randomization. After Cycle 1, pre-dose laboratory procedures can be conducted up to 72 hours prior to dosing. Safety laboratory results must be reviewed by the Investigator or qualified designee and found to be acceptable prior to each dose of trial treatment.

Exception: Thyroid function testing (T3, FT4, and TSH), Vitamin D, and tumor markers (CA15-3, CEA and CA27.29) results can be reviewed following scheduled dosing.

7.1.3.2 Pregnancy Test

For women of reproductive potential, a urine or serum pregnancy test should be performed within 72 hours prior to the first dose of trial treatment. If the urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required. If subject meets criteria for second course phase a urine or serum pregnancy test should be completed prior to restarting pembrolizumab. Pregnancy tests (serum and/or urine tests) during the study should be completed if deemed necessary by PI or required by local guidelines. Subjects must be excluded/discontinued from the trial in the event of a positive or borderline-positive test result.

7.1.3.3 Pharmacokinetic/Pharmacodynamic 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 05 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 05 may be stored. Analysis will be performed only if required.

7.1.3.4 Planned Genetic Analysis Sample Collection

Sample collection, storage and shipment instructions for Planned Genetic Analysis samples will be provided in the vendor's manual.

This sample should be drawn for planned analysis of the association between genetic variants in DNA and drug response.

If there is either a documented law or regulation prohibiting collection, or if the IRB/IEC does not approve the collection of the sample for these purposes, then this sample will not be collected at that site.

If the sample is collected, leftover extracted DNA will be stored for future biomedical research if the subject signs the FBR consent.

7.1.3.5 Blood for Correlative Studies

Blood for correlative studies (includes blood for DNA and RNA) should be collected predose Cycle 1, Cycle 2, Cycle 3, and at treatment discontinuation.

Blood for exploratory biomarkers (plasma and serum), should be collected pre-dose Cycle 1. Detailed instructions with specific time points per sample are provided in the vendor's manual.

7.1.3.6 Blood for Menopausal Status

Blood collection at screening for biochemical evidence of menopausal status (FSH and estradiol) will be completed if applicable.

7.1.3.7 Future Biomedical Research

The following specimens are to be obtained as part of Future Biomedical Research:

- Leftover DNA
- Leftover main study tumor specimens

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

7.1.4 Other Procedures

7.1.4.1 Withdrawal/Discontinuation

Subjects who discontinue/withdraw from study treatment prior to completion of the trial should be encouraged to continue to be followed for all remaining study visits and survival follow-up contacts.

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. Subjects on the pembrolizumab arm who a) attain a CR or b) complete 35 treatments with pembrolizumab may discontinue treatment with the option of restarting treatment if they meet the criteria specified in Section 7.1.5.2.1. After discontinuing treatment following assessment of CR or 35 treatments, these subjects should return to the site for a Safety Follow-up Visit (Section 7.1.5.3.2) and then proceed to the Follow-up Period of the study (Section 7.1.5.3.3).

7.1.4.1.1 Withdrawal From Future Biomedical Research

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

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

7.1.4.2 Blinding/Unblinding

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

7.1.4.3 Calibration of Critical Equipment

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

Critical Equipment for this trial includes:

- Laboratory equipment – as required for inclusion labs and trial assessments
- Imaging equipment – as required for study objectives
- Drug administration equipment – as required for storage, preparation and administration (infusion) of study drug.

See protocol-specified guidance in the Administrative Binder, vendor's manual, and Site Imaging Manual.

7.1.5 Visit Requirements

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

7.1.5.1 Screening

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 PS are to be performed within 10 days prior to randomization.
- For women of reproductive potential, a urine or serum pregnancy test will be performed within 72 hours prior to receiving the first dose of study medication.
- Newly obtained tumor tissue, and archival tissue when available, may be obtained within 56 days of treatment initiation.

Subjects may be rescreened twice after initially failing to meet the inclusion/exclusion criteria. Results from assessments performed during the initial screening period are acceptable in lieu of a repeat screening test if performed within the specified time frame and the inclusion/exclusion criteria is met.

7.1.5.2 Treatment Period

Visit timing requirements during the treatment period are as follows:

- Assessments/procedures should be performed prior to dose for each cycle unless otherwise specified in the flow chart.
- Treatment cycles are Q3W for pembrolizumab and according to local label or guidelines for TPC arm.
- 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 biopsies may be obtained while on treatment, on or after cycle 2, or at disease progression for the pembrolizumab arm only.

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

7.1.5.2.1 Second Course Phase (Retreatment Period)

7.1.5.2.1.1 Conditions of Second Course Phase

Subjects on the pembrolizumab arm who stop pembrolizumab with SD or better may be eligible for up to one year of additional pembrolizumab therapy if they progress after stopping study treatment. This retreatment 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 after attaining an Investigator-determined confirmed CR according to RECIST 1.1
  - Following at least 8 treatments with pembrolizumab before discontinuing therapy, and
  - Received at least 2 treatments with pembrolizumab beyond the date when the initial CR was declared

OR

- Had SD, PR or CR and stopped pembrolizumab treatment after 35 treatments of study therapy for reasons other than disease progression or intolerability

AND

- Experienced an Investigator-determined confirmed radiographic disease progression after stopping their initial treatment with pembrolizumab
- Did not receive any anti-cancer treatment since the last dose of pembrolizumab
- Has a performance status of 0 or 1 on the ECOG Performance Scale

- Demonstrates adequate organ function as detailed in Section 5.1.2
- Female subject of childbearing potential should have a negative urine or serum pregnancy test within 72 hours prior to receiving retreatment with study drug.
- Female subject of childbearing potential should be willing to use 2 methods of birth control or be surgically sterile, or abstain from heterosexual activity for the course of the study through 120 days (at least 6 months for subjects on gemcitabine) after the last dose of study drug (Section 5.7.2). Subjects of child bearing potential are those who have not been surgically sterilized or have been free from menses for > 1 year.
- Male subject should agree to use an adequate method of contraception starting with randomization through 120 days (at least 6 months for subjects on gemcitabine) after the last dose of study therapy.
- Does not have a history or current evidence of any condition, therapy, or laboratory abnormality that might interfere with the subject's participation for the full duration of the trial or is not in the best interest of the subject to participate, in the opinion of the treating Investigator.

7.1.5.2.1.2 Visit Requirements of Second Course Phase

7.1.5.2.1.2.1 Assessments/Procedures/Windows

Assessments are performed on Day 1 and prior to randomization for each cycle unless otherwise specified. Treatment cycles are 3 weeks and visit windows are ± 3 days unless otherwise noted. If toxicity occurs, refer to the dose modification guidelines provided in Section 5.2.1.2.1. Imaging should always be performed Q9W (± 7 days) regardless of any treatment delays.

7.1.5.2.1.2.2 Discontinuation During the Second Course Phase

In subjects who discontinue study therapy, tumor imaging should be performed at the time of treatment discontinuation (ie, date of discontinuation ± 4 week window). If a previous tumor image was obtained within 4 weeks prior to the date of discontinuation, then a tumor image at treatment discontinuation isn't mandatory.

For those subjects that discontinue study therapy without documented disease progression, every effort should be made to continue monitoring their disease status by tumor imaging every 9 weeks (± 7 days) until (1) the start of new anti-cancer treatment, (2) disease progression, (3) death, or (4) the end of the study, whichever occurs first.

7.1.5.2.1.2.3 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 of pembrolizumab. See Section 7.1.3 for details regarding laboratory tests.

For women of reproductive potential, a urine or serum pregnancy test should be performed within 72 hours prior to first re-treatment dose. Pregnancy tests should be repeated if required by local guidelines.

After Cycle 1, lab samples can be collected up to 72 hours prior to the scheduled time point. See Section 7.1.3 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 trial for any subject receiving anticoagulant therapy.

Unresolved lab abnormalities that are drug related AEs should be followed until resolution. Labs do not need to be repeated after the end of trial treatment if labs are within normal range.

Laboratory safety measurements will be graded per NCI CTCAE version 4.0.

7.1.5.2.1.2.4 Concomitant Medications During the Second Course Phase

Enter new medications started during the trial through the Safety Follow-up visit. Record all medications taken for AEs as defined in Section 7.2.

7.1.5.2.1.2.5 Vital Signs During the Second Course Phase

Vital signs to include temperature, pulse, respiratory rate, weight and blood pressure. Vitals should be taken prior to treatment administration.

7.1.5.2.1.2.6 Pembrolizumab Restart During the Second Course Phase

Subjects who restart treatment should resume pembrolizumab at the dose and interval specified in Section 6.2.

7.1.5.2.1.2.7 Tumor Imaging Second Course Phase

Tumor imaging must be performed within 28 days prior to restarting treatment with pembrolizumab. Imaging should continue to be performed Q9W (± 7 days) from first re-treatment dose or more frequently if clinically indicated, as specified in the Trial Flow Chart (Section 6.2). Local reading (site Investigator/local radiology review) will be used to determine eligibility and for subject management. The Sites will collect and send tumor imaging to the central imaging vendor. The Sponsor will collect tumor imaging for retrospective analysis by a central imaging vendor. The processes for image collection and transmission to the central vendor are in the Site Imaging Manual. The same imaging technique, acquisition, and processing parameters should be used in a subject throughout the trial.

After the start of new anti-cancer treatment or documented disease progression by the central imaging vendor, the subject should be contacted by telephone Q12W to assess for survival status.

7.1.5.3 Post-Treatment Visits

7.1.5.3.1 Discontinuation Visit

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

7.1.5.3.2 Safety Follow-up Visit

The mandatory Safety Follow-Up Visit should be conducted approximately 30 days after the last dose of trial treatment or before the initiation of a new anti-cancer treatment, whichever comes first. All AEs that occur prior to the Safety Follow-Up Visit should be recorded. Subjects with an AE of Grade > 1 will be followed until the resolution of the AE to Grade 0-1 or until the beginning of a new anti-cancer therapy, whichever occurs first. Each subject will be followed for 30 days for AEs and ECIs. Serious adverse events will be collected for 90 days after the end of trial treatment.

Subjects who are eligible for retreatment with pembrolizumab (Section 7.1.5.2.1) may have up to two safety follow-up visits, one after the Treatment Period and one after the Second Course Phase.

7.1.5.3.3 Follow-up Visits

Subjects who discontinue trial treatment for a reason other than disease progression will move into the Follow-Up Phase and should be assessed Q9W (± 7 days) by tumor imaging to monitor disease status. After 1 year, imaging will be performed Q12W (± 7 days).

Every effort should be made to collect information regarding disease status until the start of new anti-cancer therapy, disease progression determined by central imaging vendor, death, end of study or if the subject begins retreatment with pembrolizumab (Section 7.1.5.2.1). 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 7.1.5.2.1 will move from the Follow-Up Phase to the Second Course Phase when they experience disease progression. Details are provided in Section 6.0 for Retreatment with pembrolizumab.

7.1.5.3.4 Survival Follow-up

Once a subject experiences disease progression by site assessment and verified by central imaging vendor review or starts a new anti-cancer therapy, the subject moves into the Survival Follow-Up Phase and should be contacted by telephone at least Q12W (more

frequently if needed) from the last contact date to assess for survival status until death, withdrawal of consent, or the end of the study, whichever occurs first.

7.1.5.3.5 Survival Status

To ensure current and complete survival data are 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 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 participants that have previously recorded a death event in the collection tool).

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 randomization/treatment allocation 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 randomization/treatment allocation 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 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 this trial, an overdose will be defined as ≥1000 mg (5 times the dose) of pembrolizumab and as any dose ≥20% over the prescribed dose for the comparator agents. No specific information is available on the treatment of overdose of pembrolizumab. In the event of overdose, pembrolizumab should be discontinued and the subject should be observed closely for signs of toxicity. Appropriate supportive treatment should be provided if clinically indicated.

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

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

All reports of overdose with and without an adverse event must be reported by the investigator within 24 hours to the Sponsor either by electronic media or paper. Electronic reporting procedures can be found in the EDC data entry guidelines. Paper reporting procedures can be found in the Investigator Trial File Binder (or equivalent).

7.2.2 Reporting of Pregnancy and Lactation to the Sponsor

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

Pregnancies and lactations that occur after the consent form is signed but before randomization/treatment allocation 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 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 8 for additional details regarding each of the above criteria.

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

Events of clinical interest for this trial include:

1. an overdose of Sponsor's product, as defined in Section 7.2.1 - Definition of an Overdose for This Protocol and Reporting of Overdose to the Sponsor, that is not associated with clinical symptoms or abnormal laboratory results.

2. an elevated AST or ALT lab value that is greater than or equal to 3X the upper limit of normal and an elevated total bilirubin lab value that is greater than or equal to 2X the upper limit of normal and, at the same time, an alkaline phosphatase lab value that is less than 2X the upper limit of normal, as determined by way of protocol-specified laboratory testing or unscheduled laboratory testing.*

   *Note: These criteria are based upon available regulatory guidance documents. The purpose of the criteria is to specify a threshold of abnormal hepatic tests that may require an additional evaluation for an underlying etiology. The trial site guidance for assessment

and follow up of these criteria can be found in the Investigator Trial File Binder (or equivalent).

7.2.3.3 Protocol-Specific Exceptions to Serious Adverse Event Reporting

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

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

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

7.2.4 Evaluating Adverse Events

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

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

Table 8 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 a Merck product and is documented in the subject'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 Data Monitoring Committee (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.

8.0 STATISTICAL ANALYSIS PLAN

This section outlines the statistical analysis strategy and procedures for the study. If, after the study has begun, changes are made to primary and/or key secondary hypotheses, or the statistical methods related to those hypotheses, then the protocol will be amended (consistent with ICH Guideline E-9). Changes to exploratory or other non-confirmatory analyses made after the protocol has been finalized, but prior to the conduct of any analysis unblinding, 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. Post hoc exploratory analyses will be clearly identified in the CSR. A patient-reported outcome (PRO) analysis plan will be included in the sSAP.

In this section, "Subjects with PD-L1 positive tumors (CPS ≥10)" is abbreviated as "Subjects with CPS ≥10", and "Subjects with PD-L1 positive tumors (CPS ≥1)" is abbreviated as "Subjects with CPS ≥1".

8.1 Statistical Analysis Plan Summary

Key elements of the statistical analysis plan are summarized below; the comprehensive plan is provided in Section 8.2 through Section 8.12.

Study Design Overview	A Phase III Randomized Trial of Single Agent Pembrolizumab versus Single Agent Chemotherapy per Physician's Choice for Metastatic Triple Negative Breast Cancer (mTNBC)
Treatment Assignment	Approximately 600 subjects will be randomized in a 1:1 ratio between two treatment groups: (1) pembrolizumab arm and (2) Treatment of Physician's Choice (TPC) arm. Stratification factors are: 1) PD-L1 tumor status (positive [CPS ≥1] vs negative [CPS <1]), and 2) history of prior (neo)adjuvant treatment vs de novo metastatic disease at initial diagnosis.
Analysis Populations	Efficacy: Intention-to-treat Population (ITT) Safety: All Subjects as Treated (ASaT)
Primary Endpoint(s)	1 Overall survival (OS) in subjects with CPS ≥10 2 OS in subjects with CPS ≥1 3 OS in all subjects
Statistical Methods for Key Efficacy Analyses	The primary hypotheses will be evaluated by comparing pembrolizumab to TPC on OS using a stratified Log-rank test. Estimation of the hazard ratio will be performed using a stratified Cox regression model. Event rates over time will be estimated within each treatment group using the Kaplan-Meier method.
Statistical Methods for Key Safety Analyses	The analysis of safety results will follow a tiered approach. Safety parameters or adverse experiences of special interest that are identified *a priori* constitute "Tier 1" safety endpoints that will be subject to inferential testing for statistical significance with p-values and 95% confidence intervals (CIs) provided for between-group comparisons. Other safety parameters will be considered Tier 2 (with 95% confidence intervals provided) or Tier 3 (with point estimates by treatment group provided) The between-treatment difference will be analyzed using the Miettinen and Nurminen method.

Interim Analyses	One interim efficacy analysis is planned in this study. Details are provided in Section 8.7.
	• Interim Analysis
	  o Timing: approximately 14 months after enrollment is completed. It is estimated that approximately 130, 284 and 445 OS events will be accrued in subjects with CPS ≥10, CPS ≥1 and all subjects.
	  o Purpose: interim efficacy analysis for OS
	• Final analysis
	  o Triggered by duration of follow-up and OS events in subjects with CPS ≥1: Approximately 24 months after enrollment is completed or 334 OS events accrue in subjects with CPS ≥1, whichever occurs later. Approximately 154, 334 and 520 OS events will be accrued in subjects with CPS ≥10, CPS ≥1 and all subjects.
	  o If OS events in subjects with CPS ≥1 accrue slower than expected and fewer than 334 events are observed 26 months after enrollment is completed, then the Sponsor will conduct the final analysis at that time
	  o Purpose: final efficacy analysis for OS

Multiplicity	The overall Type I error over the multiple endpoints will be strongly controlled at 2.5% (one-sided) for primary hypotheses of OS endpoints (initial α of 1.7% in subjects with CPS ≥10 and 0.8% in subjects with CPS ≥1) and secondary hypotheses of PFS and ORR in all subjects. Using an extension [105] of the graphical approach of Maurer and Bretz [96], alpha can be re-allocated between hypotheses. Group sequential methods will be used to allocate alpha between the interim and final analyses for OS endpoints.
Sample Size and Power	The planned sample size is approximately 600 subjects. Details are provided in Section 8.9. • For the primary OS endpoint in subjects with CPS ≥10, with approximately 154 OS events the trial has ~85% power at a one-sided 1.7% alpha-level, if the underlying HR is 0.60, with a HR at boundary for success of ~0.70 (~4.2 month improvement). • For the primary OS endpoint in subjects with CPS ≥1, with approximately 334 OS events the trial has ~80% (90%) power at a one-sided 0.8% (2.5%) alpha-level, if the underlying HR is 0.70, with a HR at boundary for success of ~0.76 (0.80) (~3.1 [2.5] month improvement). • For the primary OS endpoint in all subjects, with approximately 520 OS events the trial has ~66% (80%) power at a one-sided 0.8% (2.5%) alpha-level, if the underlying HR is 0.78, with a HR at boundary for success of ~0.80 (0.84) (~2.4 [1.9] month improvement).

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

Although the trial is open label, analyses or summaries generated by randomized treatment assignment, actual treatment received, and/or PD-L1 biomarker status will be limited and documented. In addition, the independent radiologist(s) will perform the central imaging review without knowledge of treatment group assignment. The study team at the Sponsor consisting of clinical, statistical, statistical programming and data management personnel, will be blinded to subject-level PD-L1 biomarker results. An unblinded Sponsor clinical scientist, unblinded Sponsor statistician and unblinded Sponsor statistical programmer will have access to the subject-level PD-L1 results for the purpose of data review and event monitoring, and will have no other responsibilities associated with the study. A summary of PD-L1 biomarker prevalence may be provided to the study team at the Sponsor by the IVRS vendor or the unblinded Sponsor statistician.

Access to the allocation schedule and the subject-level PD-L1 results for summaries or analyses will be restricted to an unblinded external statistician, and, as needed, an external scientific programmer performing the analysis, who will have no other responsibilities associated with the study.

Treatment-level results at the interim efficacy will be provided by the external unblinded statistician to the eDMC. The external unblinded statistician will have access to allocation schedule, treatment group, PD-L1 status for any analysis required for eDMC review. Limited additional SPONSOR personnel may be unblinded to the treatment level and/or PD-L1 biomarker results of the efficacy interim analyses, if required, in order to act on the recommendations of the eDMC or facilitate regulatory filing after the interim efficacy analysis. The extent to which individuals are unblinded with respect to results of interim analyses will be documented by the unblinded statistician.

The eDMC will serve as the primary reviewer of the unblinded results of the interim efficacy analyses and will make recommendations for discontinuation of the study or modification to an executive oversight committee of the SPONSOR. Depending on the recommendation of the eDMC, the Sponsor may prepare a regulatory submission. If the eDMC recommends modifications to the design of the protocol or discontinuation of the study, this executive oversight committee may be unblinded to results at the treatment level in order to act on these recommendations. Additional logistical details, revisions to the above plan and data monitoring guidance will be provided in the eDMC Charter.

8.3 Hypotheses/Estimation

Objectives and hypotheses of the study are stated in Section 3.0.

8.4 Analysis Endpoints

8.4.1 Efficacy Endpoints

Primary

Overall Survival (OS)

Overall Survival (OS) is defined as the time from randomization to death due to any cause. Subjects without documented death at the time of the final analysis will be censored at the date of the last follow-up.

Secondary and Exploratory

Progression-free survival (PFS) – based on RECIST 1.1 as assessed by blinded central imaging vendor (RECIST 1.1 by site Investigator/local radiology review as a supportive analysis).

Progression-free-survival (PFS) is defined as the time from randomization to the first documented disease progression based on RECIST 1.1 as assessed by blinded central imaging vendor radiology review or death due to any cause, whichever occurs first. See Section 8.6.1 for the definition of censoring.

Overall Response Rate (ORR) – based on RECIST 1.1 (Secondary) and irRECIST (Exploratory) as assessed by blinded central imaging vendor (RECIST 1.1 by site Investigator/local radiology review as the corresponding supportive analyses; irRECIST by site Investigator/local radiology review may also be evaluated).

Overall response rate is defined as the proportion of the subjects in the analysis population who have a complete response (CR) or partial response (PR).

Duration of Overall Response (DOR) – based on RECIST 1.1 (Secondary) and irRECIST (Exploratory) as assessed by blinded central imaging vendor (RECIST 1.1 by site Investigator/local radiology review as the corresponding supportive analyses; irRECIST by site Investigator/local radiology review may also be evaluated).

For subjects who demonstrated CR or PR, response duration is defined as the time from first documented evidence of CR or PR until disease progression or death. See Section 8.6.1 for the definition of censoring.

Disease Control Rate (DCR) – based on RECIST 1.1 (Secondary) and irRECIST (Exploratory) as assessed by blinded central imaging vendor (RECIST 1.1 by site Investigator/local radiology review as the corresponding supportive analyses; irRECIST by site Investigator/local radiology review may also be evaluated).

Disease control rate (DCR) is defined as the proportion of the subjects in the analysis population who have a CR, partial response (PR) and stable disease (SD), the latter for at least 8 cycles.

PFS–based on irRECIST (Exploratory) as assessed by blinded central imaging vendor (irRECIST by site Investigator/local radiology review may be performed as supportive analysis).

8.4.2 Safety Endpoints

Safety measurements are described in Section 7.0

8.4.3 Subject-Reported Outcomes Endpoints

Patient-reported outcome endpoints are described in Section 7.1.2.9.

8.5 Analysis Populations

8.5.1 Efficacy Analysis Populations

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

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

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 drug 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.

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

8.6 Statistical Methods

8.6.1 Statistical Methods for Efficacy Analyses

This section describes the statistical methods that address the primary and secondary objectives. Methods related to exploratory objectives (and supportive analyses including PFS2) will be described in the supplemental SAP.

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. 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 Overall Survival

The non-parametric Kaplan-Meier method will be used to estimate the survival curves. The treatment difference in survival will be assessed by the stratified log-rank test. A stratified Cox proportional hazard model with Efron's method of tie handling will be used to assess the magnitude of the treatment difference (ie, the hazard ratio). The hazard ratio and its 95% confidence interval from the stratified Cox model with a single treatment covariate will be reported. The stratification factors used for randomization [PD-L1 tumor status (positive [CPS ≥1] vs negative [CPS <1]), and prior (neo)adjuvant therapy vs de novo metastatic disease at initial diagnosis] will be applied, as stratification factors used for analysis, to both the stratified log-rank test and the stratified Cox model.

Subjects in the TPC arm are expected to discontinue treatment earlier compared to subjects in the pembrolizumab arm and are not allowed to crossover to the pembrolizumab arm; however, they may be treated with another anti PD-1 drug following the verification of progressive disease by blinded central imaging vendor. As an exploratory analysis, the Rank Preserving Structural Failure Time (RPSFT) model proposed by Robins and Tsiatis (1991) [97] may be used to adjust for the effect of crossover to other PD-1 therapies on OS, based on an examination of the appropriateness of the data to the assumptions required by the methods.

8.6.1.2 Progression-Free Survival

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 (ie, hazard ratio) between the treatment arms. The hazard ratio and its 95% confidence interval 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 [PD-L1 tumor status (positive [CPS ≥1] vs negative [CPS <1]), and Prior (neo)adjuvant therapy vs *de novo* metastatic disease at initial diagnosis] 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, progressive disease (PD) can occur any time in the time interval between the last assessment where PD was not documented and the assessment when PD is documented. For the 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 blinded central imaging vendor. 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 (with exceptions described below). Sensitivity analyses will be performed for comparison of PFS based on Investigator's assessment.

In order to evaluate the robustness of the PFS endpoint based on RECIST 1.1 as assessed by blinded central imaging vendor, we will perform one primary and two sensitivity analyses with a different set of censoring rules. 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 complete follow up 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 discontinuation of treatment or initiation of an anticancer treatment subsequent to discontinuation of study-specified treatments, whichever occurs later, to be a PD event for subjects without documented PD or death. If a subject meets multiple criteria for censoring, the censoring criterion that occurs earliest will be applied. The censoring rules for primary and sensitivity analyses are summarized in Table 9.

In case there is an imbalance between the treatment groups on disease assessment schedules or censoring patterns, we may also perform the following two additional PFS sensitivity analyses: 1) a PFS analysis using time to scheduled tumor assessment visit from randomization as opposed to actual tumor assessment time; 2) Finkelstein (1986)'s likelihood-based score test [98] for interval-censored data, which modifies the Cox proportional hazard model for interval censored data, will be used as a supportive analysis for the PFS endpoint. The interval will be constructed so that the left endpoint is the date of the last disease assessment without documented PD and the right endpoint is the date of documented PD or death, whichever occurs earlier.

Table 9 Censoring Rules for Primary and Sensitivity Analyses of Progression-free Survival

Situation	Primary Analysis	Sensitivity Analysis 1	Sensitivity Analysis 2
No PD and no death; 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 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 versus time for PFS will be plotted for the comparison between pembrolizumab and the TPC arm. 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 [99] and parametric method [100].

One assumption for stratified Cox proportional hazard model is that, the treatment hazard ratio (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 2012 [101], 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.

Further details of sensitivity analyses will be described in a supplemental SAP.

Other sensitivity analyses described for the PFS endpoint will be applied to OS endpoint as appropriate. Further details of sensitivity analyses will be described in supplemental SAP.

8.6.1.3 Overall Response Rate and Disease Control Rate

The stratified Miettinen and Nurminen's method with strata weighting by sample size will be used for comparison of the overall response rate (ORR) and disease control rate (DCR) between the treatment groups. A 95% confidence interval for the difference in response rates between the pembrolizumab and TPC arm will be provided. The stratification factors used for randomization will be applied, as stratification factors used for analysis.

8.6.1.4 Duration of Response

If sample size permits, response duration will be summarized descriptively using Kaplan-Meier medians and quartiles. Only the subset of subjects who show a complete response or partial response will be included in this analysis. See Table 10 for censoring rules for duration of response.

Table 10 Censoring Rules for Duration of Response

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.		

8.6.1.5 Summary of Statistical Methods for Efficacy

Table 11 summarizes the primary analysis approach for primary and secondary efficacy endpoints. Sensitivity analysis methods are described above for each endpoint.

The strategy to address multiplicity issues with regard to multiple efficacy endpoints, multiple populations, and interim analyses is described in Section 8.7 and in Section 8.8.

Table 11 Analysis Strategy for Key Efficacy Endpoints

Endpoint/Variable (Description, Time Point)	Statistical Method†	Analysis Population	Missing Data Approach
Primary Endpoints/Hypothesis			
Primary Hypothesis #1			
OS in subjects with CPS ≥10	Test: Stratified Log-rank test Estimation: Stratified Cox model with Efron's tie handling method	ITT	Censored at last known alive date (More details are in Table 9)
Primary Hypothesis #2			
OS in subjects with CPS ≥1	Test: Stratified Log-rank test Estimation: Stratified Cox model with Efron's tie handling method	ITT	Censored at last known alive date (More details are in Table 9)
Primary Hypothesis #3			
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
Secondary Endpoints/Hypothesis			
Secondary Hypothesis #4			
PFS based on RECIST 1.1 by blinded central imaging vendor 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 9)
Secondary Hypothesis #5			
ORR based on RECIST 1.1 by blinded central imaging vendor in all subjects	Stratified M & N method‡	ITT	Subjects with missing data are considered non-responders

Endpoint/Variable (Description, Time Point)	Statistical Method†	Analysis Population	Missing Data Approach
Secondary Efficacy Objectives			
PFS based on RECIST 1.1 by blinded central imaging vendor in subjects with CPS ≥10 and subjects with 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 9)
ORR based on RECIST 1.1 by blinded central imaging vendor in subjects with CPS ≥10 and subjects with CPS ≥1	Stratified M & N method‡	ITT	Subjects with missing data are considered non-responders
DCR based on RECIST 1.1 by blinded central imaging vendor in subjects with CPS ≥10, subjects with CPS ≥1 and all subjects	Stratified M & N method‡	ITT	Subjects with missing data are considered non-responders
DOR based on RECIST 1.1 by blinded central imaging vendor in subjects with CPS ≥10, subjects with CPS ≥1 and all subjects	Summary statistics using Kaplan-Meier method	All responders in ITT	See Table 10

† Statistical models are described in further detail in the text. For stratified analyses, the stratification factors used for randomization will be as stratification factors for analysis.
‡ Miettinen and Nurminen method.

Methods related to exploratory objectives (and supportive analyses including PFS2) will be described in the supplemental SAP.

8.6.2 Statistical Methods for Safety Analyses

Safety and tolerability will be assessed by clinical review of all relevant parameters including adverse experiences (AEs), laboratory tests, vital signs, etc. Of note, safety analyses will be conducted in all subjects.

Tiered Approach

The analysis of safety results will follow a tiered approach (Table 12). The tiers differ with respect to the analyses that will be performed. Safety parameters or adverse experiences of special interest that are identified *a priori* constitute "Tier 1" safety endpoints that will be subject to inferential testing for statistical significance with p-values and 95% confidence intervals provided for between-group comparisons. Other safety parameters will be considered Tier 2 or Tier 3. Tier 2 parameters will be assessed via point estimates with 95% confidence intervals provided for between-group comparisons; only point estimates by treatment group are provided for Tier 3 safety parameters.

Adverse experiences (specific terms as well as system organ class terms) and predefined limits of change in laboratory, vital signs, that are not pre-specified as Tier-1 endpoints will be classified as belonging to "Tier 2" or "Tier 3", based on the number of events observed. Membership in Tier 2 requires that at least 4 subjects in any treatment group exhibit the event; all other adverse experiences and predefined limits of change will belong to Tier 3.

The threshold of at least 4 events was chosen because the 95% confidence interval for the between-group difference in percent incidence will always include zero when treatment groups of equal size each have less than 4 events and thus would add little to the interpretation of potentially meaningful differences. Because many 95% confidence intervals may be provided without adjustment for multiplicity, the confidence intervals 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/or, vital signs, that are not pre-specified as Tier-1 endpoints will be considered Tier 3 safety parameters. Summary statistics for baseline, on-treatment, and change from baseline values will be provided by treatment group in table format.

For this protocol there are no Tier 1 events. Based on the mechanism of action of pembrolizumab and safety data observed in historic pembrolizumab trials to date, there are no events of interest that warrant classification as Tier I events. 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. P-values (Tier 1 only) and 95% confidence intervals (Tier 1 and Tier 2) 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 (1985), an unconditional, asymptotic method.

To properly account for the potential difference in follow-up time between the study arms, which is expected to be longer in the pembrolizumab arm, AE incidence density adjusted for treatment exposure analyses may be performed as appropriate. Based on emerging external data, the supportive analysis strategy for safety parameters may be modified to improve the integrity and efficiency of the design. Should this happen, the change will be documented in supplemental SAP, if not in a protocol amendment, at the earliest time before any unblinding of the data.

Table 12 Analysis Strategy for Safety Parameters

Safety Tier	Safety Endpoint†	p-Value	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, System Organ Class, or Pre-Defined Limit of Change ‡ (incidence ≥4 of subjects in one of the treatment groups)		X	X
Tier 3	Specific AEs, System Organ Class or Pre-Defined Limit of Change ‡ ‡ (incidence <4 of subjects in all of the treatment groups)			X
	Change from Baseline Results (Labs, ECGs, Vital Signs)			X

† Adverse Experience references refer to both Clinical and Laboratory AEs.
‡ Includes only those endpoints not pre-specified as Tier 1 or not already pre-specified as Tier-2 endpoints.
Note: X = results will be provided.

Time to Grade 3-5 AE

In addition to tiered approach, exploratory analysis will be performed on time to first Grade 3-5 AE. Time to first Grade 3-5 AE is defined as the time from the first day of study medication to the first event of Grade 3-5 AE. The Kaplan-Meier method will be used to estimate the curve of time to first Grade 3-5 AE. The treatment difference in time to first Grade 3-5 AE will be assessed by the stratified log-rank test. A stratified Cox proportional hazard model with Efron's method of tie handling will be used to assess the magnitude of the treatment difference (ie, the hazard ratio). The hazard ratio and its 95% confidence interval from the stratified Cox model with a single treatment covariate will be reported. See details in sSAP.

8.6.3 Summaries of Demographic and Baseline Characteristics

The comparability of the treatment groups for each relevant characteristic will be assessed by the use of tables and/or graphs. No statistical hypothesis tests 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 (eg, age), baseline characteristics, primary and secondary diagnoses, and prior and concomitant therapies will be summarized by treatment either by descriptive statistics or categorical tables.

8.7 Interim Analyses

There is one planned interim efficacy analysis in this trial. Results will be reviewed by an external data monitoring committee (eDMC). Of note, the boundaries for interim and final analyses are presented in Section 8.8.

Interim Analysis

The purpose of the interim analysis (IA) is to evaluate the superiority of pembrolizumab compared to TPC in OS. The IA is triggered by the specified duration of follow-up after enrollment is completed rather than the number of OS events. It will be performed approximately 14 months after enrollment is completed. It is estimated at this time approximately 130 OS events will be accrued in subjects with CPS ≥10, approximately 284 OS events in subjects with CPS ≥1, and approximately 445 OS events in all subjects.

If the pembrolizumab arm demonstrates a superior OS to TPC in all subjects in this interim analysis, the secondary hypotheses for PFS and ORR in all subjects will be tested at the same time. It is estimated that approximately 575 PFS events will have accumulated in all subjects by that time.

Final Analysis

The purpose of the final analysis (FA) is to evaluate the superiority of pembrolizumab compared to TPC in OS. The final analysis is triggered by duration of follow-up and OS events in subjects with CPS ≥1: approximately 24 months after enrollment is completed or 334 OS events accrue in subjects with CPS ≥1, whichever occurs later. It is estimated at this time approximately 154 OS events will be accrued in subjects with CPS ≥10 and approximately 520 OS events in all subjects. If OS events in subjects with CPS ≥1 accrue slower than expected and fewer than 334 events are observed 26 months after enrollment is completed, then the Sponsor will conduct the final analysis at that time.

8.8 Multiplicity

The multiplicity strategy specified in this section will be applied to the 3 primary hypotheses (superiority of pembrolizumab on OS in subjects with CPS ≥10, with CPS ≥1, and in all subjects) and the 2 secondary hypotheses (superiority of pembrolizumab on PFS and ORR in all subjects).

For OS endpoints, a Hwang-Shih-DeCani alpha-spending function with the gamma parameter (-4) will be used to construct group sequential boundaries to control the Type I error. Spending time will be plugged into the pre-specified alpha spending function to calculate alpha-spending. At the time of IA, for all 3 OS endpoints the spending time will be the minimum of the actual observed information fractions among these 3 OS endpoints, i.e., number of observed events at IA/number of planned events at FA. At the time of FA, the spending time will be 1 for all 3 OS endpoints. Of note, while the spending time used for alpha-spending calculation will be the same for these 3 OS endpoints at FA, 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 both 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. [105].

Table 13 summarizes the timing, planned number of events, sample size and decision guidance of the interim efficacy analysis and final analysis. These boundaries are calculated based on the alpha-spending function and the planned number of events. The actual boundaries will be determined from the actual observed number of events, the planned number of events at FA, the timing of the analyses, the pre-specified alpha-spending function, and the rules to determine spending time and correlations as noted above. If the boundary is crossed at an interim analysis or at the final analysis, the study will be declared to have met its primary endpoint.

Of note, these calculations are based on the assumptions that the prevalence of PD-L1 positivity in mTNBC is approximately 65% for CPS ≥1 and approximately 31% for CPS ≥10 and are subject to modification if emerging data suggest the prevalence is different from these assumptions. These modifications, if made, will be documented in the sSAP prior to any efficacy analysis unblinding.

Table 13 Summary of Timing, Sample Size, and Decision Guidance of Interim Efficacy Analyses and Final Analysis under Initial Alpha Allocation

Analysis	Criteria for Conduct of Analysis	Endpoint	Parameter	Value
Interim Analysis: Interim OS Analysis	Triggered by duration of follow-up: Approximately 14 months after enrollment is completed. Projected OS events in subjects with CPS ≥10: approximately 130	OS in subjects with CPS ≥10	p value (1-sided) at boundary	0.0089
			~ HR at boundary	0.66
	Projected OS events in subjects with CPS ≥1: approximately 284	OS in subjects with CPS ≥1	p value (1-sided) at boundary	0.0043
			~ HR at boundary	0.73
	Projected OS events in all subjects: approximately 445	OS in all subjects	p value (1-sided) at boundary	n/a
			~ HR at boundary	n/a
Final Analysis: Final OS Analysis	Triggered by duration of follow-up and OS events in subjects with CPS ≥1: Approximately 24 months after enrollment is completed or 334 OS events accrue in subjects with CPS ≥1, whichever occurs later. If OS events in subjects with CPS ≥1 accrue slower than expected and fewer than 334 events are observed 26 months after enrollment is completed, then the Sponsor will conduct the final analysis at that time. Projected OS events in subjects with CPS ≥10: approximately 154	OS in subjects with CPS ≥10	p value (1-sided) at boundary	0.0146
			~ HR at boundary	0.70
	Projected OS events in subjects with CPS ≥1: approximately 334	OS in subjects with CPS ≥1	p value (1-sided) at boundary	0.0066
			~ HR at boundary	0.76
	Projected OS events in all subjects: approximately 520	OS in all subjects	p value (1-sided) at boundary	n/a
			~ HR at boundary	n/a

The trial uses an extension [105] of the graphical method of Maurer and Bretz [96] to provide strong multiplicity control for the multiple primary and secondary hypotheses.

Figure 4 shows the initial one-sided α-allocation for each hypothesis in the ellipse representing the hypothesis. The weights for reallocation from each hypothesis to the others are represented in the boxes on the lines connecting hypotheses. If H1 (OS in subjects with

CPS ≥10) is successful, then the corresponding alpha can be reallocated to H2 (OS in subjects with CPS ≥1). If H2 is successful, the alpha for that hypothesis can be reallocated to H3 (OS in all subjects). If H3 is successful, the alpha for that hypothesis can be reallocated ½ to H4 (PFS in all subjects) and ½ to H5 (ORR in all subjects). The alpha for H4 and H5 can also be reallocated to each other, if the hypothesis was successful. Of note, H3 can only be formally tested once the null hypothesis for H2 has been rejected; H4 and H5 can only be formally tested once the null hypothesis for H3 has been rejected. See Figure 4 for the multiplicity strategy diagram of the study.

H4 (PFS in all subjects) will be tested at IA if H3 (OS in all subjects) is successful. If at FA additional alpha can be reallocated to H4 (e.g., H3 is not successful at IA but successful at FA, or H1 is not successful at IA but successful at FA and H2/H3 are successful at both IA and FA), then the p-value of PFS in all subjects from the IA will be compared to the updated alpha threshold at the time of FA. Similarly, H5 (ORR in all subjects) will be tested at IA if H3 (OS in all subjects) is successful. If at FA additional alpha can be reallocated to H5, then the p-value of ORR in all subjects from the IA will be compared to the updated alpha threshold at the time of FA.

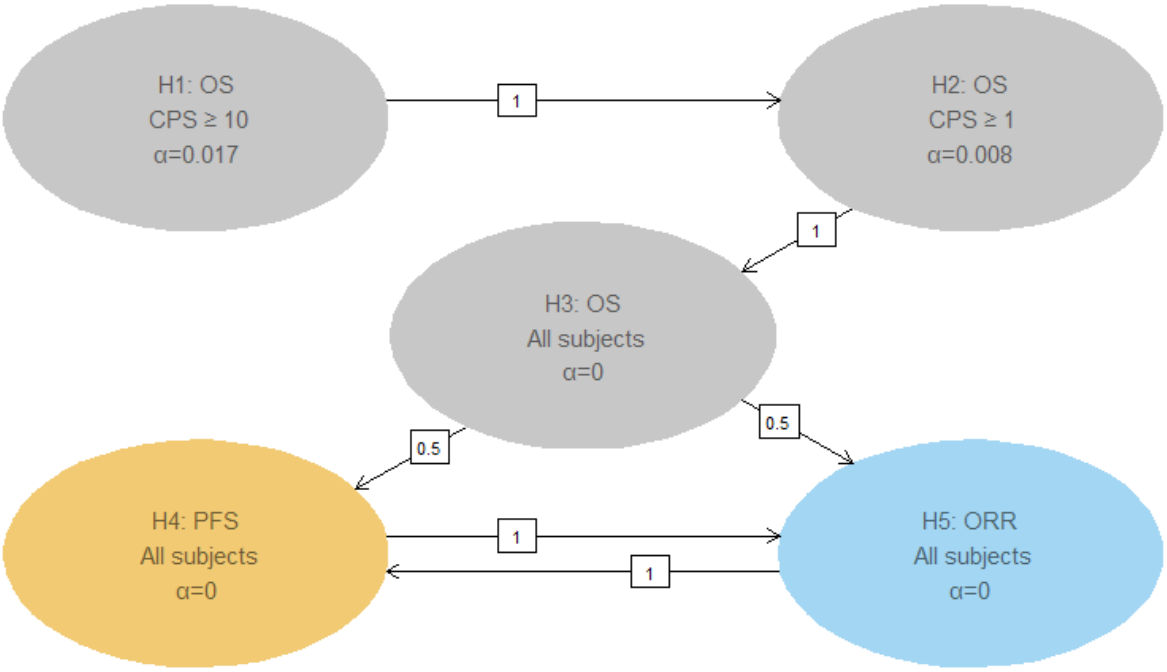


Figure 4 Multiplicity Strategy

8.9 Sample Size and Power Calculations

The study will randomize subjects in a 1:1 ratio between the pembrolizumab arm and the TPC arm. The overall sample size will be up to ~600.

Randomization will occur centrally using an interactive response system / integrated web response system (IVRS/IWRS) and will be monitored on a regular basis. When IVRS alerts that the study is approaching the desired enrollment, screening should be stopped in time.

However, subjects already in screening phase may be enrolled even after we have reached the maximum sample size. The sample size is driven by the OS events in subjects with CPS ≥10, subjects with CPS ≥1, and all subjects.

Overall survival analysis in subjects with CPS ≥10: For the primary endpoint OS in subjects with CPS ≥10, with 154 OS events at a one-sided 1.7% alpha-level the trial has approximately 85% power to demonstrate that pembrolizumab is superior to TPC, if the underlying hazard ratio of OS is 0.60. Success boundary for OS at the final analysis approximately corresponds to an observed hazard ratio of ~0.70 (~4.2 month improvement over OS of 10 months in TPC).

Overall survival analysis in subjects with CPS ≥1: For the primary endpoint OS in subjects with CPS ≥1, with 334 OS events at a one-sided 0.8% (2.5%) alpha-level the trial has approximately 80% (90%) power to demonstrate that pembrolizumab is superior to TPC, if the underlying hazard ratio of OS is 0.70. With a one-sided 0.8% (2.5%) alpha-level, success boundary for OS at the final analysis approximately corresponds to an observed hazard ratio of ~0.76 (0.80) (~3.1 [2.5] month improvement over OS of 10 months in TPC).

Overall survival analysis in all subjects: For the primary endpoint OS in all subjects, with 520 OS events and a one-sided 0.8% (2.5%) alpha-level the trial has approximately 66% (80%) power to demonstrate that pembrolizumab is superior to TPC if the underlying hazard ratio of OS is 0.78. With a one-sided 0.8% (2.5%) alpha-level, success boundary for OS at the final analysis corresponds approximately to an observed hazard ratio of ~0.80 (0.84) (~2.4 [1.9] month improvement over OS of 10 months in TPC)

The sample size and power calculation for OS endpoints is based on the following assumptions for all 3 populations: 1) OS follows an exponential distribution with a median of 10 months in the control arm; 2) An enrollment period of 16.6 months and a minimum of 24 months follow-up after enrollment completion; 3) A yearly OS dropout rate of 1%. The assumption for OS of 10 months in the TPC arm is based on estimates of OS from the trials summarized in Table 1.

PFS analysis in all subjects: This PFS power is calculated based on the following assumptions with approximately 575 PFS events: 1) the hypothesis of OS in all subject is supported and a total of 0.4% alpha is allocated to PFS hypothesis (H4); 2) PFS follows an exponential distribution with a median of 3 months in the TPC arm; 3) An enrollment period of 16.6 months; 4) A yearly PFS drop-out rate of 8%. The trial has ~99% power to demonstrate that pembrolizumab is superior to TPC on PFS at a one-sided 0.4% alpha-level, if the underlying hazard ratio of PFS is 0.6. If the underlying hazard ratio of PFS is 0.7, then the trial has ~95% power.

The assumption for PFS of 3 months in the TPC arm is based on estimates of PFS from the trials summarized in Table 1.

ORR analysis in all subjects: The ORR power calculation is based on the following assumptions: 1) the hypothesis of OS in subjects with CPS ≥1 is supported and a total of 0.4% alpha is allocated to ORR hypothesis (H5); 2) the underlying ORR is 10% in the TPC

arm, and there is 10% increase in pembrolizumab arm (ORR of 20%) in all subjects. The trial has approximately 81% power to demonstrate that pembrolizumab is superior to TPC on ORR in all subjects at a one-sided 0.4% alpha-level.

The above statistical assumptions are based on our current understanding of the prevalence of the PD-L1 biomarker in TNBC (approximately 65% for CPS ≥10 and 31% for CPS ≥1), and it is subject to modification as needed based on emerging external data on PD-L1 prevalence in TNBC, or the correlation between PD-L1 expression and treatment effect. Any modification if occurs will be described in the supplemental SAP.

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

8.10 Subgroup Analyses and Effect of Baseline Factors

To determine whether the treatment effect is consistent across various subgroups, the estimate of the between-group treatment effect (with a nominal 95% CI) for the primary endpoint will be estimated and plotted within each category of the following classification variables in subjects with CPS ≥10 and CPS ≥1 and in all subjects:

- Age Category(<65 vs. ≥65 years)
- Menopausal status (for females only; pre- vs. post-menopausal)
- Sex (Female vs. Male)
- Geographic region (Europe/Israel/North America/Australia vs. Asia vs. Rest of World)
- Ethnic origin (Hispanic vs. Non-Hispanic)
- Number of prior lines of treatments in the metastatic setting (ie one vs. two)
- Time to progression on first-line (1L) therapy (<6 months vs. ≥6 months)
- TPC
- PD-L1 status by CPS cutoff (CPS ≥1 vs CPS <1; CPS ≥10 vs CPS <10). Note subgroup analysis by PD-L1 status will only be conducted in all subjects.
- Prior (neo)adjuvant therapy vs. de novo metastatic disease at initial diagnosis.

8.11 Compliance (Medication Adherence)

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

8.12 Extent of Exposure

The extent of exposure will be summarized as duration of treatment in cycles.

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 14.

Table 14 Product Descriptions

Product Name & Potency	Dosage Form	Comments
Capecitabine 150 mg & 500 mg	Tablets	Provided centrally by the Sponsor or locally by the trial site, subsidiary, or designee depending on country
Eribulin 0.88 mg/2mL	Solution for Infusion	Provided centrally by the Sponsor or locally by the trial site, subsidiary, or designee depending on country
Gemcitabine 1000 mg	Lyophilized powder for IV infusion	Provided centrally by the Sponsor or locally by the trial site, subsidiary, or designee depending on country
Pembrolizumab (MK-3475) 100 mg / 4 mL	Solution for Infusion	Provided centrally by the Sponsor
Vinorelbine 50 mg/ 5mL	Solution for Infusion	Provided centrally by the Sponsor or locally by the trial site, subsidiary, or designee depending on country

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

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

9.4 Storage and Handling Requirements

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

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

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

9.5 Discard/Destruction/Returns and Reconciliation

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

9.6 Standard Policies

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

10.0 ADMINISTRATIVE AND REGULATORY DETAILS

10.1 Confidentiality

10.1.1 Confidentiality of Data

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

10.1.2 Confidentiality of Subject Records

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

agrees to this process. If trial documents will be photocopied during the process of verifying worksheet/case report form information, the subject will be identified by unique code only; full names/initials will be masked prior to transmission to the Sponsor.

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

10.1.3 Confidentiality of Investigator Information

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

1. name, address, telephone number and e-mail address;

2. hospital or clinic address and telephone number;

3. curriculum vitae or other summary of qualifications and credentials; and

4. other professional documentation.

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

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

10.1.4 Confidentiality of IRB/IEC Information

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

10.2 Compliance with Financial Disclosure Requirements

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

The investigator/subinvestigator(s) agree, if requested by the Sponsor in accordance with 21 CFR Part 54, to provide his/her financial interests in and/or arrangements with the Sponsor to allow for the submission of complete and accurate certification and disclosure statements. The investigator/subinvestigator(s) further agree to provide this information on a Certification/Disclosure Form, commonly known as a financial disclosure form, provided by the Sponsor or through a secure password-protected electronic portal provided by the Sponsor. The investigator/subinvestigator(s) also consent to the transmission of this information to the Sponsor in the United States for these purposes. This may involve the transmission of information to countries that do not have laws protecting personal data.

10.3 Compliance with Law, Audit and Debarment

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

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

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

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

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

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

The investigator must maintain copies of all documentation and records relating to the conduct of the trial in compliance with all applicable legal and regulatory requirements. This documentation includes, but is not limited to, the protocol, worksheets/case report forms, advertising for subject participation, adverse event reports, subject source data, correspondence with regulatory authorities and IRBs/ERCs, consent forms, investigator's curricula vitae, monitor visit logs, laboratory reference ranges, laboratory certification or quality control procedures and laboratory director curriculum vitae. By signing this protocol, the investigator agrees that documentation shall be retained until at least 2 years after the last approval of a marketing application in an ICH region or until there are no pending or contemplated marketing applications in an ICH region or until at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. Because the clinical development and marketing application process is variable, it is anticipated that the retention period can be up to 15 years or longer after protocol database lock. The Sponsor will determine the minimum retention period and notify the investigator when documents may be destroyed. The Sponsor will determine the minimum retention period and upon request, will provide guidance to the investigator when documents no longer need to be retained. The sponsor also recognizes that documents may need to be retained for a longer period if required by local regulatory requirements. All trial documents shall be made available if required by relevant regulatory authorities. The investigator must consult with and obtain written approval by the Sponsor prior to destroying trial and/or subject files.

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

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

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

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

According to European legislation, a Sponsor must designate an overall coordinating investigator for a multi-center trial (including multinational). When more than one trial site is open in an EU country, Merck, as the Sponsor, will designate, per country, a national

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

10.4 Compliance with Trial Registration and Results Posting Requirements

Under the terms of the Food and Drug Administration 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. Merck, as Sponsor of this trial, will review this protocol and submit the information necessary to fulfill these requirements. Merck entries are not limited to 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. Merck 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 Merck Code of Conduct for Clinical Trials

Merck*

Code of Conduct for Clinical Trials

I. Introduction

A. Purpose

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

B. Scope

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

II. Scientific Issues

A. Trial Conduct

1. Trial Design

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

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

2. Site Selection

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

3. Site Monitoring/Scientific Integrity

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

B. Publication and Authorship

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

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

III. Subject Protection

A. IRB/ERC review

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

B. Safety

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

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

C. Confidentiality

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

D. Genomic Research

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

IV. Financial Considerations

A. Payments to Investigators

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

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

B. Clinical Research Funding

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

C. Funding for Travel and Other Requests

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

V. Investigator Commitment

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

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

12.2 Collection and Management of Specimens for Future Biomedical Research

1. Definitions

a. Biomarker: A biological molecule found in blood, other body fluids, or tissues that is a sign of a normal or abnormal process or of a condition or disease. A biomarker may be used to see how well the body responds to a treatment for a disease or condition.[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 7.1.3.3 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 Merck 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 Merck or designees and research will be monitored and reviewed by a committee of our scientists and clinicians.

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. Information contained on the consent form alone cannot be traced

to any specimens, test results, or medical information once the specimens have been rendered de-identified

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.

Each informed consent approved by an ethics committee is assigned a unique tracking number. The tracking number on this document will be used to assign specimen permissions for each specimen into the Entrusted Keyholder's Specimen Database.

c. eCRF Documentation for Future Biomedical Research Specimens

Documentation of both consent and acquisition of Future Biomedical Research specimens will be captured in the electronic Case Report Forms (eCRFs). Reconciliation of both forms will be performed to assure that only appropriately-consented specimens are used for this sub-trial's research purposes. Any specimens for which such an informed consent cannot be verified will be destroyed.

d. Future Biomedical Research Specimen Collections

Blood specimens for DNA or RNA isolation will usually be obtained at a time when the subject is having blood drawn for other trial purposes. Specimens like tissue and bone marrow will usually be obtained at a time when the subject is having such a procedure for clinical purposes.

Specimens will be collected and sent to the laboratory designated for the trial where they will be processed (e.g., DNA or RNA extraction, etc) following the Merck approved policies and procedures for specimen handling and preparation.

If specimens are collected for a specific genotype or expression analysis as an objective to the main trial, this analysis is detailed in the main body of this protocol (**Section 8.0 – Statistical Analysis Plan**). These specimens will be processed, analyzed, and the remainder of the specimen will be destroyed. The results of these analyses will be reported along with the other trial results. A separate specimen will be obtained from properly-consented subjects in this protocol for storage in the biorepository for Future Biomedical Research.

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, Merck has developed secure policies and procedures. All specimens will be de-identified 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.

This first code will be replaced with a second code at a Merck designated storage/lab facility. The second code is linked to the first code via a second key. The specimen is now double coded. Specimens with the second code are sometimes referred to as de-identified specimens. The use of the second code provides additional confidentiality and privacy protection for subjects over the use of a single code. Access to both keys would be needed to link any data or specimens back to the subject's identification.

The second code is stored separately from the first code and all associated personal specimen identifiers. A secure link, the second key, will be utilized to match the second code to the first code to allow clinical information collected during the course of the trial to be associated with the specimen. This second key will be transferred under secure procedures by the Merck designated facility to an Entrusted Keyholder at Merck. The second code will be logged into the primary biorepository database at Merck and, in this database, this identifier will not have identifying demographic data or identifying clinical information (i.e., race, sex, age, diagnosis, lab values) associated with it. The specimen will be stored in a designated biorepository site with secure policies and procedures for specimen storage and usage.

The second key can be utilized to reconstruct the link between the results of future biomedical research and the clinical information, at the time of analysis. This linkage would not be possible for the scientist conducting the analysis, but can only be done by the Merck Entrusted Keyholder under strict security policies and procedures. The Merck Entrusted Keyholder will link the information and then issue a de-identified data set for analysis. The only other circumstance by which future biomedical research data would be directly linked to the full clinical data set would be those situations mandated by regulatory authorities (e.g., EMEA, FDA), whereby this information would be directly transferred to the regulatory authority.

5. Biorepository Specimen Usage

Specimens obtained for the Merck Biorepository will be used for analyses using good scientific practices. However, exploratory analyses will not be conducted under the highly validated conditions usually associated with regulatory approval of diagnostics. The scope of research performed on these specimens is limited to the investigation of the variability in biomarkers that may correlate with a clinical phenotype in subjects.

Analyses utilizing the Future Biomedical Research specimens may be performed by Merck, or an additional third party (e.g., a university investigator) designated by Merck. The investigator conducting the analysis will be provided with double coded specimens. Re-association of analysis results with corresponding clinical data will only be conducted by the Merck Entrusted Keyholder. 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 the specific analysis is performed will be returned to the sponsor or destroyed and documentation of destruction will be reported to Merck.

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 Merck using the designated mailbox (clinical.specimen.management@merck.com) and a form will be provided by Merck 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 Merck 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 acquisition. 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 Merck 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 Merck policies and procedures and this destruction will be documented in the biorepository database.

8. Data Security

Separate databases for specimen information and for results from the Future Biomedical Research sub-trial will be maintained by Merck. This is done to separate the future exploratory test results (which include genetic data) from the clinical trial database thereby maintaining a separation of subject number and these results. The separate databases are accessible only to the authorized Sponsor 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 in international standards (e.g., ISO17799) to protect against unauthorized access. The Merck Entrusted Keyholder maintains control over access to all specimen data. These data are collected for future biomedical research purposes only as specified in this sub-trial will not be used for any other purpose.

9. Reporting of Future Biomedical Research Data to Subjects

There is no definitive requirement in either authoritative ethical guidelines or in relevant laws/regulations globally that research results have to be, in all circumstances, returned to the trial participant. Some guidelines advocate a proactive return of data in certain instances. No information obtained from exploratory laboratory studies will be reported to the subject or family, and this information will not be entered into the clinical database maintained by Merck on subjects. Principle reasons not to inform or return results to the subject include: lack of relevance to subject health, limitations of predictive capability, concerns of misinterpretation and absence of good clinical practice standards in exploratory research typically used for diagnostic testing.

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 as to how to offer clinical diagnostic testing (paid for by Merck) to subjects enrolled and will be advised that counseling should be made available for all who choose to participate in this diagnostic testing.

If any exploratory results are definitively associated with clinical significance after completion of a clinical trial, Merck will publish the results without revealing specific subject information, inform all trial sites who participated in the Merck clinical trial and post anonymized results on our website or other accredited website(s) that allow for public access (e.g., disease societies who have primary interest in the results) in order that physicians and subjects may pursue clinical diagnostic testing if they wish to do so.

10. Gender, Ethnicity and Minorities

Although many diagnoses differ in terms of frequency by ethnic population and gender, every effort will be made to recruit all subjects diagnosed and treated on Merck clinical trials for future biomedical research. When trials with specimens are conducted and subjects identified to serve as controls, every effort will be made to group specimens from subjects and controls to represent the ethnic and gender population representative of the disease under current investigation.

11. Risks Versus Benefits of Future Biomedical Research

For future biomedical research, risks to the subject have been minimized. Risks include those associated with venipuncture to obtain the whole blood specimen. This specimen will be obtained at the time of routine blood specimens drawn in the main trial.

Merck 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.

It is necessary for subject-related data (i.e., ethnicity, diagnosis, drug therapy and dosage, age, toxicities, etc.) to be re-associated to double coded specimens at the time of data analysis. These subject data will be kept in a separate, secure Merck database, and all specimens will be stripped of subject identifiers. No information concerning results obtained from future biomedical research will be entered into clinical records, nor will it

be released to outside persons or agencies, in any way that could be tied to an individual subject.

12. Self-Reported Ethnicity

Subjects who participate in future biomedical research will be asked to provide self-reported ethnicity. Subjects who do not wish to provide this data may still participate in future biomedical research.

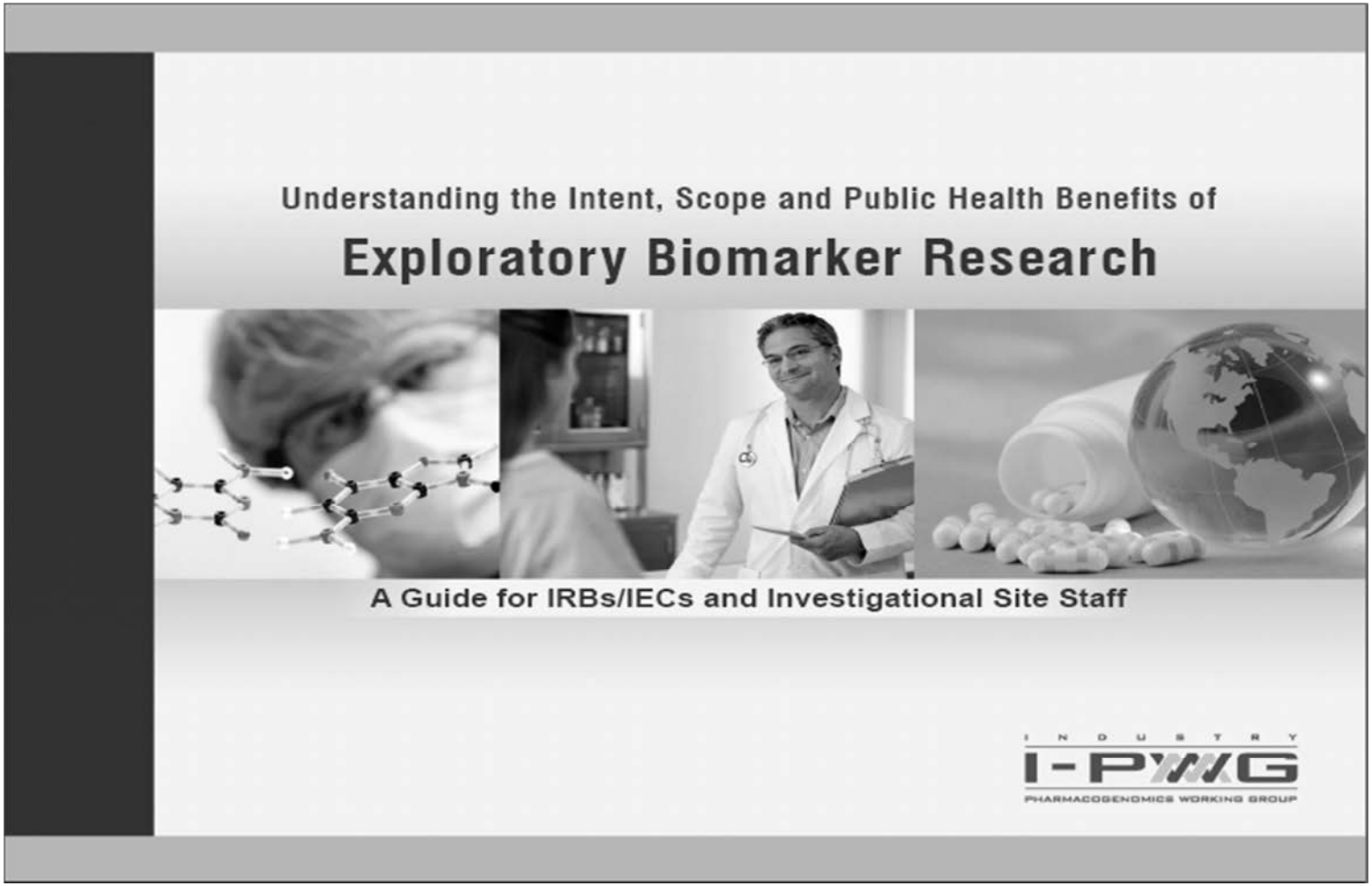
13. Questions

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

14. 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

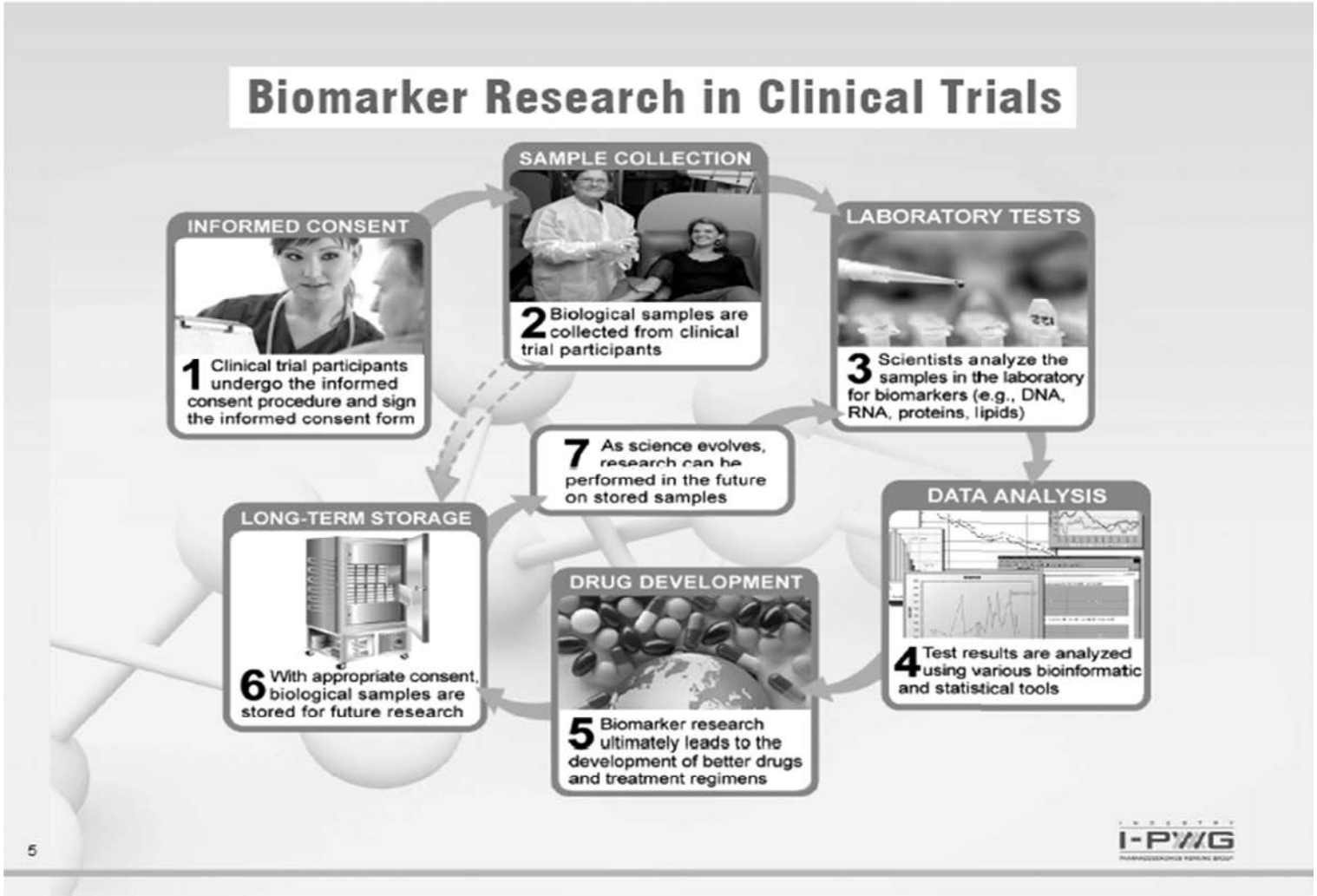
While it can be a challenge to specify the details of the research that will be conducted in the future, the I-PWG holds the view that future use of samples collected for exploratory biomarker research in clinical trials should be permissible when i) the research is scientifically sound, ii) participants 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.


Biomarker Research in Clinical Trials
INFORMED CONSENT
1 Clinical trial participants undergo the informed consent procedure and sign the informed consent form
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)
DATA ANALYSIS
4 Test results are analyzed using various bioinformatic and statistical tools
DRUG DEVELOPMENT
5 Biomarker research ultimately leads to the development of better drugs and treatment regimens
LONG-TERM STORAGE
6 With appropriate consent, biological samples are stored for future research
7 As science evolves, research can be performed in the future on stored samples
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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*. 2006 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

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

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9

I-PWG

www.i-pwg.org

12.4 Abbreviations

Abbreviation/Term	Definition
1L	First line
2L	Second line
3L	Third line
AE	Adverse event
ADA	Anti-drug antibodies
ALT	Alanine aminotransferase
ANC	Absolute neutrophil count
AP	Alkaline phosphatase
aPTT	Activated partial thromboplastin time
ASaT	All subjects as treated
ASCO	American Society of Clinical Oncology
AST	Aspartate aminotransferase
ß-hCG	Beta human chorionic gonadotropin
BSA	Body surface area
CBC	Complete blood count
CI	Confidence interval
CNS	Central nervous system
CR	Complete response
CrCl	Calculated Creatinine Clearance
CRF	Case report form
CSR	Clinical study report
CT	Computed tomography
CTCAE	Common toxicity criteria for adverse events
CTLA-4	Cytotoxic t-lymphocyte-associated antigen 4
DMC	Data Monitoring Committee
DNA	Deoxyribonucleic acid
ECI	Events of clinical interest
ECG	Electrocardiogram
eCRF	Electronic case report form
eDMC	External Data Monitoring Committee
ECOG	Eastern Cooperative Oncology Group
EOC	Executive Oversight Committee
EORTC	European Organisation for Research and Treatment of Cancer
ePRO	Electronic subject reported outcomes
ERC	Ethics Review Committee
FBR	Future biomedical research

Abbreviation/Term	Definition
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act
FDAMA	Food and Drug Administration Modernization Act
FNA	Fine needle aspirate
GCP	Good Clinical Practice
GFR	Glomerular filtration rate
HBsAg	Hepatitis B surface antigen
MBC	Metastatic breast cancer
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
IB	Investigator's brochure
ICF	Informed consent form
ICH	International Conference on Harmonisation
IHC	Immunohistochemistry
INR	International normalized ratio
irAEs	Immune-related adverse events
irRECIST	Immune-related response evaluation criteria in solid tumors
IRB	Institutional Review Board
ITIM	Immunoreceptor tyrosine-based inhibition motif
ITSM	Immunoreceptor tyrosine-based switch motif
ITT	Intention-to-treat
IV	Intravenous
IVRS	Interactive voice response system
IWRS	Integrated web response system
Kg	Kilogram
LDH	Lactate dehydrogenase
mAb	Monoclonal antibody
mcL	Microliters
Mg	Milligram
Mg/kg	Milligram per kilogram
mL	milliliter
MRI	Magnetic resonance imaging
mTNBC	Metastatic triple negative breast cancer
NCI	National Cancer Institute
NSAID	Non-steroidal anti-inflammatory drug
NSCLC	Non-small cell lung cancer
ORR	Overall response rate
OS	Overall survival

Abbreviation/Term	Definition
OTC	Over-the-counter
PD	Progressive disease
PFS	Progression-free survival
PGt	Pharmacogenetic
PIN	Personal identification number
PK	Pharmacokinetic
PK/PD	Pharmacokinetic-pharmacodynamic
PO	Oral administration
PR	Partial response
PRO	Patient reported outcomes
PT	Prothrombin time
PS	Performance status
RECIST	Response evaluation criteria in solid tumors
RNA	Ribonucleic acid
Q2W	Every 2 weeks
Q3W	Every 3 weeks
Q9W	Every 9 weeks
SAE	Serious adverse events
SAP	Statistical analysis plan
SGOT	Serum glutamic oxaloacetic transaminase
SGPT	Serum glutamic pyruvic transaminase
SOC	Standard of care
SOP	Standard operating procedures
TIL	Tumor infiltrating lymphocytes
TNBC	Triple negative breast cancer
TPC	Treatment of physician's choice
TSH	Thyroid stimulating hormone
ULN	Upper limit of normal

12.5 Eastern Cooperative Oncology Group 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, eg, light house work, office work
2	Ambulatory and capable of all self-care but unable to carry out any work activities; up and about more than 50% of waking hours
3	Capable of only limited self-care; confined to bed or chair more than 50% of waking hours
4	Completely disabled; cannot carry on any self-care; totally confined to bed or chair
5	Dead

*Oken M, Creech R, Tormey D, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. *Am J Clin Oncol.* 1982;5:649-655

http://ecog-acrin.org/resources/ecog-performance-status

12.6 Common Terminology Criteria for Adverse Events V4.0

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

12.7 Response Evaluation Criteria in Solid Tumors 1.1 Criteria for Evaluating Response in Solid Tumors

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

* As published in the European Journal of Cancer:

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

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 7.2 – 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	