Official Protocol Title:	A Phase II Clinical Trial of Pembrolizumab (MK-3475) as Monotherapy for Metastatic Triple-Negative Breast Cancer (mTNBC) – (KEYNOTE-086)
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TITLE:

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

IND NUMBER: 124,442

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SUMMARY OF CHANGES

PRIMARY REASON(S) FOR THIS AMENDMENT:

Section Number (s)	Section Title(s)	Description of Change (s)	Rationale
5.2.1.2 and Table 4	Dose Modification (Escalation/Titration/Other)	Insertion of revised language and revised dose modification table that includes myocarditis specific guidelines.	To add/clarify language in alignment with pembrolizumab current label and core data sheet, including addition of myocarditis grade clarification and actions for dose modification evaluations.
2.1	Trial Design	Clarification that subjects should be contacted *approximately* every 12 weeks.	To specify the timepoints for survival status assessment during the course of the study, during the study follow-up period, and after study discontinuation, as necessary. To introduce flexibility of survival status activities to ensure that current and complete survival data are available at the time of database locks.
6.0 6.1 6.2	Trial Flow Chart Initial Treatment Phase Second Course Phase (Retreatment)	Amended rows for survival status to allow assessment throughout the trial. Clarification of existing footnotes for survival status follow-up.	
7.1.5.3.3	Follow-up Visits	Addition of text to enable survival follow-up activities throughout the study.	
7.1.5.3.4	Survival Follow-up (SFU)	Clarification that subjects should be contacted *approximately* every 12 weeks. Deletion of redundant text that is now captured in a separate new section (Section 7.1.5.4).	
7.1.5.4	New Section: Survival Status	Addition of text to enable survival follow-up activities throughout the study.	

ADDITIONAL CHANGE(S) FOR THIS AMENDMENT:

Section Number (s)	Section Title (s)	Description of Change (s)	Rationale
1.0	Trial Summary	Addition of text referring to extension study.	To add information on the transfer of patients to the extension study.
2.2	Trial Diagram (Figure 1, Figure 2)	Addition of information to trial diagrams for extension study.	
4.2.2	Rationale for Dose Selection/Regimen/Modification	Rationale for dose selection replaced.	To provide the most current information supporting a pembrolizumab 200 mg fixed dose, based on recent data obtained in the pembrolizumab development program.
4.2.3.4	Pharmacokinetic Endpoints	Clarification that pharmacokinetics (PK) of pembrolizumab will be explored per existing modeling analysis plan.	To allow flexibility regarding PK analysis.
5.5.2	Prohibited Concomitant Medication	Clarification of allowed and prohibited vaccines.	To update prohibited concomitant medications, based on the current pembrolizumab label and core data sheet.

Section Number (s)	Section Title (s)	Description of Change (s)	Rationale
5.6	Rescue Medications & Supportive Care	Addition of cross-reference to Table 4. Deletion of bulleted description of treatment guidance for management of adverse events. Clarification of guidance in Table 5.	To add a cross-reference the section containing treatment guidance for infusion-related AEs, and to reduce repetition. To clarify timing of the use of epinephrine, and to provide the location where further guidance is available.
5.8	Subject Withdrawal/ Discontinuation Criteria	Addition of new discontinuation criteria in case of malignancy or pneumonitis.	To improve consistency with Dose Modification Guidelines and include all conditions that should lead to discontinuation of pembrolizumab, based on the current pembrolizumab label and core data sheet.
5.10	Beginning and End of the Trial	Addition of text referring to the extension study.	To add information on the transfer of patients to the extension study.
6.1	Initial Treatment Phase	Addition of 'X' at discontinuation visit to the rows for blood for plasma and serum for correlative studies	Correction of error, for consistency with Section 7.1.3.5.

Section Number (s)	Section Title (s)	Description of Change (s)	Rationale
7.1.3.3	Pharmacokinetic/Pharmacodynamic Evaluations	Clarification that collected PK and anti-drug antibodies (ADA) samples may only be stored at this time. Further analysis may be performed if required. Ongoing PK and/or ADA sampling may be reduced or discontinued.	The accumulation of robust PK and ADA data in the program has allowed for the adequate characterization the clinical pharmacology of pembrolizumab across indications. Samples will be stored and may be analyzed at a later date.
7.1.5.2.1	Second Course Phase (Retreatment Period)	Treatment duration clarified from one year to 17 cycles. Clarification of text and eligibility criteria for second course (retreatment) in terms of previous pembrolizumab treatment cycles. Addition of eligibility criteria for meeting safety criteria and status of the study. Clarification that an objective response or disease progression that occurs during the Second Course Phase will not be counted as an event for the primary analysis.	To clarify the number of treatment cycles for second course treatment, and to clarify the eligibility requirements for second course treatment.
12.2	Collection and Management of Specimens for Future Biomedical Research	Reference 2 source corrected for ICH E15 guideline.	Correction of current website link.

1.0 TRIAL SUMMARY

Abbreviated Title	A Phase II Study of Pembrolizumab as Monotherapy for Metastatic Triple-Negative Breast Cancer (mTNBC)
Trial Phase	II
Clinical Indication	Metastatic Triple-Negative Breast Cancer
Trial Type	Interventional
Type of control	No Treatment Control
Route of administration	Intravenous
Trial Blinding	Unblinded Open-label
Treatment Groups	Cohort A - Pembrolizumab as 2L+ monotherapy for mTNBC Cohort B - Pembrolizumab as 1L monotherapy for PD-L1 (+) mTNBC Cohort C - Expansion of the PD-L1 strong (+) subpopulation from Cohort A
Number of trial subjects	Approximately 285 subjects will be enrolled.
Estimated duration of trial	The sponsor estimates that the trial will require approximately 30--36 months from the time the first subject signs the informed consent until the last subject's last visit.
Duration of Participation	Each subject will participate in the trial from the time the subject signs the Informed Consent Form (ICF) through the final contact. After a screening phase, eligible subjects will receive treatment on Day 1 of each 3-week dosing cycle. Treatment with pembrolizumab as single agent will continue until disease progression is confirmed by the Investigator/local radiology review, unacceptable adverse event(s), intercurrent illness that prevents further administration of treatment, Investigator's decision to discontinue subject's treatment with pembrolizumab, subject withdraws consent, pregnancy of the subject, noncompliance with trial treatment or procedure requirements, subject receives 24 months of study medication, or administrative reasons requiring cessation of treatment. Subjects receiving pembrolizumab who attain a complete response (CR) may consider stopping trial treatment if they meet criteria for holding therapy. Subjects who stop trial treatment 24 months after initiation of trial treatment for reasons other than disease progression or intolerability, or subjects who attain a complete response and stop trial treatment, may be eligible for up to one year of retreatment upon experiencing disease progression. The decision to retreat will be at the discretion of the investigator, only if the subject meets the criteria for retreatment after experiencing disease progression and the trial is ongoing. After the end of treatment, each patient will be followed for 30 days for adverse event monitoring [serious adverse events (SAEs) and events of clinical interest (ECIs) will be collected for 90 days after the end of

	treatment or until the patient initiates new anticancer therapy, but for at least 30 days after the end of treatment, whichever is earlier]. Subjects who discontinue treatment for reasons other than disease progression will have post-treatment follow-up for disease status until disease progression, initiating a non-study cancer treatment, death, withdrawing consent, becoming lost to follow-up, or the end of the study. All subjects will be followed by telephone for overall survival (OS) until death, withdrawal of consent, becoming lost to follow-up or the end of the study. Once the subject has achieved the study objective or study has ended, the subject is discontinued from this study and will be enrolled in an extension study to continue protocol-defined assessments and treatment.

Randomization Ratio	N/A

A list of abbreviations used in this document can be found in Section 12.5.

2.0 TRIAL DESIGN

2.1 Trial Design

Definitions

***Line of treatment for metastatic triple-negative breast cancer (mTNBC)*:**

Second line and above (2L+) monotherapy: for subjects with centrally confirmed mTNBC, who have received at least one systemic treatment 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 a taxane in the (neo)adjuvant or metastatic setting.

First line (1L) monotherapy: for subjects with centrally confirmed PD-L1 (+) mTNBC, who have not received any prior systemic treatment for metastatic breast cancer.

***Study cohorts*:**

Cohort A - Pembrolizumab as 2L+ monotherapy for mTNBC
Cohort B - Pembrolizumab as 1L monotherapy for PD-L1 (+) mTNBC
Cohort C - Expansion of the PD-L1 strong (+) subpopulation from Cohort A

This is a two-part, non-randomized, multi-site, open-label trial of pembrolizumab monotherapy in subjects with metastatic triple-negative breast cancer (mTNBC).

Part 1: Approximately 240 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 (+) mTNBC, ~80 subjects) to examine the efficacy and safety of single agent pembrolizumab in the treatment of mTNBC. Cohorts A and B will be enrolled in parallel.

The relationship between response to treatment and PD-L1 protein expression in mTNBC will be explored in Cohort A. Furthermore, two interim analyses (IA 1 and 2) are planned for Cohort A.

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

Second Interim Analysis: IA 2 may be done in Cohort A to look at responses in subjects with PD-L1 strong (+) tumors. In this subpopulation, at least 10 subjects with PD-L1 strong (+) tumors need to be enrolled for response assessment and at least one responder is required to consider initiating Part 2 after enrollment in Cohort A is completed. Additional subjects beyond the planned 160 subjects may be enrolled in Cohort A to identify at least 10 subjects with PD-L1 strong (+) tumors.

Results of both interim analyses (IA 1 and IA 2) will be reviewed by an internal unblinded biomarker statistician who will report the outcome to the clinical team.

Part 2: Taking into account that higher tumor PD-L1 expression, as determined by a prototype immunohistochemistry (IHC) assay, is associated with increased probability of response to pembrolizumab in different tumor types, such as advanced NSCLC [Garon et al., ESMO 2014], we may examine whether the same holds true in mTNBC. To this effect, if at least one responder is observed in 10-15 subjects with PD-L1 strong (+) tumors from Cohort A, Part 2 of the study may be initiated. In this case, up to an additional ~40-45 subjects with PD-L1 strong (+) tumors may be enrolled in a third cohort, **Cohort C**, to expand the PD-L1 strong (+) subpopulation from Cohort A for further analysis. Enrollment may continue until up to ~55 subjects with PD-L1 strong (+) tumors have enrolled in Cohorts A and C combined. Cohort C will not open until Cohort A has been fully enrolled.

The primary efficacy objectives are:

1. **Cohort A**: To estimate the Objective Response Rate (ORR) to pembrolizumab as 2L+ monotherapy for PD-L1 (+) centrally confirmed mTNBC and centrally confirmed mTNBC independent of PD-L1 status (all comers), based on RECIST 1.1 as assessed by central imaging vendor.
2. **Cohorts A+C**: To estimate the ORR to pembrolizumab as 2L+ monotherapy in subjects with PD-L1 strong (+) centrally confirmed mTNBC, based on RECIST 1.1 as assessed by central imaging vendor.

All subjects in this study will be required to provide a fresh biopsy of a tumor lesion to be evaluated at a central laboratory for PD-L1 expression by immunohistochemistry (IHC) and triple-negative status for breast cancer. Samples will be sent to a central laboratory for real time evaluation to ensure adequate tumor tissue is present and to fulfill eligibility requirements. Subjects must have measureable metastatic disease, based on Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 as assessed by the central imaging vendor,

and will be treated with single agent pembrolizumab at 200 mg intravenously (IV) every 3 weeks (Q3W).

Treatment with pembrolizumab monotherapy will continue until disease progression is confirmed by the Investigator/local radiology review, unacceptable adverse events (as reported by the site), intercurrent illness that prevents further administration of treatment, Investigator's decision to discontinue subject's treatment with pembrolizumab, subject withdraws consent, pregnancy of the subject, noncompliance with trial treatment or procedure requirements, completion of 24 months of treatment with pembrolizumab, or administrative reasons requiring the cessation of treatment. Subjects who attain complete response (CR) confirmed by the Investigator/local radiology review may consider stopping trial treatment after receiving at least 24 weeks of treatment and at least two pembrolizumab administrations after initial evidence of CR. Subjects who discontinue treatment after 24 months of therapy for reasons other than disease progression or intolerability or who discontinue treatment after attaining a CR may be eligible for up to one year of retreatment after they have experienced disease progression by tumor imaging. The decision to retreat will be at the discretion of the Investigator, only if no cancer treatment was administered since the last dose of pembrolizumab, the subject still meets the safety parameters listed in the Inclusion/Exclusion criteria and the trial remains open (refer to Section 7.1.5.2.1 for further details).

After treatment discontinuation, each subject will be followed for 30 days for adverse event monitoring [serious adverse events (SAEs) and events of clinical interest (ECIs) will be collected for 90 days after the end of treatment or until the patient initiates new anticancer therapy, but for at least 30 days after the end of treatment, whichever is earlier]. Subjects who discontinue for reasons other than disease progression will have post-treatment follow-up for disease status every 9 weeks (± 7 days) in the first year and every 12 weeks (84 ± 7 days) after year 1 until disease progression is confirmed by the Investigator/local radiology review, a non-study cancer treatment is initiated, consent is withdrawn, death, becoming lost to follow-up, or the end of study. After trial discontinuation, all subjects will be followed by telephone for overall survival (OS) approximately every 12 weeks or more frequently as requested by the Sponsor until death, consent is withdrawn, becoming lost to follow-up, or the end of study.

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

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

2.2 Trial Diagram

The trial design for each cohort is depicted in schematics below.

The study will begin by enrolling subjects in Cohorts A and B of Part 1.

Cohort A will enroll subjects receiving pembrolizumab as 2L+ monotherapy and is displayed in Figure 1.

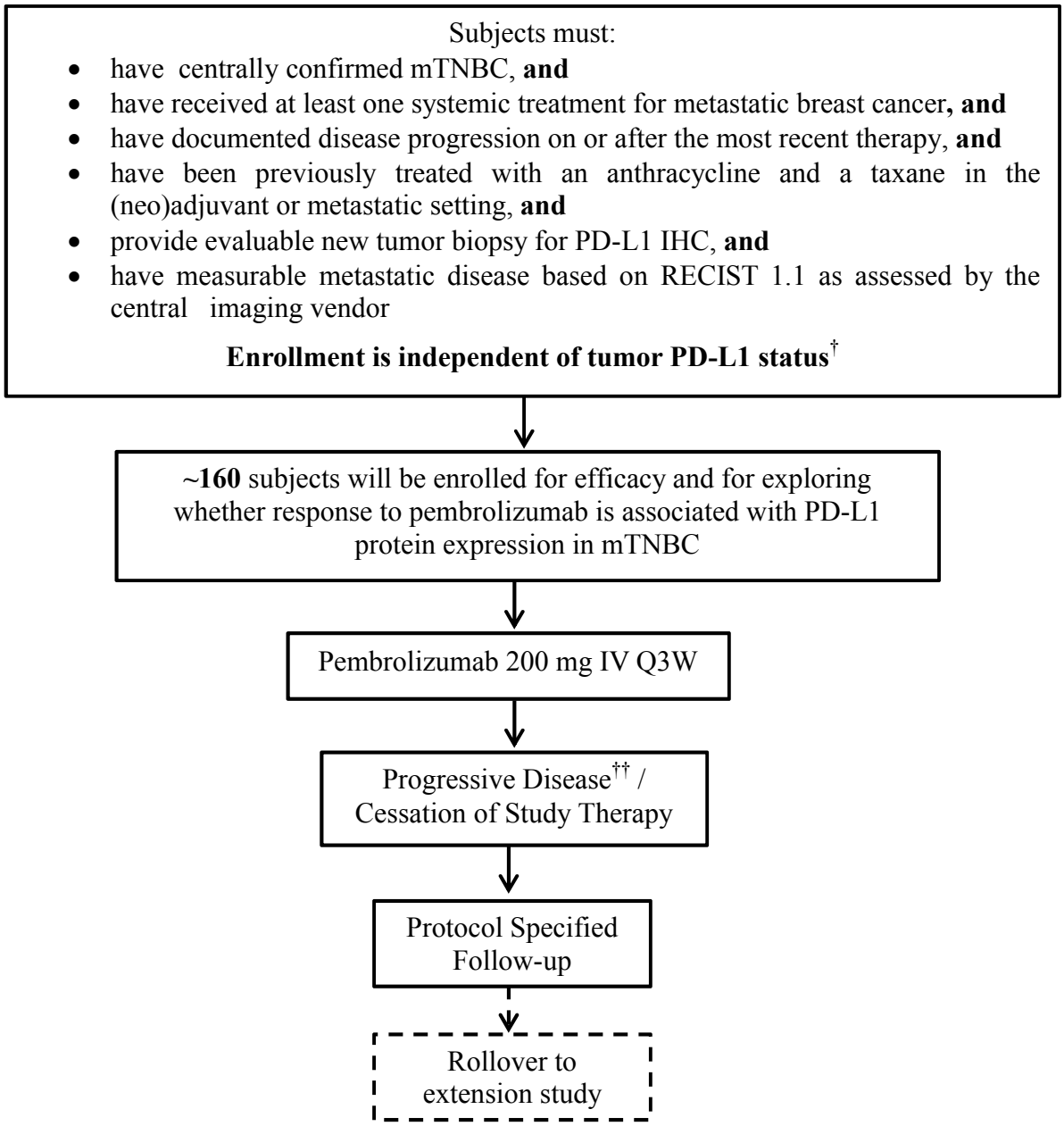


Figure 1 **Cohort A**: 2L+ Monotherapy for mTNBC - Study Schematic†

† A futility analysis (IA 1) for subjects with PD-L1 (-) tumors will be performed on Cohort A. During the futility analysis, Cohort A will continue to enroll subjects independent of tumor PD-L1 status, provided that they have measurable metastatic disease confirmed by the central imaging vendor and submit an evaluable new tumor biopsy. It is possible that following futility analysis, subjects with PD-L1 (-) tumors may be excluded from the study, if no benefit was observed in this subgroup.

†† Confirmed by the Investigator/local radiology review

Cohort B will enroll subjects receiving pembrolizumab as 1L monotherapy and is displayed in Figure 2.

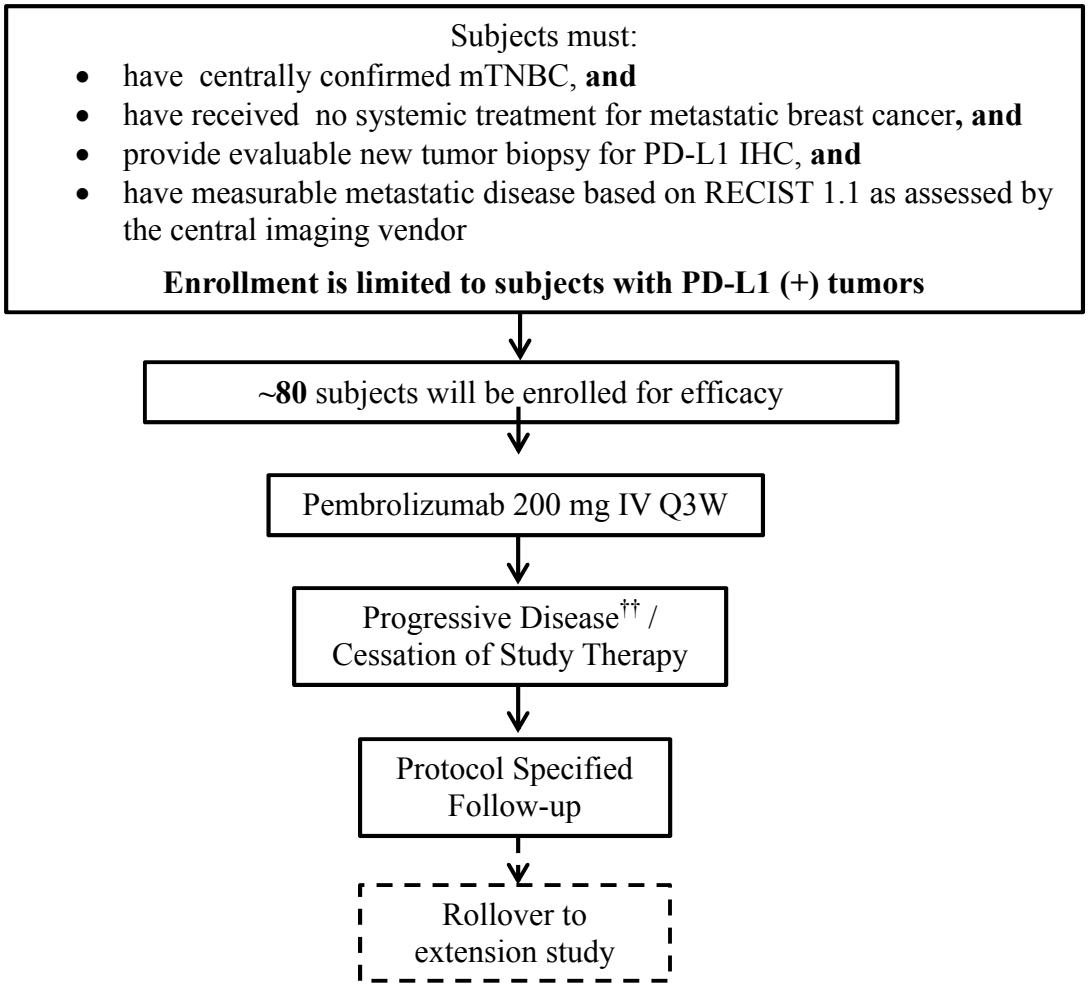


Figure 2 **Cohort B**: 1L Monotherapy for PD-L1 (+) mTNBC - Study Schematic†

† Cohort B will enroll subjects in parallel to Cohort A.

†† Confirmed by the Investigator/local radiology review

Cohort C may be initiated, only if at least one responder is observed in at least 10 subjects with PD-L1 strong (+) tumors from Cohort A. Cohort C will start enrolling subjects with PD-L1 strong (+) tumors receiving pembrolizumab as 2L+ monotherapy after enrollment in Cohort A has been completed and is displayed in Figure 3.

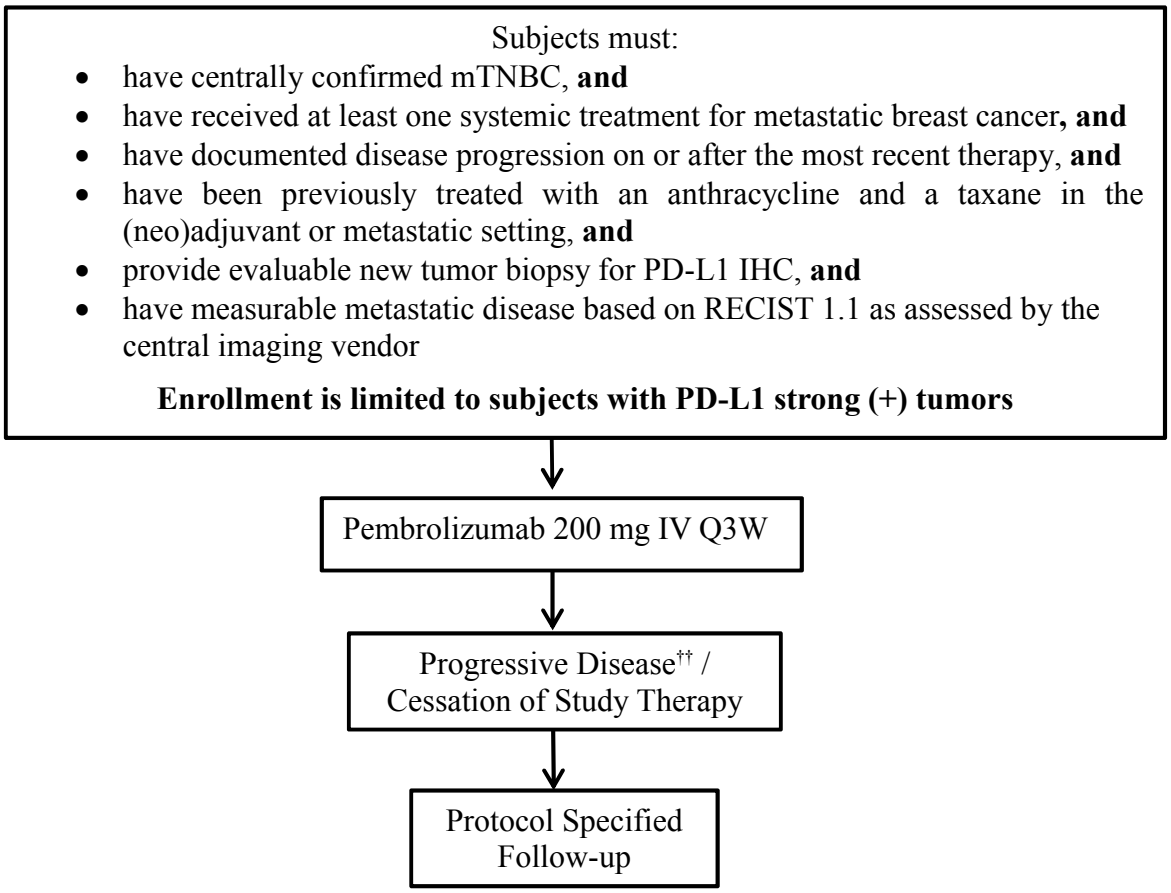


Figure 3 Cohort C: Expansion of the PD-L1 strong (+) subpopulation from Cohort A - Study Schematic

†† Confirmed by the Investigator/local radiology review

3.0 OBJECTIVE(S) & HYPOTHESIS(ES)

3.1 Primary Objective(s) & Hypothesis(es)

1. **Objective (Cohort A):** To estimate the Objective Response Rate (ORR) to pembrolizumab as 2L+ monotherapy for PD-L1 (+) centrally confirmed mTNBC and centrally confirmed mTNBC independent of PD-L1 status (all comers), based on RECIST 1.1 as assessed by the central imaging vendor.
2. **Objective (Cohorts A+C):** To estimate the ORR to pembrolizumab as 2L+ monotherapy in subjects with PD-L1 strong (+) centrally confirmed mTNBC, based on RECIST 1.1 as assessed by the central imaging vendor.
3. **Objective (Cohorts A-C):** To determine the safety and tolerability of pembrolizumab monotherapy for mTNBC across cohorts and by PD-L1 status within lines of treatment for mTNBC.

3.2 Secondary Objective(s) & Hypothesis(es)

Key Secondary Objectives (*centrally confirmed):

1. **Objective:** To estimate the Duration of Response (DOR) to pembrolizumab as 2L+ monotherapy for PD-L1 (+) mTNBC* **(Cohort A)**, mTNBC* independent of PD-L1 status **(Cohort A)**, and PD-L1 strong (+) mTNBC* **(Cohorts A+C)**, based on RECIST 1.1 as assessed by the central imaging vendor.
2. **Objective**: To estimate the Disease Control Rate (DCR), Progression-Free Survival (PFS) and Overall Survival (OS) in patients receiving pembrolizumab as 2L+ monotherapy for PD-L1 (+) mTNBC* **(Cohort A)**, mTNBC* independent of PD-L1 status **(Cohort A)**, and PD-L1 strong (+) mTNBC* **(Cohorts A+C)**, based on RECIST 1.1 as assessed by the central imaging vendor.

Other (non-key) Secondary Objectives (*centrally confirmed):

1. **Objective (Cohort B):** To estimate the antitumor efficacy (as measured by ORR, DOR, DCR, PFS, and OS) of pembrolizumab as 1L monotherapy for PD-L1 (+) mTNBC*, based on RECIST 1.1 as assessed by the central imaging vendor.
2. **Objective (Cohort A):** To explore the association between PD-L1 protein expression by IHC and antitumor efficacy of pembrolizumab in 2L+ monotherapy mTNBC based on RECIST 1.1 as assessed by the central imaging vendor.

3.3 Exploratory Efficacy Objectives (*centrally confirmed)

1. **Objective**: To estimate the antitumor efficacy of pembrolizumab as 2L+ monotherapy for PD-L1 (+) mTNBC* **(Cohort A)**, mTNBC* independent of PD-L1 status **(Cohort A)**, and PD-L1 strong (+) mTNBC* **(Cohorts A+C)**, based on immune-related Response Evaluation Criteria in Solid Tumor (irRECIST) as assessed by the central imaging vendor.

2. **Objective (Cohort B):** To estimate the antitumor efficacy of pembrolizumab as 1L monotherapy for PD-L1 (+) mTNBC*, based on irRECIST as assessed by the central imaging vendor.

4.0 BACKGROUND & RATIONALE

4.1 Background

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

4.1.1 Pharmaceutical and Therapeutic Background

Programmed Death-1 (PD-1) checkpoint inhibition and cancer treatment. The importance of intact immune surveillance in controlling outgrowth of neoplastic transformation has been known for decades [1]. Accumulating evidence shows a correlation between tumor-infiltrating lymphocytes (TILs) in cancer tissue and prognosis in various malignancies [2-14]. In particular, the presence of (Cluster of Differentiation 8 positive) CD8+ T cells and the ratio of CD8+ effector T cells/FoxP3+ regulatory T cells seem to correlate with improved prognosis and long-term survival in many solid tumors [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, expressed on the cell surface of activated T cells under healthy conditions, is to down-modulate unwanted or excessive immune responses, including autoimmune reactions. PD-1 (encoded by the gene Pdcd1) is an immunoglobulin (Ig) superfamily member related to CD28 and Cytotoxic T-Lymphocyte-Associated Protein 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], and more recently the nuclear magnetic resonance (NMR)-based structure of the human PD-1 extracellular region and analyses of its interactions with its ligands were also reported [26]. PD-1 and family members are type I transmembrane glycoproteins containing an Ig Variable-type (V-type) domain responsible for ligand binding and a cytoplasmic tail which is responsible for the binding of signaling molecules. The cytoplasmic tail of PD-1 contains 2 tyrosine-based signaling motifs, an immunoreceptor tyrosine-based inhibition motif (ITIM) and an immunoreceptor tyrosine-based switch motif (ITSM). Following T cell stimulation, PD-1 recruits the tyrosine phosphatases Src-Homology 2 domain-containing phosphatase-1 and -2 (SHP-1 and SHP-2) to the ITSM motif within its cytoplasmic tail, leading to the dephosphorylation of effector molecules, such as CD3ζ, Protein Kinase C theta (PKCθ) and Zeta-chain-Associated Protein kinase 70 (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, regulatory T cells (Tregs) and Natural Killer (NK) 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 Immunoglobulin Variable (IgV)- and Immunoglobulin Constant (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].

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 [38-44]. 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, 43-46]. In such studies, tumor infiltration by CD8+ T cells and increased interferon gamma (IFN-γ), granzyme B and perforin expression were observed, indicating that the mechanism underlying the antitumor activity of PD-1 checkpoint inhibition involved local infiltration and activation of effector T cell function *in vivo* [43]. 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 Investigator's Brochure).

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 United States (US) for the treatment of advanced, unresectable or metastatic malignant melanoma, and for use in melanoma patients with disease progression after prior treatment with (a) ipilimumab or (b) a BRAF inhibitor, in the case of BRAF V600-mutant disease [47]. It is the first anti-PD-1 therapy to receive regulatory approval in the US, and is currently under regulatory review in the European Union (EU).

Melanoma (KN 001): Pembrolizumab was administered intravenously at a dose of 10 mg/kg every 2 or 3 weeks or 2 mg/kg every 3 weeks in patients with advanced melanoma, both those who had received prior treatment with the immune checkpoint inhibitor ipilimumab and those who had not. Tumor responses were assessed every 12 weeks. A total of 135 patients with advanced melanoma were treated. Common adverse events attributed to treatment were fatigue, rash, pruritus, and diarrhea; most of the adverse events were low grade. The confirmed response rate across all dose cohorts, evaluated by the central imaging vendor according RECIST 1.1, was 38% [95% confidence interval (CI), 25 to 44], with the highest confirmed response rate observed in the cohort that received 10 mg/kg every 2 weeks

(52%; 95% CI, 38 to 66). The response rate did not differ significantly between patients who had received prior ipilimumab treatment and those who had not (confirmed response rate, 38% [95% CI, 23 to 55] and 37% [95% CI, 26 to 49], respectively). Responses were durable in the majority of patients (median follow-up, 11 months among patients who had a response); 81% of the patients who had a response (42 of 52) were still receiving treatment at the time of analysis in March 2013. The overall median progression-free survival (PFS) among the 135 patients was longer than 7 months [48].

In an open-label, international, multicenter expansion cohort of a phase 1 trial, patients (aged ≥18 years) with advanced melanoma whose disease had progressed after at least two ipilimumab doses were randomly assigned with a computer-generated allocation schedule (1:1 final ratio) to intravenous pembrolizumab at 2 mg/kg every 3 weeks or 10 mg/kg every 3 weeks until disease progression, intolerable toxicity, or consent withdrawal. 173 patients received pembrolizumab 2 mg/kg (n=89) or 10 mg/kg (n=84). Median follow-up duration was 8 months. ORR was 26% at both doses - 21 of 81 patients in the 2 mg/kg group and 20 of 76 in the 10 mg/kg group (difference 0%, 95% CI -14 to 13; p=0·96). Treatment was well tolerated, with similar safety profiles in the 2 mg/kg and 10 mg/kg groups and no drug-related deaths [49].

NSCLC (KN 001): A phase I study included 450 patients with NSCLC who had received prior chemotherapy, 305 patients (67.7 %) were eligible for therapy based on PD-L1 tumor expression. Strong PD-L1 expression was defined as staining ≥50% of tumor cells, weak PD-L1 expression was 1-49% of tumor cells. Approximately 25% of samples were classified as strong staining [Gandhi et al., AACR Annual Meeting 2014]. Pembrolizumab was administered as 10 mg/kg IV every 2 weeks or every 3 weeks. In preliminary data reported on the 159 patients with tumors that were positive for expression of PD-L1, the response rate was 23%, median time to response was 9 weeks, and duration of response was 31 weeks. The response rate (RR) was similar for Q2W dosing (26%) or Q3W dosing (21%) prompting an expansion of enrollment of an additional cohort of patients with Q3W dosing. In 35 patients with tumors that were PD-L1 (-), the response rate was 9%, and median time to response was longer at 14 weeks [Garon et al., ASCO 2014]. In treatment-naïve patients, PFS was 27 weeks with a 24-week PFS rate of 51%. In the same group, median overall survival (OS) had not been yet reached and 6-month OS rate was 86%. In previously treated patients, median PFS was 10 weeks, and 24-week PFS rate was 26%. The median OS was 8.2 months and 6-month OS rate was 59%. In pooled population, median PFS was 13 weeks and 24-week PFS rate 30%; the median OS was 8.2 months with 6-month OS rate of 64%. The data for PD-L1 staining using the clinical trial IHC assay was available for nearly half of the patients. In these patients, the objective response rate (ORR), PFS (hazard ratio, HR, 0.52), and OS (HR, 0.59) were higher in patients with strong PD-L1 expression (≥50% staining) than in patients with weak/negative PD-L1 expression [Garon et al., ESMO 2014].

Gastric cancer (KN 012): The safety, tolerability, and antitumor activity of pembrolizumab in gastric cancer were assessed in a phase Ib study. PD-L1 expression was assessed in archival tumor samples from patients with recurrent/metastatic adenocarcinoma of the stomach or gastroesophageal junction. Eligible patients with PD-L1 staining in stroma or ≥1% of tumor cells were enrolled and treated with pembrolizumab 10 mg/kg every 2 weeks for up to 24 months or until complete response, disease progression, or unacceptable toxicity.

Of the 162 patients screened, 65 (40%) were PD-L1-positive of which 39 enrolled: 19 from Asia Pacific, 20 from rest of world. Median age was 63 years, and 72% of patients were men. Patients from Asia Pacific were more heavily pretreated than patients from rest of world (≥2 prior therapies in 79% vs 55%). Median follow-up duration was approximately 6 months. The ORR (confirmed and unconfirmed) was 31.6% in Asia Pacific and 30% in the rest of world. Responses were ongoing for 6/6 Asia Pacific patients and 5/6 patients from the rest of world (median response duration not reached; range 8+ to 20+ weeks). The most common adverse events deemed treatment-related by investigators were hypothyroidism and fatigue. Grade ≥3 adverse events deemed treatment-related occurred in 3 patients (1 each for hypoxia, peripheral neuropathy, and pneumonitis). Evidence of an association between PD-L1 expression and PFS ($p = 0.032$) and ORR ($p = 0.071$) was observed [Muro et al., ESMO 2014].

Urothelial tract cancer (KN 012): Archival or newly obtained tumor samples from patients with advanced carcinoma of the renal pelvis, ureter, bladder, or urethra were screened for PD-L1 expression using a prototype IHC assay. PD-L1 expression in stroma or ≥1% of tumor cells was required for study entry. Patients received pembrolizumab 10 mg/kg every 2 weeks until complete response, progression, or unacceptable toxicity. Patients deriving benefit could remain on pembrolizumab beyond initial progression. Response was assessed every 8 weeks per RECIST 1.1 by an independent central imaging vendor (primary efficacy endpoint). In total 33 patients were enrolled, including 30 with transitional cell histology and 3 with non-transitional cell or mixed histology. Median age was 70 years (range 44-85), 70% had Eastern Cooperative Oncology Group performance status (ECOG PS) 1, 52% received ≥2 prior therapies for advanced disease, 21% had liver metastases; and 22 patients (67%) received ≥3 pembrolizumab doses. Median follow-up duration was 11 months (range 10-13), and 7 patients (21%) remained on therapy. The ORR by the central imaging vendor was 24.1%, with 10.3% complete responses. Response duration was 16 to 40+ weeks (median not reached), with 6 of 7 responses ongoing. In the patients evaluable for response, median PFS was 8.6 weeks. In all patients, median OS was 9.3 months (6-months OS rate, 58%). Adverse events were reported in 61% of patients (≥1 drug-related), most commonly fatigue, peripheral oedema, and nausea; 4 patients (12%) reported grade 3-4 drug-related adverse events, with only rash seen in more than 1 patient [Plimack et al., ESMO 2014].

Head and neck cancer (KN 012): During screening, PD-L1 expression in archival or newly obtained tumor samples was assessed using a prototype IHC assay; PD-L1 expression in stroma or ≥1% of tumor cells was required for study entry. Pembrolizumab 10 mg/kg was given every 2 weeks until complete response, progression, unacceptable toxicity, physician decision, or consent withdrawal. Adverse events were recorded throughout the study. Response was assessed every 8 weeks. Primary endpoint was ORR per RECIST 1.1. Out of 104 head and neck cancer patients screened, 81 (78%) were PD-L1-positive of which 61 enrolled, and 60 received ≥1 pembrolizumab dose: 23 Human Papilloma Virus (HPV)-positive, 37 HPV-negative. After a median follow-up of 10.2 months, 15 patients (25%) remained on pembrolizumab. The ORR (confirmed and unconfirmed) per RECIST 1.1 by investigator review was 20%, and response duration ranged from 8+ to 41+ weeks (median not reached). Nine of 11 responders had a smaller target lesion burden at baseline. The ORR was similar in HPV-positive and HPV-negative patients, whereas PFS and OS were longer in HPV-positive patients. PD-L1 expression was positively correlated with ORR ($p = 0.018$)

and PFS (p = 0.024). The ORR was 50% in the 12 patients with high PD-L1 expression. Drug-related adverse events of any grade occurred in 58% of patients (grade ≥3 in 17%). The most common drug-related adverse events were fatigue (18%), pruritus (10%), and nausea (8%). There were no drug-related deaths [Chow et al., ESMO 2014].

Ongoing clinical trials are being conducted in advanced melanoma, non-small cell lung cancer, a number of other advanced solid tumor indications and in hematologic malignancies. For study details, please refer to the Investigator's Brochure (IB).

4.2 Rationale

4.2.1 Rationale for the Trial and Selected Subject Population

Excluding basal cell and squamous cell skin cancers, breast cancer is the most commonly diagnosed malignancy in women, accounting for 29% of all new cancers. It is also the second leading cause of cancer death (after lung cancer) among women. About 232,670 new cases of breast cancer and 40,000 deaths due to breast cancer are expected in women in the United States in 2014 [50]. Triple-negative breast cancer (TNBC) is phenotypically defined by a lack of estrogen receptor (ER) and progesterone receptor (PR) expression and the absence of human epidermal growth factor receptor-2 (HER2) overexpression and/or amplification [51]. TNBC represents 15-20% of all breast cancers [52] and is overlapping, but not synonymous, with the basal-like subtype defined by gene expression, as about 70% of TNBCs have basal-like characteristics [53, 54].

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 an intense immune cell infiltrate, stem cell features, and epithelial-to-mesenchymal transition (EMT), is associated with poor prognosis [55]. 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) [56].

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 [52]. As reported in a seminal study on TNBC, 34% of all patients 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; patients with TNBC also have shorter median OS compared to patients with non-TNBC (4.2 *versus* 6.0 years) [51]. Finally, patients 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 [57].

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) [58]. The majority of patients with metastatic TNBC (mTNBC) have experienced relapse after neoadjuvant or adjuvant therapy for early or locally advanced disease. In a frequently referenced study, the median OS of all (at any line of therapy) patients with mTNBC was 13.3 months; median duration of first line (1L) therapy for mTNBC was 11.9 weeks; 80% of patients 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 [59].

Immune checkpoint inhibition for the treatment of TNBC. Several studies have demonstrated that presence of tissue infiltrating lymphocytes (TILs) is the most consistent prognostic factor in TNBC, thus implicating the immune system in the pathophysiology and potentially the treatment of such tumors. Greater lymphocytic infiltration confers better prognosis in TNBC, independent of systemic therapy [60, 61]. In addition, unsupervised gene expression profiling of TNBCs has identified a gene signature enriched for cytotoxic CD8+ T cell genes and natural killer cell (NKC) activity, which is predictive of good clinical outcome [62]. 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 [63].

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 [64]. 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 [65]. 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 [66]. 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 [67]. 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 [68]. 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 (Basu et al). 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.

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 Q2W is a well-tolerated and effective treatment with significant therapeutic activity in a subset of heavily pre-treated patients with mTNBC.

Methods: PD-L1 expression in ≥1% tumor cells or in stroma [i.e., PD-L1 (+) mTNBC)] was required for study entry. Tumor PD-L1 status was determined by immunohistochemical analysis of archival tumor specimens using the Merck proprietary 22C3 antibody. Primary objectives of this study were to determine the safety, tolerability, and antitumor activity of pembrolizumab in patients with PD-L1 (+) mTNBC. Secondary objectives included assessments of progression-free survival (PFS), overall survival (OS), and duration or response (DOR). Adverse events (AEs) reported in any patient 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 (NCI CTCAE v. 4.0). Radiographic imaging was obtained every 8 weeks and evaluated by both investigator and an independent radiologist to assess clinical responses as defined by RECIST 1.1.

Results: A total of 32 female patients with a median age of 50.5 years (range 29-72 years) and PD-L1 (+) mTNBC were enrolled in the study. Most of these patients had received and progressed on multiple lines of therapy for advanced disease (the median number of prior treatments in the metastatic setting was 3). According to data through 06-Nov-2014, five patients (15.6%) experienced at least one drug-related serious adverse event (SAE); each of four patients experienced one of the following: Grade 3 anemia, headache, aseptic meningitis or pyrexia, and a fifth patient experienced Grade 5 disseminated intravascular coagulation (DIC) with thrombocytopenia and decreased blood fibrinogen. Of the 27 patients with centrally confirmed measurable disease, one patient (3.7%) had a complete response (CR), 4 patients (14.8%) had a confirmed partial response (PR), 25.9% had stable disease (SD), and 44.4% had progressive disease (PD), as assessed by the central imaging vendor. As of 06-Nov-2014, the median duration of response had not been reached (range 15 to 40+ weeks), and three patients (1 CR; 2 PR) were still on treatment after at least 11 months.

KN 086: Subjects receiving pembrolizumab as 2L+ monotherapy for mTNBC (Cohorts A and C)

1. **Rationale for using pembrolizumab as 2L+ monotherapy for mTNBC.** Patients with TNBC whose disease has progressed on at least one systemic treatment for mTNBC have dismal prognosis with a median PFS of 2-3 months and OS of 9-12 months [75]. Nearly all have been previously treated with anthracycline(s) and taxane(s), and will receive single agent chemotherapy as a 2L+ regimen [75]. As no specific chemotherapy has been established as standard of care (SOC) for mTNBC, any of the following drugs may be used: another taxane, capecitabine, gemcitabine, vinorelbine, eribulin, liposomal doxorubicin, ixabepilone. 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 metastatic breast

cancer (mBC) [76], single agent taxane, gemcitabine, capecitabine, or vinorelbine as 2L mono-therapy for mTNBC resulted in an ORR of 18%, PFS of 2.7 months, and OS of 12.6 months [77]. In the EMBRACE Phase III open-label, randomized study comparing eribulin to treatment of physician's choice (TPC, including single agent taxane, gemcitabine, capecitabine, vinorelbine) as 3L+ therapy for mBC (all subtypes), eribulin was superior to TPC for all mBC subtypes considered collectively, as it 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 TCP. Eribulin was most effective in patients with hormone-receptor (HR)-negative tumors and TNBCs, who had a 34% and 29% reduction in risk of death, respectively; according to retrospective subgroup analysis, for eribulin-treated TNBC patients, ORR was not reported, PFS was 2.8 months and OS was 12.4 months [78]. 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 [79]. As mentioned earlier, the response rate to pembrolizumab monotherapy in PD-L1 (+) mTNBC was 18.5% based on RECIST 1.1 as assessed by the central imaging vendor (KN 012) and, as of 06-Nov-2014, the median duration of response had not been reached (range 15 to 40+ weeks) and 3 patients (1 SD, 2 PR) were still on treatment after at least 11 months. Based on these data, and taken into account the results from published studies [77-79], pembrolizumab is active (and well-tolerated) as monotherapy in heavily pretreated patients with mTNBC and, thus, worthy of further investigation.

Table 1 Efficacy of Currently Used Monotherapy Regimens in mTNBC

Study	Line Tx	Drug/Drug Combo	$ORR_{\%}/PFS_{mo}/OS_{mo}$	Reference
Meta-analysis of 3 Phase III trials: E2100, AVADO, RIBBON-1 (TNBC subgroup)	1L	Paclitaxel or docetaxel or cape	23/5.4/17.5	[69]
RIBBON-2 Phase III-TNBC subgroup	2L	Taxane or cape or gem or vinorelbine	18/2.7/12.6	[77]
Phase III (#301)-TNBC subgroup	1-3L	Eribulin	NR/NR/14.4	(Kaufman, SABCS 2012)
Phase III (#301)-TNBC subgroup	1-3L	Cape	NR/NR/9.4	
EMBRACE Phase III TNBC subgroup *mBC, all subtypes	3L+	Eribulin	(12)*/2.8/12.4	[78]
EMBRACE Phase III-*mBC, all subtypes	3L+	Taxanes or cape or gem or vinorelbine	(5/2.1/10.6)*	
Phase III-prespecified TNBC subgroup analysis	2L+	Capecitabine	9/2.1/9	[79]

2. **Rationale for including subjects with PD-L1 (-) tumors in Cohort A.** The KN 012 TNBC proof-of-concept data was obtained in patients with PD-L1 (+) mTNBC tumors (i.e., PD-L1 staining in ≥1% tumor cells or in stroma); no data is currently available on the performance of pembrolizumab in mTNBC patients with PD-L1 (-) tumors. Due to the limited efficacy of treatment options currently available **in later line mTNBC**, patients with PD-L1 (-) tumors may benefit from pembrolizumab. The performance of pembrolizumab in these patients will be explored and a futility analysis will be conducted as described in Section 8.1. Should the efficacy of pembrolizumab be non-futile in this subgroup, then enrollment of patients with PD-L1 (-) tumors will continue in future studies.

3. **Rationale for investigating the antitumor efficacy of pembrolizumab as 2L+ monotherapy for PD-L1 strong (+) mTNBC (Cohorts A+C)**. Results from KN 012 suggested that higher PD-L1 score by IHC may be associated with increased probability of response to pembrolizumab in mTNBC (logistic regression analysis

showed statistical significance with one-sided *p*-value of 0.020). Furthermore, ORR, PFS (HR 0.52), and OS (HR 0.59) in response to pembrolizumab monotherapy for advanced NSCLC were higher in patients with strong PD-L1 expression (≥50% staining) than in patients with weak/negative PD-L1 expression (<50%) [Garon et al., ESMO 2014]; evidence of an association between PD-L1 expression and PFS (p = 0.032) and ORR (p = 0.071) was also observed in gastric cancer [Muro et al., ESMO 2014].

KN 086: Subjects receiving pembrolizumab as 1L monotherapy for mTNBC (Cohort B)

Rationale for investigating pembrolizumab as 1L monotherapy for PD-L1 (+) mTNBC. As mentioned above, the TNBC proof-of-concept data available from KN 012 is limited to patients with PD-L1 (+) mTNBC tumors. Given that: (1) the prevalence of PD-L1 tumor positivity in mTNBC was around 58% in the screening phase for subject enrollment to KN 012, (2) the response rate to pembrolizumab monotherapy in PD-L1 (+) mTNBC was 18.5% based on RECIST 1.1 as assessed by the central imaging vendor (KN 012), (3) similar to NSCLC, subjects with PD-L1 (-) tumors may benefit less from pembrolizumab monotherapy than subjects with PD-L1 (+) tumors, and (4) subjects receiving 1L therapy for mTNBC have several treatment options, including combination regimens with ORR of 30-40% [69-74] and monotherapies with ORR around 23% [69], enrollment to Cohort B will be limited to subjects with PD-L1 (+) tumors. Should treatment with pembrolizumab as 2L+ monotherapy be non-futile in the PD-L1 (-) subpopulation from Cohort A, enrollment of subjects with PD-L1 (-) tumors will be considered in future larger studies of pembrolizumab as 1L monotherapy for mTNBC.

The objective of Cohort B is to provide further data assessing the performance of single agent pembrolizumab as 1L monotherapy for mTNBC to support future trials of pembrolizumab as early therapy for mTNBC.

Rationale for requiring central confirmation of TNBC status. Several studies have reported discordance in evaluation of ER, PR and HER2 status between local and central laboratories, due to both technical issues in IHC testing and interpretation issues in fluorescent in-situ hybridization (FISH) testing [80-82]. 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 [80].

4.2.2 Rationale for Dose Selection/Regimen/Modification

The planned dose of pembrolizumab for this trial is 200 mg Q3W. Based on the totality of data generated in the KEYTRUDA® development program, 200 mg Q3W is the appropriate dose of pembrolizumab across all indications, 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 2 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 PK analysis) at 200 mg Q3W

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

Additionally, pharmacology data clearly show target saturation at 200 mg Q3W. First, PK data in KN001 evaluating target-mediated drug disposition conclusively demonstrated saturation of PD-1 in systemic circulation at doses much lower than 200 mg Q3W. Secondly, a physiologically based PK 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

The primary efficacy objectives of KN 086 are to estimate the ORR to pembrolizumab as 2L+ monotherapy for PD-L1 (+) centrally confirmed mTNBC (Cohort A), centrally confirmed mTNBC independent of PD-L1 status (Cohort A), and PD-L1 strong (+) centrally confirmed mTNBC (Cohorts A+C), based on RECIST 1.1 as assessed by the central imaging vendor.

The first key secondary objective is to evaluate the DOR to pembrolizumab as 2L+ monotherapy for PD-L1 (+) centrally confirmed mTNBC (Cohort A), centrally confirmed

mTNBC independent of PD-L1 status (Cohort A), and PD-L1 strong (+) centrally confirmed mTNBC (Cohorts A+C), based on RECIST 1.1 as assessed by the central imaging vendor.

The second key secondary objective is to estimate the DCR, PFS and OS in subjects receiving pembrolizumab as 2L+ monotherapy for PD-L1 (+) centrally confirmed mTNBC (Cohort A),, centrally confirmed mTNBC independent of PD-L1 status (Cohort A), and PD-L1 strong (+) centrally confirmed mTNBC (Cohorts A+C), based on RECIST 1.1 as assessed by the central imaging vendor.

Other (non-key) secondary efficacy objective is to evaluate the antitumor activity of pembrolizumab as 1L monotherapy for PD-L1 (+) centrally confirmed mTNBC (Cohort B), based on RECIST 1.1 as assessed by the central imaging vendor.

Exploratory efficacy objectives are to evaluate the antitumor activity of pembrolizumab as 2L+ monotherapy for PD-L1 (+) centrally confirmed mTNBC (Cohort A), centrally confirmed mTNBC independent of PD-L1 status (Cohort A), and PD-L1 strong (+) centrally confirmed mTNBC (Cohorts A+C), based on irRECIST* as assessed by the central imaging vendor; also, to evaluate the antitumor activity of pembrolizumab as 1L monotherapy for PD-L1 (+) centrally confirmed mTNBC (Cohort B), based on irRECIST as assessed by the central imaging vendor.

As a supportive analysis, the antitumor activity of pembrolizumab as 2L+ and 1L monotherapy for mTNBC will also be evaluated based on RECIST 1.1 as assessed by Investigators/local radiology review.

*__Rationale for use of irRECIST criteria__: Immunotherapeutic agents may produce antitumor effects by potentiating endogenous cancer-specific immune responses, which may be functionally anergic prior to treatment. 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 (transient tumor flare). Thus, standard RECIST criteria may not provide a complete response assessment of immunotherapeutic agents, such as pembrolizumab. To address this issue, RECIST 1.1 with the adaptation outlined in Section 7.1.2.6.5, termed irRECIST, will also be used.

4.2.3.2 Safety endpoints

The primary safety objective of this trial is to characterize the safety and tolerability of pembrolizumab in subjects with mTNBC (Cohorts A-C). The primary safety analysis will be based on subjects who experienced toxicities as defined by CTCAE, Version 4.0 criteria. The attribution to drug, time-of-onset, duration of the event, its resolution, and any concomitant medications administered will be recorded. AEs will be analyzed including but not limited to all AEs, SAEs, fatal AEs, and laboratory changes. Furthermore, specific immune-related adverse events (irAEs) will be collected and designated as immune-related events of clinical interest (ECIs) as described in Section 7.2.3.2.

4.2.3.3 PD-L1 Biomarker Endpoint

Given a positive correlation between pembrolizumab antitumor activity and PD-L1 tumor expression in advanced NSCLC [Garon et al., ESMO 2014] and gastric cancer [Muro et al., ESMO 2014], the association between PD-L1 protein expression by IHC and response to single agent pembrolizumab for mTNBC will be evaluated as a (non-key) secondary objective, based on RECIST 1.1 as assessed by the central imaging vendor.

4.2.3.4 Pharmacokinetic Endpoints

Pharmacokinetics of pembrolizumab will be explored per the existing modeling analysis plan (MAP).

4.2.3.5 Biomedical Exploratory Endpoints

Fresh tumor biopsies 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 fresh biopsies, so that it may be possible to use archival tumor specimens in future clinical studies.

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, post-treatment and at the time of disease progression tumor biopsies and blood samples (including serum and plasma) will be collected. Tumor and blood specimens will 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.

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

Immunohistochemistry (IHC)

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

Tissue Infiltrating Lymphocytes (TILs)

TILs have been shown to provide prognostic and potentially predictive value, particularly in TNBC [67, 83-85] and HER2-overexpressing breast cancer [84, 86, 87]. Hematoxylin and eosin (H&E)-stained breast tumor sections can be evaluated for TILs, according to a recently published standardized methodology [3] (Salgado et al. Harmonization of the evaluation of TILs in breast cancer: Recommendation by an international TILs-working group 2014. Annals Oncology, Epub 9Sept2014).

Transcriptional analyses

Messenger RNA (mRNA) expression profiling in tumor specimens and peripheral blood will be completed to assess expression 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 will also be pursued. Expression of individual genes related to the immune system may also be evaluated, such as immune signatures and critical cytokines (e.g., IL-10). MicroRNA profiling may also be pursued in serum samples.

Genomic analyses

The application of new technologies such as NGS, WES, 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 [88-90]. 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 will be used to evaluate whether somatic genetic variations, i.e., in tumors, circulating tumor cells (CTCs) and circulating tumor deoxyribonucleic acid (DNA) [91], and/or germline DNA mutations correlate with response to pembrolizumab in mTNBC. Particular emphasis will be placed on the following biological determinants/pathways: PhosphoInositide-3-Kinase (PI3K), PTEN, BRCA1/2, Epidermal Growth Factor Receptor (EGFR), Mitogen-Activated Protein Kinase Kinase (MAPKK, also known as MEK), Fibroblast Growth Factor Receptor (FGFR), Hepatocyte Growth Factor Receptor (HGFR, also known as MET), and Notch signaling [92-95]. 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 [96]. 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 patient selection for pembrolizumab therapy in TNBC.

Circulating myeloid-derived suppressor cells

There is recent evidence for increased circulating myeloid-derived suppressor cells (MDSCs) in several cancers, and these cells may correlate with increased response of melanoma patients to ipilimumab [97]. Using MDSCs as a biomarker could be beneficial, as MDSCs can be assessed in peripheral blood. In KN 086, MDSCs will be collected prior to treatment and at several times following initiation of treatment to explore their potential utility as a biomarker that predicts response to pembrolizumab in TNBC.

4.2.3.6 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/vaccination during participation, as clinical trials are designed to provide information about the safety and effectiveness of an investigational medicine.

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

5.0 METHODOLOGY

5.1 Entry Criteria

5.1.1 Diagnosis/Condition for Entry into the Trial

Female and male subjects of at least 18 years of age with metastatic triple-negative breast cancer (mTNBC) 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:

For Cohorts A and C (2L+ monotherapy), potential subjects must:

1. Have received at least one systemic treatment 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 a taxane in the (neo)adjuvant or metastatic setting.

Note for Cohort A: In the event that the interim analysis shows that pembrolizumab monotherapy is futile in subjects with PD-L1 (-) mTNBC, subsequent enrollment to Cohort A may be limited to subjects with PD-L1 (+) tumors. If this is the case, sites will be notified via a Protocol Clarification Letter.

For the purposes of this study, neoadjuvant and/or adjuvant chemotherapy regimens do not count as a prior line of therapy.

For Cohort B (1L monotherapy), potential subjects must:

2. Have not received prior systemic anti-cancer therapy for mTNBC, **and**
3. Have PD-L1 (+) mTNBC.

For the purposes of this study, neoadjuvant and/or adjuvant chemotherapy regimens do not count as a prior line of therapy.

For Cohort C (2L+ monotherapy), potential subjects must:

4. Have PD-L1 strong (+) mTNBC, i.e. subject's tumor must meet or exceed the PD-L1 cut point for high positivity.

For all cohorts, potential subjects must:

5. Be willing and able to provide written informed consent/assent for the trial. The subject may also provide consent/assent for Future Biomedical Research. However, the subject may participate in the main trial without participating in Future Biomedical Research.
6. Be ≥ 18 years of age on day of signing informed consent.
7. Be a female or male subject with mTNBC. Central determination of triple-negative breast cancer status is required for enrollment.

8. Have provided tumor tissue for PD-L1 biomarker analysis from a newly obtained core or excisional biopsy of a not-previously-irradiated metastatic tumor lesion (mandatory). Adequacy of the biopsy specimen for PD-L1 biomarker analysis must be confirmed by the central analysis laboratory. Repeat samples may be required if adequate tissue is not provided.
    a. Note: Subjects for whom tumor biopsies cannot be newly obtained (e.g. inaccessible tumor or subject safety concern) may submit an archived metastatic tumor specimen only upon agreement from the Sponsor.
    b. Note: If emerging data demonstrates that there is no difference in the clinical utility of PD-L1 assessment in newly obtained samples relative to archived ones, then archived samples may be acceptable without Sponsor agreement. If this is the case, sites will be notified via an Administrative Memo.
    c. Note: For subjects with mTNBC at the time of initial breast cancer diagnosis, who did not have breast surgery and/or breast radiation therapy, a newly obtained core or excisional biopsy from the existing breast tumor mass may be obtained for eligibility determination.
9. Have measurable metastatic disease based on RECIST 1.1 as determined by the central imaging vendor. Tumor lesions situated in a previously irradiated area are considered measurable, if radiographic progression has been demonstrated in such lesions.
    a. Note: The same imaging modality, acquisition and technical parameters should be used throughout the study for tumor imaging.
10. Have a performance status of 0 or 1 on the ECOG Performance Scale. Assessment should be performed within 10 days of treatment initiation.
11. Female subjects 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 after the last dose of study medication (Reference Section 5.7.2). Subjects of childbearing potential are those who have not been surgically sterilized or have not been free from menses for > 1 year.

    Male subjects should agree to use an adequate method of contraception starting with the first dose of study therapy through 120 days after the last dose of study therapy.

    Abstinence is acceptable if this is the usual lifestyle and preferred contraception for the subject.
12. Demonstrate adequate organ function as defined in Table 2. All screening labs should be performed within 10 days of treatment initiation.

Table 2 Adequate Organ Function Laboratory Values

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 transfusion or EPO dependency
Renal	
Creatinine **OR** Measured or calculated[a] creatinine clearance (CrCl) [Glomerular filtration rate (GFR) can also be used in place of creatinine or CrCl]	≤1.5 X upper limit of normal (ULN) **OR** ≥30 mL/min for subject with creatinine levels > 1.5 X institutional ULN
Hepatic	
Total bilirubin	≤ 1.5 X ULN **OR** Direct bilirubin ≤ULN for subjects with total bilirubin levels >1.5xULN
Aspartate aminotransferase [AST (SGOT)] and alanine aminotransferase [ALT (SGPT)]	≤ 2.5 X ULN
Albumin	≥3.0 g/dL
Lactate Dehydrogenase (LDH)	< 2.5 X ULN
Coagulation	
International Normalized Ratio (INR) or Prothrombin Time (PT) Activated Partial Thromboplastin Time (aPTT)	≤1.5 X ULN unless subject is receiving anticoagulant therapy as long as PT or PTT is within therapeutic range of intended use of anticoagulants ≤1.5 X ULN unless subject is receiving anticoagulant therapy as long as PT or PTT is within therapeutic range of intended use of anticoagulants
[a]Creatinine clearance should be calculated per institutional standard.	

13. 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. If the urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required.

5.1.3 Subject Exclusion Criteria

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

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

   Note: Subjects who have entered the follow-up phase of an investigational study may participate as long as it has been 4 weeks since the last dose of the previous investigational agent or device.

2. Has an active autoimmune disease that has required systemic treatment in past 2 years (i.e. with use of disease modifying agents, corticosteroids or immunosuppressive drugs). Replacement therapy (eg., thyroxine, insulin, or physiologic corticosteroid

replacement therapy for adrenal or pituitary insufficiency, etc.) is not considered a form of systemic treatment.

3. Has a diagnosis of immunodeficiency or is receiving systemic steroid therapy or any other form of immunosuppressive therapy within 7 days prior to the first dose of trial treatment.
4. Has had a prior anti-cancer monoclonal antibody (mAb) for direct anti-neoplastic treatment within 4 weeks prior to study Day 1 or who has not recovered (i.e., ≤ Grade 1 or at baseline) from adverse events due to agents administered more than 4 weeks earlier.
5. Has had prior chemotherapy, targeted small molecule therapy, or radiation therapy within at least 2 weeks prior to study Day 1 or who has not recovered (i.e., ≤ Grade 1 or at baseline) from adverse events due to a previously administered agent.

   Note: Subjects with ≤ Grade 2 neuropathy 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 intervention prior to starting therapy.
6. Has a known additional malignancy that progressed or required active treatment within the last 5 years. Exceptions include basal cell carcinoma of the skin, squamous cell carcinoma of the skin that has undergone potentially curative therapy, or in situ cervical cancer.
7. Has radiographically detectable (even if asymptomatic and/or previously treated) central nervous system (CNS) metastases and/or carcinomatous meningitis. Brain imaging at screening is required.
8. Has a history of (non-infectious) pneumonitis that required steroids or current pneumonitis or a history of interstitial lung disease..
9. Has an active infection requiring systemic therapy.
10. 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.
11. Has known psychiatric or substance abuse disorders that would interfere with cooperation with the requirements of the trial.
12. 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.
13. Has received prior therapy with an anti-PD-1, anti-PD-L1, anti-PD-L2 agent or with an agent directed to another co-inhibitory T-cell receptor (e.g. CTLA-4, OX-40, CD137) or has participated in Merck MK-3475 trials.
14. Has a known history of Human Immunodeficiency Virus (HIV) (HIV 1/2 antibodies).

15. Has known active Hepatitis B (e.g., HBsAg reactive) or Hepatitis C (e.g., HCV RNA [qualitative] is detected).
16. Has received a live vaccine within 30 days of planned start of study therapy.

    Note: Seasonal influenza vaccines for injection are generally inactivated flu vaccines and are allowed; however intranasal influenza vaccines (e.g., Flu-Mist®) are live attenuated vaccines, and are not allowed.
17. Is or has an immediate family member (e.g., spouse, parent/legal guardian, sibling or child) who is investigational site or sponsor staff directly involved with this trial, unless prospective IRB approval (by chair or designee) is given allowing exception to this criterion for a specific subject.

5.2 Trial Treatment(s)

The treatment to be used in this trial is outlined below in Table 3.

Table 3 Trial Treatment

Drug	Dose	Dose Frequency	Route of Administration	Regimen/Treatment Period	Use
Pembrolizumab	200 mg	Q3W	IV infusion	Day 1 of each 3 week cycle	Experimental

Trial treatment should begin on the day of randomization or as close as possible to the date on which the subject is allocated/assigned.

Study drug should be administered on Day 1 of each 3 week cycle after all procedures/assessments have been completed as detailed on the Trial Flow Chart (Section 6.0).

Pembrolizumab will be administered as a 30 minute IV infusion every 3 weeks. Sites should make every effort to target infusion timing to be as close to 30 minutes as possible.

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

5.2.1 Dose Selection/Modification

5.2.1.1 Dose Selection (Preparation)

The rationale for selection of doses to be used in this trial is provided in Section 4.0 – Background & Rationale. Details on preparation and administration of pembrolizumab are provided in the Pharmacy Manual.

5.2.1.2 Dose Modification (Escalation/Titration/Other)

Pembrolizumab dose reductions are not applicable to this study. However, pembrolizumab must be withheld for drug-related toxicities and severe or life-threatening AEs as described in Table 4 below. If a dose must be held/delayed do not complete a cycle visit until the subject is dosed again. When pembrolizumab is restarted, this dose would be considered Day 1 of the missed cycle.

Adverse events (both non-serious and serious) associated with pembrolizumab exposure may represent an immunologic etiology. These immune-related adverse events (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 trial data, most irAEs were reversible and could be managed with interruptions of pembrolizumab, administration of corticosteroids and/or other supportive care. For suspected irAEs, ensure adequate evaluation to confirm etiology or exclude other causes. Additional procedures or tests such as bronchoscopy, endoscopy, skin biopsy may be included as part of the evaluation. Based on the severity of irAEs, withhold or permanently discontinue pembrolizumab and administer corticosteroids. Dose modification and toxicity management guidelines for irAEs associated with pembrolizumab are provided in Table 4. See Section 5.6 for supportive care guidelines, including use of corticosteroids.

Table 4 Dose Modification and Toxicity Management Guidelines for Immune-related AEs Associated with Pembrolizumab

General instructions:

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

Immune-related AEs	Toxicity grade or conditions (CTCAEv4.0)	Action taken to pembrolizumab	irAE management with corticosteroid and/or other therapies	Monitor and follow-up
Pneumonitis	Grade 2	Withhold	• Administer corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper	• Monitor subjects for signs and symptoms of pneumonitis • Evaluate subjects with suspected pneumonitis with radiographic imaging and initiate corticosteroid treatment • Add prophylactic antibiotics for opportunistic infections
	Grade 3 or 4, or recurrent Grade 2	Permanently discontinue		
Diarrhea / Colitis	Grade 2 or 3	Withhold	• Administer corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper	• Monitor subjects for signs and symptoms of enterocolitis (ie, diarrhea, abdominal pain, blood or mucus in stool with or without fever) and of bowel perforation (ie, peritoneal signs and ileus). • Subjects with ≥ Grade 2 diarrhea suspecting colitis should consider GI consultation and performing endoscopy to rule out colitis. • Subjects with diarrhea/colitis should be advised to drink liberal quantities of clear fluids. If sufficient oral fluid intake is not feasible, fluid and electrolytes should be substituted via IV infusion.
	Grade 4	Permanently discontinue		

Immune-related AEs	Toxicity grade or conditions (CTCAEv4.0)	Action taken to pembrolizumab	irAE management with corticosteroid and/or other therapies	Monitor and follow-up
AST / ALT elevation or Increased bilirubin	Grade 2	Withhold	• Administer corticosteroids (initial dose of 0.5- 1 mg/kg prednisone or equivalent) followed by taper	• Monitor with liver function tests (consider weekly or more frequently until liver enzyme value returned to baseline or is stable
	Grade 3 or 4	Permanently discontinue	• Administer corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper	
Type 1 diabetes mellitus (T1DM) or Hyperglycemia	Newly onset T1DM or Grade 3 or 4 hyperglycemia associated with evidence of β-cell failure	Withhold	• Initiate insulin replacement therapy for subjects with T1DM • Administer anti-hyperglycemic in subjects with hyperglycemia	• Monitor subjects for hyperglycemia or other signs and symptoms of diabetes.
Hypophysitis	Grade 2	Withhold	• Administer corticosteroids and initiate hormonal replacements as clinically indicated.	• Monitor for signs and symptoms of hypophysitis (including hypopituitarism and adrenal insufficiency)
	Grade 3 or 4	Withhold or permanently discontinue[1]		
Hyperthyroidism	Grade 2	Continue	• Treat with non-selective beta-blockers (eg, propranolol) or thionamides as appropriate	• Monitor for signs and symptoms of thyroid disorders.
	Grade 3 or 4	Withhold or permanently discontinue[1]		
Hypothyroidism	Grade 2-4	Continue	• Initiate thyroid replacement hormones (eg, levothyroxine or liothyroinine) per standard of care	• Monitor for signs and symptoms of thyroid disorders.
Nephritis and Renal dysfunction	Grade 2	Withhold	• Administer corticosteroids (prednisone 1-2 mg/kg or equivalent) followed by taper.	• Monitor changes of renal function
	Grade 3 or 4	Permanently discontinue		

Immune-related AEs	Toxicity grade or conditions (CTCAEv4.0)	Action taken to pembrolizumab	irAE management with corticosteroid and/or other therapies	Monitor and follow-up
Myocarditis	Grade 1 or 2	Withhold	• Based on severity of AE administer corticosteroids	• Ensure adequate evaluation to confirm etiology and/or exclude other causes
	Grade 3 or 4	Permanently discontinue		
All other immune-related AEs	Intolerable/ persistent Grade 2	Withhold	• Based on type and severity of AE administer corticosteroids	• Ensure adequate evaluation to confirm etiology and/or exclude other causes
	Grade 3	Withhold or discontinue based on the type of event. Events that require discontinuation include and not limited to: Guillain-Barre Syndrome, encephalitis		
	Grade 4 or recurrent Grade 3	Permanently discontinue		

AE=adverse event; ALT=alanine aminotransferase; AST= aspartate aminotransferase; CTCAE= Common Toxicity Criteria for Adverse Events; GI=gastrointestinal; irAE=immune related adverse event; IV=intravenous; T1DM=Type 1 diabetes mellitus.

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

NOTE:
For subjects with Grade 3 or 4 immune-related endocrinopathy where withhold of pembrolizumab is required, pembrolizumab may be resumed when AE resolves to ≤ Grade 2 and is controlled with hormonal replacement therapy or achieved metabolic control (in case of T1DM).

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

5.2.2 Timing of Dose Administration

Pembrolizumab should be administered on Day 1 of each three week cycle after all procedures/assessments have been completed as detailed on the Trial Flow Chart (Section 6.0). On Cycle 1 Day 1 trial treatment should begin on the day of allocation or as close as possible to the date on which the subject is allocated/assigned. After Cycle 1 Day 1, trial treatment may be administered up to 3 days before or 3 days after the scheduled Day 1 of each cycle due to administrative reasons.

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

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

5.2.3 Trial Blinding/Masking

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

The subject-level PD-L1 biomarker results in Cohort A will be masked in the database to the investigator and the study team at the Sponsor including clinical, statistical, statistical programming, and data management personnel. Access to the PD-L1 subject-level biomarker results will be limited to designated team at the Sponsor (see Section 8.2.1) who will be responsible for data review to ensure validity of results but who will have no other responsibilities associated with the study.

5.3 Randomization or Treatment Allocation

Centralized interactive voice response system / integrated web response system (IVRS/IWRS) will be utilized. Subjects will be assigned to all study therapies in an unblinded fashion. Subjects participating in this trial will be allocated by non-random assignment.

5.4 Stratification

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

5.5 Concomitant Medications/Vaccinations (Allowed & Prohibited)

Medications or vaccinations specifically prohibited in the exclusion criteria are not allowed during the ongoing trial. If there is a clinical indication for any medication or vaccination specifically prohibited during the trial, discontinuation from trial therapy or vaccination may be required. The investigator should discuss any questions regarding this with the Sponsor Clinical Director. The final decision on any supportive therapy or vaccination rests with the investigator and/or the subject's primary physician. However, the decision to continue the subject on trial therapy or vaccination schedule requires the mutual agreement of the investigator, the Sponsor and the subject.

5.5.1 Acceptable Concomitant Medications

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

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

5.5.2 Prohibited Concomitant Medication

Subjects are prohibited from receiving the following therapies during the Screening and Treatment Phase (including retreatment for post-complete response relapse) 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).
- Live vaccines within 30 days prior to the first dose of trial treatment and while participating in the trial. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, varicella/zoster, yellow fever, rabies, BCG, and typhoid vaccine. Seasonal influenza vaccines for injection are generally killed virus vaccines and are allowed; however, intranasal influenza vaccines (eg, FluMist®) are live attenuated vaccines and are not allowed.

- Glucocorticoids for any purpose other than to modulate symptoms from an event of clinical interest (ECI) of suspected immunologic etiology or from symptomatic brain metastasis(es) [also during whole brain radiation therapy (WBRT)]. The use of physiologic doses of corticosteroids may be approved after consultation with the Sponsor.

    - *Note: Inhaled steroids are allowed for management of asthma.*

    - *Note: Use of prophylactic corticosteroids to avoid allergic reactions (e.g., to IV contract dye) is permitted.*

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

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

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

5.6 Rescue Medications & Supportive Care

Subjects should receive appropriate supportive care measures as deemed necessary by the treating investigator. Suggested supportive care measures for the management of adverse events with potential immunologic etiology are outlined along with the dose modification guidelines in Section 5.2.1.2 (Table 4) and in greater detail in the ECI guidance document. Where appropriate, these guidelines include the use of oral or intravenous treatment with corticosteroids as well as additional anti-inflammatory agents if symptoms do not improve with administration of corticosteroids. Note that several courses of steroid tapering may be necessary as symptoms may worsen when the steroid dose is decreased. For each disorder, attempts should be made to rule out other causes such as metastatic disease or bacterial or viral infection, which might require additional supportive care. The treatment guidelines are intended to be applied when the investigator determines the events to be related to pembrolizumab.

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

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

Table 5 below shows treatment guidelines for subjects who experience an infusion reaction associated with administration of pembrolizumab.

Table 5 Infusion Reaction Treatment Guidelines

NCI CTCAE Grade	Treatment	Premedication at Subsequent Dosing
Grade 1 Mild reaction; infusion interruption not indicated; intervention not indicated	Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator.	None
Grade 2 Requires 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 and monitor symptoms.** 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 one hour of stopping drug infusion, the infusion may be restarted at 50% of the original infusion rate (e.g., from 100 mL/hr to 50 mL/hr). Otherwise dosing will be held until symptoms resolve and the subject should be premedicated for the next scheduled dose. **Subjects who develop Grade 2 toxicity despite adequate premedication should be permanently discontinued from further trial treatment administration.**	Subject may be premedicated 1.5h (± 30 minutes) prior to infusion of pembrolizumab (MK-3475) with: Diphenhydramine 50 mg po (or equivalent dose of antihistamine). Acetaminophen 500-1000 mg po (or equivalent dose of antipyretic).
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: IV fluids Antihistamines NSAIDS Acetaminophen Narcotics Oxygen Pressors Corticosteroids Epinephrine ** Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator. Hospitalization may be indicated. **In cases of anaphylaxis, epinephrine should be used immediately. **Subject is permanently discontinued from further trial treatment administration.**	No subsequent dosing
Appropriate resuscitation equipment should be available in the room and a physician readily available during the period of drug administration. For further information, please refer to the Common Terminology Criteria for Adverse Events v4.0 (CTCAE) at http://ctep.cancer.gov		

5.7 Diet/Activity/Other Considerations

5.7.1 Diet

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

5.7.2 Contraception

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

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

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

Subjects should be informed that taking the study medication may involve unknown risks to the fetus (unborn baby) if pregnancy were to occur during the study. In order to participate in the study they must adhere to the contraception requirement (described above) for the duration of the study and during the follow-up period defined in section 7.2.2-Reporting of Pregnancy and Lactation to the Sponsor. If there is any question that a subject will not reliably comply with the requirements for contraception, that subject should not be entered into the study.

5.7.3 Use in Pregnancy

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

5.7.4 Use in Nursing Women

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

5.8 Subject Withdrawal/Discontinuation Criteria

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

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

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

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

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

- The subject or legal representative (such as a parent or legal guardian) withdraws consent for treatment
- Confirmed radiographic disease progression per the terms outlined in Section 7.1.2.6.5

  Note: For unconfirmed radiographic disease progression, please see Section 7.1.2.6.5
- Unacceptable adverse experiences as described in Section 5.2.1.2
- 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 withdraw the subject from study treatment
- The subject has a confirmed positive serum pregnancy test

- Noncompliance with trial treatment or procedure requirements
- Completed 24 months of treatment with pembrolizumab

  Note: 24 months of study medication is calculated from the date of first dose. Subjects who stop pembrolizumab after 24 months may be eligible for up to one year of additional study treatment if they progress after stopping study treatment at 24 months provided they meet the requirements detailed in Section 7.1.5.2.1.

- Administrative reasons

The End of Treatment and Follow-up visit procedures are listed in Section 6 (Protocol Flow Chart) and Section 7.1.5 (Visit Requirements). After the end of treatment, each subject will be followed for 30 days for adverse event monitoring (serious adverse events and events of clinical interest will be collected for 90 days after the end of treatment or 30 days after the end of treatment if the subject initiates new anticancer therapy, whichever is earlier, 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 or becoming lost to follow-up. After documented disease progression each subject will be followed by telephone for overall survival until death, withdrawal of consent, or the end of the study, whichever occurs first.

5.8.1 Discontinuation of Study Therapy after CR

Discontinuation of treatment may be considered for subjects who have attained a confirmed CR that have been treated for at least 24 weeks with pembrolizumab and had at least two treatments with pembrolizumab beyond the date when the initial CR was declared. Subjects who then experience radiographic disease progression may be eligible for up to one year of additional treatment with pembrolizumab via the Second Course 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 as 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:

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

2. Poor adherence to protocol and regulatory requirements

3. Incidence or severity of adverse drug reaction in this or other studies indicates a potential health hazard to subjects

4. Plans to modify or discontinue the development of the study drug

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

6.0 TRIAL FLOW CHART

6.1 Initial Treatment Phase

Trial Period:		Screening Phase		Treatment Cycles[a]						End of Treatment	Post-Treatment		
Treatment Cycle/Title:		Screening (Visit 1)		1	2	3	4	To be repeated beyond 6 cycles: 5	6	Discon	Safety Follow-up	Follow Up Visits[b]	Survival Follow-up[c]
Scheduling Window (Days)[d]:	-56 to -1	-28 to -1	-10 to -1	± 3[d]	± 3	± 3	± 3	± 3	± 3	At time of discon	30 days post discon (± 3 days)	Every 9 weeks post discon (± 7 days)	Every 12 weeks (± 7 days)
Administrative Procedures													
Informed Consent	X[e]												
Informed Consent for Future Biomedical Research		X[f]											
Inclusion/Exclusion Criteria		X											
Subject Identification Card		X											
Demographics and Medical History		X											
Prior and Concomitant Medication Review[g]		X		X	X	X	X	X	X	X	X		
Clinical Procedures/Assessments													
Review Adverse Events[h]	X	X	X	X	X	X	X	X	X	X	X[i]	X[i]	
12-Lead Electrocardiogram [(ECG) (Local]		X											
Full Physical Examination		X								X			
Directed Physical Examination				X	X	X	X	X	X				
Vital Signs, Weight and Height[j]		X		X	X	X	X	X	X	X			
ECOG Performance Status			X	X	X	X	X	X	X	X			
Obtain randomization number and study drug information using IVRS/IWRS				X[k]									
Pembrolizumab Administration[k]				X[k]	X	X	X	X	X				
Post-study Anticancer Therapy Status												X	X
Survival Status[c]				<- ->									X
Laboratory Procedures/Assessments: Analysis performed by LOCAL													

Trial Period:		Screening Phase		Treatment Cycles[a]						End of Treatment	Post-Treatment		
Treatment Cycle/Title:		Screening (Visit 1)		1	2	3	4	To be repeated beyond 6 cycles 5	6	Discon	Safety Follow-up	Follow Up Visits[b]	Survival Follow-up[c]
Scheduling Window (Days)[d]:	-56 to -1	-28 to -1	-10 to -1	± 3[d]	± 3	± 3	± 3	± 3	± 3	At time of discon	30 days post discon (± 3 days)	Every 9 weeks post discon (± 7 days)	Every 12 weeks (± 7 days)
laboratory													
Pregnancy Test – Serum or Urine[l]			X										
Blood for menopausal status (if applicable) [m]			X										
PT/INR and aPTT[n]			X[o]										
CBC with Differential[p]			X[o]		X	X	X	X	X[q]	X	X[r]		
Chemistry Panel[p]			X[o]		X	X	X	X	X[q]	X	X[r]		
Urinalysis			X[o]										
T3, FT4 and TSH[q]			X[o]		X		X		X[q]		X[r]		
Laboratory Procedures/Assessments: Analysis performed by CENTRAL laboratory													
Blood for Pharmacokinetics[s,t]				X[s]	X[s]		X[s]				X[s]	X[s]	
Blood for Anti-Drug (pembrolizumab) Antibodies[s]				X[s]	X[s]		X[s]				X[s]	X[s]	
Blood for Genetics[u]				X									
Blood for plasma for Correlative Studies[v]				X						X			
Blood for serum for Correlative Studies[v]				X						X			
Blood for DNA for Correlative Studies[w]				X	X	X				X			
Blood for RNA for Correlative Studies[w]				X	X	X				X			
Blood for MDSC Assays[w]				X	X	X				X			
Efficacy Measurements													
Tumor Imaging		X[x]					X[y]		X[y]	X[z]		X[b]	
Brain Imaging		X[x]											
Tumor Tissue Collection													
Newly Obtained (required) and Archival (if available) Tissue Collection for biomarker analysis[aa]	X[aa]			X[bb]									

a. In general, assessments/procedures are to be performed on Day 1 and prior to the first dose of treatment for each cycle unless otherwise specified
b. 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) in the first year and every 12 weeks (84 ± 7 days) after year 1 until (1) the start of new anti-cancer treatment, (2) disease progression as assessed by the investigator/site radiologist, (3) death, or (4) the end of the study, whichever occurs first.
c. After the start of new anti-cancer treatment or documented disease progression as assessed by the Investigator/local radiologist, the subject should be contacted by telephone approximately every 12 weeks to assess for survival status. Updated survival status may be requested by the Sponsor at any time during the course of the study. Upon Sponsor notification, all subjects who do not/will not have a scheduled study visit or study contact during the Sponsor defined time period will be contacted for their survival status (excluding subjects that have a death event previously recorded).
d. In general, the window for each visit is ± 3 days unless otherwise noted. Study personnel will access IVRS/IWRS to obtain randomization number and study drug assignment. Cycle 1 treatment must be given within 3 days of randomization number assignment in IVRS/IWRS.
e. Written informed consent must be obtained prior to performing any protocol specified procedure. Please note that the window for acquiring the "newly obtained" tissue specimen is within 56 days of the first dose of study drug and written consent should be obtained prior to acquiring the specimen if a biopsy for the study is performed. 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 window specified for screening procedures (e.g., within 28 days prior to the first dose of trial treatment for required lab tests). Screening number will be assigned when the study informed consent is signed.
f. Signing the informed consent for future biomedical research (FBR) sample is optional. Detailed instructions for the collection and management of specimens for FBR are provided in the Procedures Manual and Section 12.2.
g. Prior medications – Record all medications taken within 28 days of screening visit. Concomitant medications – Enter new medications started during the trial through the Safety Follow-up visit. Record all medications taken for SAEs as defined in Section 7.2
h. AEs and laboratory safety measurements will be graded per NCI CTCAE version 4.0. All AEs, whether gradable by CTCAE or not, will also be evaluated for seriousness.
i. Record all AEs occurring within 30 days after the last dose of trial treatment. Report all SAEs (related and unrelated to trial treatment) and ECIs occurring up until 90 days after the end of treatment or 30 days after the end of treatment if the subject initiates new anticancer therapy, whichever is earlier. Afterwards, report only SAEs and ECIs that are related to trial treatment.
j. Vital signs to include temperature, pulse, respiratory rate, weight and blood pressure. Height will be measured at screening visit only. Vital signs will be collected at screening, prior to the administration of each dose of trial treatment at every cycle and at treatment discontinuation.
k. Study personnel will access IVRS/IWRS to obtain randomization number and study drug assignment. Pembrolizumab is given as a 200 mg dose on the first day of each 3 week cycle. Cycle 1 treatment must be given within 3 days of randomization number assignment in IVRS/IWRS.
l. For women of reproductive potential, a urine or serum pregnancy test should be performed within 72 hours prior to 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) should be repeated if required by local guidelines.
m. Blood for menopausal status may be required for certain subjects as described in Section 7.1.3.2.
n. Coagulation factors (PT/INR and aPTT) should be tested as part of the screening procedures for all subjects.
o. Laboratory tests for screening are to be performed within 10 days prior to the first dose of trial treatment. See Section 7.1.3 for details regarding laboratory tests.
p. 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.
q. Blood draws for thyroid function tests should be done prior to dosing at the scheduled timepoint, however results can be reviewed after dosing. These tests are to be repeated every 2 cycles after Cycle 6.
r. Unresolved abnormal labs that are drug related AEs should be followed until resolution. Labs do not need to be repeated after the end of treatment if labs are within normal range.
s. Both PK and anti-pembrolizumab antibody for subjects who receive pembrolizumab; Pre-dose trough PK and anti-pembrolizumab antibody samples will be collected at Cycles 1, 2, 4, 6, 8 and every 4 cycles thereafter, 30 days after discontinuation of study drug, and 3 months after discontinuation of study drug (or until the subject starts new anti-cancer therapy). All pre-dose trough PK samples should be drawn within 24 hours before infusion of pembrolizumab.
t. PK for pembrolizumab sample collection only: Additional post-dose peak PK samples will be drawn within 30 minutes after end of pembrolizumab infusion at Cycles 1 and 8. An additional single PK sample should be drawn at 24 hours (Day 2), between 72 and 168 hours (Day 4-8) and 336 hours (Day 15) after Cycle 1 dosing.
u. This sample should be drawn for planned genetic analysis of DNA and drug response unless there is either a documented law or regulation prohibiting collection, or unless the IRB/IEC does not approve of the collection of the sample for these purposes. If the sample is collected, any leftover extracted DNA will be stored for future biomedical research if the subject signs the FBR consent. Detailed instructions for the collection and management of these specimens are provided in the Procedures Manual and Section 12.2.
v. Blood for serum and blood for plasma correlative studies is to be collected only predose at Cycle 1. See Procedures Manual.
w. Blood samples for RNA, DNA, and MDSCs for correlative studies should be collected predose at Cycles 1, 2, and 3, and again at treatment discontinuation. MDSCs will only be collected in the participating countries as described in the Procedures Manual. Collection and processing instructions for all correlative study samples can also be found in the Procedures Manual.
x. The initial tumor imaging and brain imaging will be performed within 28 days prior to the date of allocation. Tumor imaging performed as part of routine clinical management are acceptable for use as screening imaging if they are of diagnostic quality and performed within 28 days prior to the date of allocation. Measureable disease based on RECIST 1.1 must be confirmed by the central imaging

	vendor before enrollment. For subjects with new symptoms suggestive of osseous metastasis, a bone scan should be obtained. Additionally, plain X-ray evaluation should be obtained for symptomatic sites with negative bone scan. Refer to Section 7.1.2.6.3 of the protocol and site imaging manual (SIM). If FDG-PET or MRI are also obtained at baseline or follow up as part of SOC and clinically indicated; send to vendor.
y.	The first on-study tumor imaging time point will be performed at 9 weeks (± 7 days) after the date of allocation and then every 9 weeks (± 7 days) thereafter or more frequently if clinically indicated in the first year. After 12 months, imaging frequency should be reduced to every 12 weeks (84 ± 7 days). Timing of tumor imaging should follow calendar days and should not be adjusted due to dose modifications. The same imaging technique should be used in a subject throughout the trial. On-study scheduled or unscheduled imaging should be submitted immediately to the central imaging vendor. Refer to the SIM for detailed imaging information.
z.	In subjects who discontinue study therapy without disease progression, tumor imaging should be performed at the time of treatment discontinuation (i.e., date of discontinuation ± 4 week window). If a previous tumor imaging was obtained within 4 weeks prior to the date of discontinuation, then tumor imaging at treatment discontinuation is not required.
aa.	Baseline tumor tissue for biomarker analysis from a newly obtained core or excisional biopsy [fine needle aspirate (FNA) not adequate] **(**must be provided (mandatory) to the central vendor prior to randomization and an archival tissue sample (if available) will also be collected. Adequacy of the fresh mandatory biopsy specimen for PD-L1 biomarker analysis must be confirmed by the central laboratory before enrollment. Detailed instructions for tissue collection, processing and shipment of both the fresh mandatory tumor tissue and the optional archival tumor tissue are provided in the Procedures Manual. 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.
bb.	An optional newly obtained core or excisional biopsy (FNA not adequate) is requested at any time point during the study, (preferably as close to dosing at C4 as possible). A biopsy is also requested at the time of discontinuation for progression, but will not be required.

6.2 Second Course Phase (Retreatment)

Trial Period:	Treatment Cycles[a]						End of Treatment	Post-Treatment		
Treatment Cycle/Title:	1	2	3	4	To be repeated beyond 6 cycles		Discon	Safety Follow-up	Follow Up Visits[b]	Survival Follow-up[c]
					5	6				
Scheduling Window (Days)[d]:		± 3	± 3	± 3	± 3	± 3	At time of discon	30 days post discon	Every 9 weeks post discon	Every 12 weeks
Administrative Procedures										
Eligibility Criteria[e]	X									
Concomitant Medication Review[f]	X	X	X	X	X	X	X	X		
Clinical Procedures/Assessments										
Review Adverse Events	X	X	X	X	X	X	X	X[g]	X[g]	
Full Physical Examination	X						X			
Directed Physical Examination		X	X	X	X[h]	X	X			
Vital Signs and Weight[i]	X	X	X	X	X	X	X	X		
ECOG Performance Status	X	X	X	X	X	X	X	X		
Pembrolizumab Administration[j]	X	X	X	X	X	X				
Post-study Anticancer Therapy Status									X	X
Survival Status [c]	<- ->									X
Laboratory Procedures/Assessments: Analysis performed by LOCAL laboratory										
Pregnancy Test – Urine or Serum β-HCG[k]	X									
PT/INR and aPTT	X[l]									
Complete Blood Count (CBC) with Differential[m]	X[l]	X	X	X	X	X	X	X[n]		
Chemistry Panel[m]	X[l]	X	X	X	X	X	X	X[n]		
Urinalysis	X									
T3, FT4 and TSH[m]	X[l]		X		X[h]			X[n]		
Efficacy Measurements										
Tumor Imaging[o]	X				X		X[p]		X	

a. In general, assessments/procedures are to be performed on Day 1 and prior to the first dose of treatment for each cycle unless otherwise specified. Treatment cycles are 3 weeks.
b. 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 (63 ± 7 days) in the first year and every 12 weeks (84 ± 7 days) after year 1 until (1) the start of new anti-cancer treatment, (2) disease progression as assessed by the investigator/site radiologist, (3) death, or (4) the end of the study, whichever occurs first.
c. After the start of new anti-cancer treatment or documented disease progression as assessed by the Investigator/local radiologist, the subject should be contacted by telephone approximately every 12 weeks to assess for survival status. Updated survival status may be requested by the Sponsor at any time during the course of the study. Upon Sponsor notification, all subjects who do not/will not have a scheduled study visit or study contact during the Sponsor defined time period will be contacted for their survival status (excluding subjects that have a death event previously recorded).
d. In general, the window for each visit is ± 3 days unless otherwise noted.
e. Subjects who either a) attain a CR and discontinue treatment or b) discontinue treatment after 24 months on pembrolizumab for reasons other than disease progression or intolerability may restart trial treatment if they meet the criteria specified in Section 7.1.5.2.1.
f. Concomitant medications – Enter new medications started during the trial through the Safety Follow-up visit. Record all medications taken for SAEs as defined in Section 7.2.
g. Record all AEs occurring within 30 days after the last dose of trial treatment. Report all SAEs (related and unrelated to trial treatment) and ECIs occurring up until 90 days after the end of treatment or 30 days after the end of treatment if the subject initiates new anticancer therapy, whichever is earlier. Afterwards, report only SAEs and ECIs that are related to trial treatment.
h. To be repeated every 2 cycles after Cycle 5.
i. Vital signs to include temperature, pulse, respiratory rate, weight and blood pressure.
j. Pembrolizumab is given as a 200 mg dose on the first day of each 3 week cycle. Subjects who restart treatment should resume at the same dose and cycle interval which they were receiving prior to discontinuation.
k. For women of reproductive potential, a urine or serum pregnancy test should be performed within 72 hours prior to 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) should be repeated if required by local guidelines.
l. 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.
m. After Cycle 1, lab samples can be collected up to 72 hours prior to the scheduled time point. Blood draws for thyroid function tests should be done prior to dosing at the scheduled timepoint, however results can be reviewed after dosing. See Section 7.1.3 for details regarding laboratory tests.
n. Unresolved labs 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.
o. Tumor imaging must be performed within 28 days prior to restarting treatment with pembrolizumab. Tumor imaging should continue to be performed every 9 weeks (63 ± 7 days) after the date of allocation or more frequently if clinically indicated in the first year. After 12 months, imaging frequency should be reduced to every 12 weeks (84 ± 7 days). Tumor imaging timing should follow calendar days and should not be adjusted for any dose modifications. The same image modality acquisition and technical parameters should be used throughout the study.
p. In subjects who discontinue study therapy without confirmed disease progression, tumor imaging should be performed at the time of treatment discontinuation (i.e., 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 in not required.

7.0 TRIAL PROCEDURES

7.1 Trial Procedures

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

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

7.1.1 Administrative Procedures

7.1.1.1 Informed Consent

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

7.1.1.1.1 General Informed Consent

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

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

The initial informed consent form, any subsequent revised written informed consent form and any written information provided to the subject must receive the IRB/ERC's approval/favorable opinion in advance of use. The subject or his/her legally acceptable representative should be informed in a timely manner if new information becomes available that may be relevant to the subject's willingness to continue participation in the trial. The communication of this information will be provided and documented via a revised consent form or addendum to the original consent form that captures the subject's dated signature or by the subject's legally acceptable representative's dated signature.

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

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

7.1.1.1.2 Consent and Collection of Specimens for Future Biomedical Research

The investigator or qualified designee will explain the Future Biomedical Research consent to the subject, answer all of his/her questions, and obtain written informed consent before performing any procedure related to the Future Biomedical Research sub-trial. A copy of the informed consent will be given to the subject.

7.1.1.2 Inclusion/Exclusion Criteria

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

7.1.1.3 Subject Identification Card

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

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

7.1.1.4 Medical History

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 mTNBC cancer will be recorded separately and not listed as medical history. As well, any autoimmune disorders, regardless of onset date, should be recorded.

7.1.1.4.1 Disease Details

The investigator or qualified designee will obtain prior and current details regarding the subject's metastatic triple-negative breast cancer.

7.1.1.4.2 Menopausal Status

The investigator or qualified designee will obtain details regarding the subject's menopausal status.

7.1.1.5 Prior and Concomitant Medications Review

7.1.1.5.1 Prior Medications

The investigator or qualified designee will review prior medication use, including any protocol-specified washout requirement, and record prior medication taken by the subject within 28 days before first dose of trial medication. Prior treatment for breast cancer will be recorded separately and not listed as a prior medication.

7.1.1.5.1.1 Prior Treatment Details for Breast Cancer

The investigator or qualified designee will review and record all prior cancer treatments including systemic treatments, radiation and surgeries. For Cohorts A and C documentation of disease progression on or after the most recent therapy will be collected. Sites should obtain a dated imaging report documenting progressive disease on or after the most recent treatment.

7.1.1.5.2 Concomitant Medications

The investigator or qualified designee will record medication, if any, taken by the subject during the trial. All medications related to reportable SAEs and ECIs should be recorded as defined in Section 7.2.

7.1.1.5.2.1 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.

7.1.1.6 Assignment of Screening Number

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

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

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

7.1.1.7 Assignment of Randomization Number

All eligible subjects will be allocated, by non-random assignment, and will receive a randomization number. The randomization number identifies the subject for all procedures

occurring after treatment allocation. 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**.**

All subjects will be assigned a randomization number, however all subjects will receive the same pembrolizumab 200 mg every three weeks (Q3W) as trial treatment by non-random assignment in an unblinded fashion.

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

Interruptions from the protocol specified treatment plan for greater than 12 weeks between pembrolizumab doses require consultation between the investigator and the Sponsor and written documentation of the collaborative decision on subject management.

Administration of trial medication will be witnessed by the investigator and/or trial staff.

The total volume of trial treatment infused will be compared to the total volume prepared to determine compliance to each dose administered. The instructions for preparing and administering pembrolizumab will be provided in the Pharmacy Manual.

7.1.2 Clinical Procedures/Assessments

7.1.2.1 Adverse Event (AE) Monitoring

The investigator or qualified designee will assess each subject to evaluate for potential new or worsening AEs as specified in the Trial Flow Chart and more frequently if clinically indicated. Adverse events will be graded and recorded throughout the study and during the follow-up period according to NCI CTCAE Version 4.0 (see Appendix 12.7). Toxicities will be characterized in terms regarding seriousness, causality, toxicity grading, and action taken with regard to trial treatment.

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

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

7.1.2.2 Physical Exam

7.1.2.2.1 Full Physical Exam

The investigator or clinical designee will perform a complete (full) physical exam during the screening period and at discontinuation of treatment. Clinically significant abnormal

findings should be recorded as medical history. A full physical exam should be performed as specified in the Trial Flow Chart. After the first dose of trial treatment new clinically significant abnormal findings should be recorded as AEs.

7.1.2.2.2 Directed Physical Exam

For cycles that do not require a full physical exam per the Trial Flow Chart, the investigator or qualified designee will perform a directed physical exam as clinically indicated prior to dosing on Day 1 of each treatment cycle. New clinically significant abnormal findings should be recorded as AEs.

7.1.2.3 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. Vital signs should include temperature, pulse, respiratory rate, weight and blood pressure. Height will be measured at screening only.

7.1.2.4 12-Lead Electrocardiogram

A standard 12-lead 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.

7.1.2.5 Eastern Cooperative Oncology Group (ECOG) Performance Status

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

7.1.2.6 Tumor Imaging and Assessment of Disease

The process for image collection and transmission to the central imaging vendor can be found in the SIM. Tumor imaging may be performed by computed tomography (CT-chest, abdomen, pelvis) (strongly preferred) or magnetic resonance imaging (MRI), but **the same imaging technique should be used in a subject throughout the trial**.

Bone scans will also be utilized to assess osseous metastases. Additionally, plain X-ray evaluation will be obtained for symptomatic sites with negative bone scan evaluations. If clinically indicated, sites may also obtain MRI or FDG-PET if it is part of the institutional standards to evaluate baseline bone metastasis. If considered positive per site interpretation, they should be sent to the central imaging vendor, in addition to the bone scan.

A central imaging vendor using RECIST 1.1 will be used to determine subject eligibility.

The central imaging vendor will receive all scheduled images at the timepoints specified in the Study Flow Chart from the sites as well as any unscheduled imaging data. All tumor

imaging, including confirmatory tumor imaging, should be submitted to the central imaging vendor for evaluation and should be submitted in a timely fashion.

The Sponsor will also receive results for a retrospective analysis of treatment response/progression to be performed by the central imaging vendor, using RECIST 1.1/irRECIST. Imaging data will be documented in the Sponsor data collector on the appropriate electronic case report forms (eCRFs).

Treatment decisions will be based on the site's assessment of tumor response and progression.

7.1.2.6.1 Baseline Tumor Imaging

To meet screening criteria, tumor imaging must be performed within 28 days prior to the date of allocation. The baseline tumor imaging (CT strongly preferred) should be submitted immediately to the central imaging vendor for determination of measurable disease per RECIST 1.1 and inclusion into the study. Central imaging vendor confirmation of this eligibility criterion is required prior to allocation of the subject.

Tumor imaging performed as part of routine clinical management are acceptable for use as the screening imaging if they are of diagnostic quality, meet the requirements specified in the SIM, and are performed within 28 days prior to the date of allocation.

In addition, brain imaging is required at screening for all subjects to confirm that there are no detectable brain metastases present at baseline. MRI is the preferred imaging modality however CT is acceptable if an MRI is clinically contraindicated.

A bone scan should be performed at screening for all subjects with known bone metastases or active bone pain, and for subjects with new symptoms concerning of osseous metastasis [e.g., new bone pain and/or new persistently elevated alkaline phosphatase (AP)].

7.1.2.6.2 On Study Tumor Imaging

The first post treatment tumor imaging assessment should be performed at 9 weeks (63 days ± 7 days) from the date of allocation. Thereafter, subsequent tumor imaging should be performed every 9 weeks (63 days ± 7 days) or more frequently, if clinically indicated. After 12 months, imaging frequency should be reduced to every 12 weeks (84 ± 7 days). Imaging should follow calendar days and not be delayed for any dose interruptions that may occur.

Per RECIST 1.1, partial or complete response should be confirmed by a repeat tumor imaging not less than 4 weeks from the date the response was first documented. The tumor imaging 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, whichever is clinically indicated.

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

Subjects who have unconfirmed disease progression may continue on treatment until progression is confirmed (or possibly even later) provided they have met the conditions detailed in Section 7.1.2.6.5.

7.1.2.6.3 Bone Scans and X-Rays

Subjects with new symptoms concerning of osseous metastasis [e.g., new bone pain and/or new persistently elevated alkaline phosphatase (AP)] a bone scan should be obtained. Additionally, plain X-ray evaluation should be obtained for symptomatic sites with negative bone scan evaluations. If clinically indicated, sites may also obtain MRI or FDG-PET if it is part of the institutional standards to evaluate new osseous update. If the additional imaging modalities confirm site based progression by RECIST 1.1, they should be sent to the central imaging vendor, in addition to the bone scan.

Subjects achieving Complete Response should have a bone scan if one was obtained at baseline and was positive for metastatic disease.

7.1.2.6.4 RECIST 1.1

RECIST 1.1 will be applied by the central imaging vendor retrospectively as the primary measure for assessment of tumor response. All tumor imaging should be submitted to the central imaging vendor.

7.1.2.6.5 irRECIST

irRECIST is RECIST 1.1 adapted as described below to account for the unique tumor response seen with immuno-therapeutics.

irRECIST will be used by site investigators and local radiology review to assess tumor response and progression, and make treatment decisions. This data will be collected in the clinical database.

irRECIST will be used by the central imaging vendor, however, this evaluation will be done retrospectively.

irRECIST takes into account the clinical condition/stability of subjects, as described in Table 6, in addition to response or progression via tumor imaging

Clinically stable is defined by the following criteria:

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

Table 6 irRECIST: Tumor Imaging and Treatment after 1st Radiologic Evidence of PD **or** SD, CR or PR

	Clinically Stable		**Clinically Unstable**	
	Tumor Imaging	**Treatment**	**Tumor Imaging**	**Treatment**
1st radiologic evidence of PD	Repeat tumor imaging at ≥ 4 weeks at site to confirm PD	May continue study treatment at the site Investigator's discretion while awaiting confirmatory scan by site	Repeat tumor imaging at ≥ 4 weeks to confirm PD by the site investigator/local radiology review	Discontinue treatment
Repeat tumor imaging confirms PD	No additional tumor imaging required	Discontinue treatment (exception is possible upon consultation with Sponsor).	No additional tumor imaging required	N/A
Repeat tumor imaging shows SD, PR or CR	Continue regularly scheduled tumor imaging assessments	Continue study treatment at the site Investigator's discretion	Continue regularly scheduled tumor imaging assessments	May restart study treatment if condition has improved and/or clinically stable per site Investigator's discretion. Next tumor imaging should occur according to the every 9 week (63 ± 7 days) imaging schedule in the first year or every 12 weeks after one year.

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

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

For a **clinically stable** subject with first radiologic evidence of progressive disease (i.e., **unconfirmed progression of disease**), it is at the discretion of the site investigator/local radiology review to continue treating the subject with the assigned treatment per protocol until progression of disease is confirmed by the site investigator/local radiology review at least 28 days from the date of the tumor imaging first suggesting PD. If progression is not confirmed on the subsequent tumor imaging, the subject should continue to receive study therapy and have tumor imaging performed every 9 weeks (± 7 days) in the first year or

every 12 weeks after the first year, or sooner if clinically indicated, to monitor disease status. If radiologic progression is confirmed by subsequent tumor imaging, then the subject will be discontinued from trial treatment.

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

Subjects exhibiting toxicity from trial therapy as outlined in Sections 5.2.1 and 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) in the first year and every 12 weeks (84 ± 7 days) after year 1 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 modality (i.e., CT or MRI), acquisition and technical parameters should be used throughout the study for a given subject.

Additional information is included in the SIM.

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 Procedures Manual.

7.1.3.1 Laboratory Safety Evaluations (Hematology, Chemistry and Urinalysis)

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)[d]
Platelet count	Alanine aminotransferase (ALT)	Protein	aPTT [d]
White Blood Cell - WBC (total and differential)	Aspartate aminotransferase (AST)	Specific gravity	Total thriiodothyronine (T3)[e]
Red Blood Cell Count	Bicarbonate [b]	Microscopic exam, if abnormal results are noted	Free thyroxine (FT4)
Absolute Neutrophil Count	Calcium	Urine pregnancy test[a]	Thyroid stimulating hormone (TSH)
Absolute Lymphocyte Count	Chloride		FSH, estradiol [f]
	Creatinine		Blood for correlative studies
	Glucose		Blood for genetics
	Lactate Dehydrogenase		Blood for MDSCs
	Phosphorus		
	Potassium		
	Sodium		
	Total Bilirubin		
	Direct Bilirubin, if total bilirubin is elevated above the upper limit of normal		
	Total protein		
	Blood Urea Nitrogen		
	Carbon dioxide (CO_2 or bicarbonate)[b]		
	Uric acid		
	Urea[c]		

[a] Perform on women of childbearing potential only. Urine pregnancy test is preferred. If the urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required.
[b] If considered standard of care in your region. If these tests are not done as part of standard of care in your region then these tests do not need to be performed.
[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 7.1.3.2

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

7.1.3.2 Blood for Menopausal Status

Blood for evaluation of postmenopausal status (FSH and estradiol) will be evaluated if clear documentation of post-menopausal status in not obtained.

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

Pre-menopausal

- ≤12 months since LMP

  OR

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

Post-menopausal

- Subject has undergone prior bilateral ovariectomy/oophorectomy

  OR

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

  OR

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

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

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

7.1.3.3 Pharmacokinetic/Pharmacodynamic Evaluations

To evaluate the immunogenicity and exposure of pembrolizumab in this indication, sample collections for analysis of anti-pembrolizumab antibodies (ADA) and PK are currently planned as shown in the Trial Flowchart. Blood samples collected for PK and ADA may only be stored at this time. Further analysis may be performed, if required. If ongoing PK and/or ADA sampling is deemed to be unnecessary by the Sponsor, it may be reduced or discontinued.

7.1.3.3.1 Blood Collection for Serum Pembrolizumab Pharmacokinetics - PK

Sample collection, storage and shipment instructions for serum PK samples will be provided in the Procedures Manual.

7.1.3.3.2 Blood Collection for Anti-Drug (Pembrolizumab) Antibodies - ADA

Sample collection, storage and shipment instructions for anti-drug antibody samples will be provided in the Procedures Manual.

7.1.3.4 Tumor Tissue Collection

A newly obtained core or excisional biopsy (fine needle aspirate not adequate) must be submitted to a central lab for characterization of PD-L1 expression as well HR, PR, and HER2 negative status. The tumor tissue must be received by the central vendor and be deemed adequate for evaluation in real time prior to subject allocation for all cohorts.

Testing for hormone receptor status will be performed with commercially validated assays that meet the following requirements:

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

b) Progesterone receptor (PR) negative status is defined as <1% tumor cells positive for PR 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

Newly-obtained specimens of tissue can be collected up to 8 weeks (56 days) prior to Day 1 provided the proper consent has been obtained. 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 14 days from site slide sectioning date otherwise a new specimen will be requested.

Additionally, if available, archived tumor tissue specimens from prior biopsies will be collected for determination of tumor PD-L1 status to compare biomarker expression in archived specimens against the in newly obtained tumor tissue that is collected as a requirement for entry into the trial. If after agreement with the Sponsor unstained slides are submitted, the slides should be freshly cut and submitted to the testing laboratory within 14 days from site slide sectioning date otherwise a new specimen will be requested.

Tumor tissue collected may also be used to support analysis of exploratory biomarkers as described in Section 4.2.3.5.

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. Details regarding time points for collection of tumor tissue are outlined in the Study Flow Chart – Section 6.1.

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

7.1.3.5 Correlative Blood Collections – Samples for Correlative, Genetic, and Circulating MDSC Analyses

Details regarding time points for blood collection to support analysis of exploratory biomarkers presented in Section 4.2.3.5 are outlined in the Study Flow Chart – Section 6.1.

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

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

MDSCs will only be collected in the participating countries as described in the Procedures Manual.

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

7.1.3.6 Future Biomedical Research

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

- Leftover DNA
- Leftover tumor tissue

7.1.4 Other Procedures

7.1.4.1 Withdrawal/Discontinuation

When a subject discontinues/withdraws from participation in the trial, all applicable activities scheduled for the final trial visit should be performed at the time of discontinuation. Any adverse events which are present at the time of discontinuation/withdrawal should be followed in accordance with the safety requirements outlined in Section 7.2 - Assessing and Recording Adverse Events. Subjects who a) attain a CR or b) complete 24 months of treatment 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 24 months of treatment, these subjects are expected to return to the site for a Safety Follow-up Visit (described in Section 7.1.5.3.2) and then proceed to the Follow-up Period of the study (described in 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 satisfaction of entry criteria and trial assessments and routine safety evaluation of subjects
- Imaging equipment – as required for study objectives
- Drug administration equipment – as required for storage, preparation and administration (infusion) of pembrolizumab

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

Written consent for the main study must be obtained prior to performing any protocol specific procedure including the mandatory newly obtained (fresh) tumor biopsy that is required for eligibility. Potential subjects will be evaluated to determine that they fulfill the entry requirements as set forth in Section 5.1. 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 the first dose trial treatment except for the following:

- Laboratory tests and evaluation of ECOG status are to be performed within 10 days prior to the first dose of trial treatment.

- For women of reproductive potential, a urine pregnancy test will be performed within 72 hours prior to the first dose of trial treatment. If urine pregnancy results cannot be confirmed as negative, a serum pregnancy test will be required (performed by the local study site laboratory).

- Initial tumor imaging must be performed within 28 days prior to the date of allocation.

- A "newly obtained" tumor biopsy sample may be obtained within approximately 56 days of the first dose of trial treatment. See Section 7.1.3.4 for additional details regarding tumor tissue requirements.

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

7.1.5.2 Treatment Cycles

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

7.1.5.2.1 Second Course Phase (Retreatment Period)

Subjects who stop pembrolizumab with SD or better may be eligible for up to an additional 17 cycles (approximately one year) of 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, and
    - Was treated for at least 8 cycles (24 weeks) with pembrolizumab before discontinuing therapy
    - Received at least two treatments with pembrolizumab beyond the date when the initial CR was declared

OR

  - Had SD, PR or CR and stopped pembrolizumab treatment after 35 administrations (approximately 24 months) 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 serum or urine pregnancy test within 72 hours prior to receiving retreatment with study medication.
- 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 after the last dose of study medication (Reference 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.
- 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.
- The subject meets the safety parameters listed in the inclusion/exclusion criteria.
- The trial is ongoing.

Subjects who restart treatment will be retreated at the same dose and dose interval as when they last received pembrolizumab. Treatment will be administered for up to one additional year.

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

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

7.1.5.3 Post-Treatment

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 – Trial Flow Chart. Specific procedure-related details are provided above in Section 7.1 – Trial Procedures. Additional details regarding subject withdrawal and discontinuation are presented in Section 5.8.

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. SAEs that occur within 90 days of the end of treatment or before initiation of a new anti-cancer treatment should also be followed and recorded regardless of causality. Beyond 90 days, only SAE and ECIs that are considered related to trial treatment should be reported.

Subjects who are eligible for retreatment with pembrolizumab (as described in 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 every 9 weeks (63 ± 7 days) in the first year and every 12 weeks (84 ± 7 days) after year 1 by tumor imaging to monitor disease status. The Sponsor may request survival status to be assessed at additional time points during the course of the study (not to exceed approximately 12 weeks). Every effort should be made to collect information regarding disease status until the start of new anti-cancer therapy, disease progression, death, end of study or if the subject begins retreatment with pembrolizumab as detailed in 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 6.2 – Trial Flow Chart for Retreatment with pembrolizumab.

7.1.5.3.4 Survival Follow-up

Once a subject experiences confirmed disease progression or starts a new anti-cancer therapy, the subject moves into the Survival Follow-Up Phase and should be contacted by telephone approximately every 12 weeks to assess for survival status until death, withdrawal of consent, or the end of the study, whichever occurs first.

7.1.5.4 Survival Status

To ensure current and complete survival data is available at the time of database locks, updated survival status may be requested during the course of the study by the Sponsor. For example, updated survival status may be requested prior to but not limited to an external Data Monitoring Committee (eDMC) review, interim and/or final analysis. Upon Sponsor notification, all subjects who do not/will not have a scheduled study visit or study contact during the Sponsor defined time period will be contacted for their survival status (excluding subjects that have a previously recorded death event in the collection tool).

7.2 Assessing and Recording Adverse Events

An adverse event is defined as any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily

have to have a causal relationship with this treatment. An adverse event can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product or protocol-specified procedure, whether or not considered related to the medicinal product or protocol-specified procedure. Any worsening (i.e., any clinically significant adverse change in frequency and/or intensity) of a preexisting condition that is temporally associated with the use of the Sponsor's product, is also an adverse event.

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

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

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

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

All adverse events that occur after the consent form is signed but before treatment allocation/randomization must be reported by the investigator if they cause the subject to be excluded from the trial, or are the result of a protocol-specified intervention, including but not limited to washout or discontinuation of usual therapy, diet, placebo treatment or a procedure. From the time of treatment allocation/randomization through 30 days following cessation of treatment, all adverse events must be reported by the investigator. Such events will be recorded at each examination on the Adverse Event case report forms/worksheets. The reporting timeframe for adverse events meeting any serious criteria is described in section 7.2.3.1. The investigator will make every attempt to follow all subjects with non-serious adverse events for outcome.

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

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

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

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

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

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

7.2.2 Reporting of Pregnancy and Lactation to the Sponsor

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

Pregnancies and lactations that occur after the consent form is signed but before treatment allocation/randomization must be reported by the investigator if they cause the subject to be excluded from the trial, or are the result of a protocol-specified intervention, including but not limited to washout or discontinuation of usual therapy, diet, placebo treatment or a procedure. Pregnancies and lactations that occur from the time of treatment allocation/randomization through 120 days following cessation of Sponsor's product, or 30 days following cessation of treatment if the subject initiates new anticancer therapy, whichever is earlier, must be reported by the investigator. All reported pregnancies must be followed to the completion/termination of the pregnancy. Pregnancy outcomes of spontaneous abortion, missed abortion, benign hydatidiform mole, blighted ovum, fetal death, intrauterine death, miscarriage and stillbirth must be reported as serious events (Important Medical Events). If the pregnancy continues to term, the outcome (health of infant) must also be reported.

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

7.2.3 Immediate Reporting of Adverse Events to the Sponsor

7.2.3.1 Serious Adverse Events

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

- Results in death;
- Is life threatening;
- Results in persistent or significant disability/incapacity;

- Results in or prolongs an existing inpatient hospitalization;
- Is a congenital anomaly/birth defect;
- Is an other important medical event.

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

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

Refer to Table 8 for additional details regarding each of the above criteria.

For the time period beginning when the consent form is signed until treatment allocation/randomization, any serious adverse event, or follow up to a serious adverse event, including death due to any cause other than progression of the cancer under study (see Section 7.2.3.3 for additional details), that occurs to any subject must be reported within 24 hours to the Sponsor if it causes the subject to be excluded from the trial, or is the result of a protocol-specified intervention, including but not limited to washout or discontinuation of usual therapy, diet, placebo treatment or a procedure.

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

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

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

7.2.3.2 Events of Clinical Interest

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

For the time period beginning when the consent form is signed until treatment allocation/randomization, any ECI, or follow up to an ECI, that occurs to any subject must be reported within 24 hours to the Sponsor if it causes the subject to be excluded from the trial,

or is the result of a protocol-specified intervention, including but not limited to washout or discontinuation of usual therapy, diet, placebo treatment or a procedure.

For the time period beginning at treatment allocation/randomization through 90 days following cessation of treatment, or 30 days following cessation of treatment if the subject initiates new anticancer therapy, whichever is earlier, 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).

3. Additional adverse events:

A separate guidance document has been provided entitled "Event of Clinical Interest Guidance Document" (previously entitled, "Event of Clinical Interest and Immune-Related Adverse Event Guidance Document"). This document can be found in the administrative binder and provides guidance regarding identification, evaluation and management of ECIs and irAEs.

ECIs (both non-serious and serious adverse events) identified in this guidance document from the date of first dose through 90 days following cessation of treatment, or 30 days after the initiation of a new anticancer therapy, whichever is earlier, need to be reported to the SPONSOR within 24 hours of the event, regardless of attribution to trial treatment, consistent with standard SAE reporting guidelines and either by electronic media or paper. Sponsor Contact information can be found in the administrative binder.

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

7.2.3.3 Protocol-Specific Exceptions to Serious Adverse Event Reporting

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

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

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

7.2.4 Evaluating Adverse Events

An investigator who is a qualified physician will evaluate all adverse events according to the NCI Common Terminology for Adverse Events (CTCAE), version 4. 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 patient's medical history.); or	
	†**Is a congenital anomaly/birth defect** (in offspring of subject taking the product regardless of time to diagnosis);or	
	Is a new **cancer** (that is not a condition of the study) **(**although not serious per ICH definition, is reportable to the Sponsor within 24 hours to meet certain local requirements); **or**	
	Is an overdose (whether accidental or intentional). Any adverse event associated with an overdose is considered a serious adverse event for collection purposes. An overdose that is not associated with an adverse event is considered a non-serious event of clinical interest and must be reported within 24 hours.	
	Other important medical events that may not result in death, not be life threatening, or not require hospitalization may be considered a serious adverse event when, based upon appropriate medical judgment, the event may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed previously (designated above by a †).	
Duration	Record the start and stop dates of the adverse event. If less than 1 day, indicate the appropriate length of time and units	
Action taken	Did the adverse event cause the Sponsor's product to be discontinued?	
Relationship to Sponsor's Product	Did the Sponsor's product cause the adverse event? The determination of the likelihood that the Sponsor's product caused the adverse event will be provided by an investigator who is a qualified physician. The investigator's signed/dated initials on the source document or worksheet that supports the causality noted on the AE form, ensures that a medically qualified assessment of causality was done. This initialed document must be retained for the required regulatory time frame. The criteria below are intended as reference guidelines to assist the investigator in assessing the likelihood of a relationship between the test drug and the adverse event based upon the available information. **The following components are to be used to assess the relationship between the Sponsor's product and the AE**; the greater the correlation with the components and their respective elements (in number and/or intensity), the more likely the Sponsor's product caused the adverse event (AE):	
	Exposure	Is there evidence that the subject was actually exposed to the Sponsor's product such as: reliable history, acceptable compliance assessment (pill count, diary, etc.), expected pharmacologic effect, or measurement of drug/metabolite in bodily specimen?
	Time Course	Did the AE follow in a reasonable temporal sequence from administration of the Sponsor's product? Is the time of onset of the AE compatible with a drug-induced effect (applies to trials with investigational medicinal product)?
	Likely Cause	Is the AE not reasonably explained by another etiology such as underlying disease, other drug(s)/vaccine(s), or other host or environmental factors

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

7.2.5 Sponsor Responsibility for Reporting Adverse Events

All Adverse Events will be reported to regulatory authorities, IRB/IECs and investigators in accordance with all applicable global laws and regulations, i.e., per ICH Topic E6 (R1) Guidelines for Good Clinical Practice.

7.3 Trial Governance and Oversight

7.3.1 Data Monitoring Committee

There will be no data monitoring committee.

The interim analyses will be conducted by the Sponsor. The main Sponsor study team will remain blinded to PD-L1 scores of subjects in Cohort A.

An unblinded biomarker statistician who has the access to subject level PD-L1 score for biomarker cutoff analysis will inform the main study team about the outcome of both interim analyses (IA 1 and IA 2) and whether the pre-specified go/no go decision criteria is met. For additional information please see Section 8.2.1 and Section 8.2.9.

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, will be documented in a supplemental SAP (sSAP) and referenced in the Clinical Study Report (CSR) for the study. A biomarker analysis plan will be provided. Post hoc exploratory analyses will be clearly identified in the CSR.

8.1 Statistical Analysis Plan Summary

This section contains a brief summary of the statistical analyses for this trial. Full detail is in the Statistical Analysis Plan (SAP) (Section 8.2).

In addition, a separate analysis plan document will be issued prior to biomarker unblinding for each of the following laboratory procedures and assessments: (1) Biomarkers (detailed in Section 7.1.3.4 and 7.1.3.5) and their association with antitumor efficacy and (2) Pharmacokinetic and pharmacodynamics evaluation (detailed in Section 7.1.3.3)

Study Design Overview	A Phase II Clinical Trial of Pembrolizumab as Monotherapy in Subjects with Metastatic Triple-Negative Breast Cancer (mTNBC)
Treatment Assignment	Treatment assignment is open label.
Analysis Populations	Efficacy: All Subjects as Treated (ASaT) Safety: All Subjects as Treated (ASaT)
Primary Endpoint(s)	Objective Response Rate (ORR)
Statistical Methods for Key	ORR estimation

Efficacy Analyses	• 2L+ population
	  o PD-L1 (+) population (Cohort A)
	  o Overall population (Cohort A)
	  o PD-L1 strong (+) population (Cohorts A+C)
	• 1L population (Cohort B)
	• Counts and percentages
	• 95% Agresti-Coull confidence intervals

Statistical Methods for Key Safety Analyses	Counts and percentages of AEs will be provided. Confidence intervals for rates of AEs of clinical interest will be computed using the exact binomial method.

Interim Analyses	• Futility analysis for 2L+ subjects (Cohort A) with PD-L1 (-) tumors based on no progression
	  o ~25 PD-L1 (-) subjects
	  o If no response or stable disease, continue 2L+ population (Cohort A) in PD-L1 (+) patients only
	• Evaluation of expansion to Cohort C for PD-L1 strong (+) population based on ORR.
	  o ~10 patients evaluable through response, progression or 18-week scan, whichever comes first.
	  o Cohort C may start if ≥ 1 responses observed
	The final analysis of Cohorts A and C combined is to be completed when subjects are evaluable through response, progression or 18-week scan, whichever comes first.

Multiplicity	This is an estimation study. No multiplicity adjustment will be applied.
Sample Size	The planned sample size is up to approximately 285 subjects. • ~160 subjects in the 2L+ overall population (Cohort A) • ~93/160 2L+ subjects (~58%) expected to be PD-L1 (+), if PD-L1 (-) is not futile at the futility analysis; ~135 2L+ subjects expected to be PD-L1 (+), if PD-L1 (-) is discontinued after the futility analysis • ~55 PD-L1 strong (+) subjects (Cohort C and PD-L1 strong (+) subgroup from Cohort A) • ~80 PD-L1 (+) first line subjects (Cohort B)

8.2 Statistical Analysis Plan

8.2.1 Responsibility for Analyses/In-House Blinding

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

This trial is being conducted as an open-label non-randomized single-arm clinical trial for each cohort, i.e., subjects, investigators, and SPONSOR personnel will be aware of subject treatment assignments after each subject is enrolled and treatment is assigned. The investigator and 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 in Cohort A. A designated Sponsor team (may include unblinded Sponsor

statisticians, unblinded Sponsor statistical programmers, unblinded Sponsor clinical scientists, unblinded clinical directors, and unblinded data management personnel) will have access to the subject-level PD-L1 results for the purpose of data review and will have no other responsibilities associated with the study. A summary of PD-L1 biomarker prevalence and biomarker cutoff analysis will be provided to the study team at the Sponsor by the unblinded Sponsor statistician. Biomarker cutoff analysis will inform the team about the outcome of the interim analyses and whether or not the pre-specified go/no go decision criteria are met. The estimation of tumor efficacy, e.g., ORR, DOR and DCR, etc. based on RECIST 1.1 by the central imaging vendor may be provided by the unblinded statistician while the trial is ongoing.

The Clinical Biostatistics department will generate the allocation schedule for study treatment assignment. Allocation will be implemented in an interactive voice response system (IVRS).

8.2.2 Hypotheses/Estimation

This is an estimation study. Objectives of the study are stated in Section 3.0.

8.2.3 Analysis Endpoints

The efficacy and safety endpoints that will be evaluated are listed below, followed by the descriptions of the derivations of selected endpoints.

8.2.3.1 Efficacy Endpoints

The primary efficacy endpoint is objective response rate (ORR), defined as the proportion of subjects in the analysis population who have complete response (CR) or partial response (PR), based on RECIST 1.1 by the central imaging vendor at any time during the study. As supportive analyses, ORR will also be evaluated by a) site investigator and local radiology review based on RECIST 1.1 and b) irRECIST by the central imaging vendor.

Secondary efficacy endpoints include:

- Duration of response (DOR), defined as the time from first documented evidence of CR or PR until disease progression or death due to any cause, whichever occurs first, for subjects who demonstrate CR or PR, based on RECIST 1.1 by the central imaging vendor.

- Disease control rate (DCR), defined as the percentage of subjects who have achieved confirmed CR or PR or have demonstrated SD for at least 24 weeks prior to any evidence of progression, based on RECIST 1.1 by the central imaging vendor.

- Progression-free survival (PFS), defined as the time from first dose of study medication to the first documented disease progression or death due to any cause, whichever comes first, based on RECIST 1.1 by the central imaging vendor.

- Overall survival (OS), defined as the time from first dose of study medication to death due to any cause.

As exploratory endpoints, DOR and DCR and PFS will also be evaluated based on a) RECIST 1.1 by study site and local radiology review and b) irRECIST by the central imaging vendor.

8.2.3.2 Safety Endpoints

Safety measurements are described in Section 4.2.3.2 Safety Endpoints and Section 7.

Safety and tolerability will be assessed by clinical review of all relevant parameters including adverse events (AEs), laboratory tests, and vital signs. Safety parameters to be analyzed include, but are not limited to, AEs, SAEs, fatal AEs, and laboratory changes. Furthermore, specific events will be collected and designated as events of clinical interest (ECIs) as described in Section 7.2.3.2.

8.2.3.3 Biomarker Endpoints

A separate biomarker SAP will be provided for the following endpoints/analyses.

- The association between PD-L1 protein expression by IHC and antitumor activity to pembrolizumab as monotherapy for mTNBC.
- The association between antitumor activity of pembrolizumab in mTNBC and efficacy/resistance biomarkers, utilizing tumor and blood specimens obtained before/after treatment and at disease progression.
- The performance comparison of PD-L1 assessment by IHC in newly-obtained vs. archived tumor samples.

8.2.3.4 Pharmacokinetic Endpoints

Pharmacokinetic parameters and the presence of anti-drug antibodies, following IV administration of 200 mg pembrolizumab Q3W as monotherapy in subjects with mTNBC (details see Section 4.2.3.4.)

8.2.3.5 Other Endpoints

Other endpoints include association between genetic variation and response to the treatment(s) administered, variation across the human genome for the association with clinical data (details see Sections 4.2.3.5 and 4.2.3.6.) and the association between LDH and efficacy response to pembrolizumab as monotherapy for mTNBC.

8.2.4 Analysis Populations

8.2.4.1 Efficacy Analysis Populations

The All-Subjects-as-Treated (ASaT) population, which consists of as all enrolled subjects who receive at least one dose of study medication with measurable metastatic disease at baseline, will serve as the primary population for the analyses of efficacy data in this trial.

Details on the approach to handling missing data for efficacy analyses are provided in Section 8.2.5 Statistical Methods.

8.2.4.2 Safety Analysis Populations

The All-Subjects-as-Treated (ASaT) population will be used for the analysis of safety data. At least one laboratory or vital sign measurement obtained subsequent to at least one dose of study treatment is required for inclusion in the analysis of each specific parameter. To assess change from baseline, a baseline measurement is also required.

8.2.5 Statistical Methods

8.2.5.1 Statistical Methods for Efficacy Analyses

Efficacy of pembrolizumab as 2L+ monotherapy for mTNBC will be evaluated primarily in PD-L1 (+) and overall population (all comers) in Cohort A, and also in subjects with PD-L1 strong (+) tumors from Cohorts A and C combined. Cohort A will be evaluated for association between PD-L1 biomarker expression and antitumor activity. A separate biomarker SAP will be devoted to association between PD-L1 biomarker expression and antitumor activity analysis.

The primary efficacy endpoints are ORR based on RECIST 1.1 by the central imaging vendor in subjects with PD-L1 (+) mTNBC of Cohorts A, overall population (all comers) of Cohort A and in subjects with PD-L1 strong (+) mTNBC. The point estimate 95% Agresti-Coull (A-C) confidence interval (CI) (as determined by the upper and lower 97.5% one-sided confidence bounds) will be provided based on normal approximation for the binomial distribution. Subjects without response data will be counted as non-responders.

Similarly, a supportive analysis to the primary method, ORR based on RECIST 1.1 by study site investigator and local radiology review will also be performed in the same fashion.

For the secondary endpoint of DCR, similar estimation methods used for ORR will be applied.

For DOR, PFS and OS, Kaplan-Meier (KM) curves, median estimates, and survival at 6 and 12 months based on the KM curves (95% CI is based on Greenwood's formula) will be provided as appropriate. Subjects without efficacy evaluation data or without survival data will be censored at Day 1. The restricted mean survival time (RMST) for DOR will also be provided as a supportive analysis.

Censoring rules for DOR are summarized in Table 9.

Table 9 Censoring Rules for DOR

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

Similar estimation methods will be applied to the efficacy analyses for the subjects with PD-L1 (+) mTNBC in Cohort B.

Table 10 summarizes the key efficacy analyses for primary and secondary endpoints in this study.

Table 10 Analysis Strategy for Primary/Secondary Efficacy Endpoints in Cohorts A and C

Endpoint/Variable (Description, Time Point)	Statistical Method	Analysis Population	Missing Data Approach
Primary:			
ORR, based on RECIST1.1 by the central imaging vendor	95% Agresti-Coull CI	ASaT - PD-L1 (+) - overall - PD-L1 strong (+)	Subjects with missing data are considered non-responders
Secondary:			
Response duration (DOR) Based on RECIST1.1 o by the central imaging vendor o by study site investigator and local radiology teview	Summary statistics using Kaplan-Meier method	All responders - PD-L1 (+) - overall - PD-L1 strong (+)	Non-responders are excluded in analysis
ORR Based on RECIST1.1 o by study site investigator and local radiology review	Agresti-Coull 95% CI	ASaT - PD-L1 (+) - overall - PD-L1 strong (+)	Subjects with missing data are considered non-responders
DCR Based on RECIST1.1 o by the central imaging vendor o by study site investigator and local radiology review	Agresti-Coull 95% CI	ASaT - PD-L1 (+) - overall - PD-L1 strong (+)	Subjects with missing data are considered non-responders
Progression-free survival (PFS) Based on RECIST1.1 o by the central imaging vendor o by study site investigator and local radiology review	Summary statistics using Kaplan-Meier method	ASaT - PD-L1 (+) - overall - PD-L1 strong (+)	Censored at last assessment
Overall survival (OS)	Summary statistics using Kaplan-Meier method	ASaT - PD-L1 (+) - overall - PD-L1 strong (+)	Censored at last assessment
95% confidence interval is determined by the upper and lower 97.5% one-sided confidence bounds.			

Similar efficacy methods will be applied to Cohort B for subjects with PD-L1 (+) tumors receiving pembrolizumab as 1L monotherapy for mTNBC.

8.2.5.2 Statistical Methods for Safety Analyses

Safety and tolerability will be assessed by clinical review of all relevant parameters including adverse experiences (AEs), laboratory tests, and vital signs by cohort and total (combining across Cohorts A-C). Summary statistics (counts, percentage, mean, standard deviation, etc.) will be provided for the safety endpoints as appropriate. The confidence interval for the

incidence rate of Grade 2 or higher adverse events with an immune etiology and the incidence rate of Grade 4/5 AEs will be provided as appropriate.

8.2.5.3 Summaries of Baseline Characteristics, Demographics, and Other Analyses

8.2.5.3.1 Demographic and Baseline Characteristics

Baseline characteristics will be assessed by the use of tables and/or graphs for each cohort. No statistical hypothesis tests will be performed on these characteristics. The number and percentage of subjects screened, treated, primary reasons for screening failure, and discontinuation will be displayed. Demographic variables (e.g., age, region), baseline characteristics, primary and secondary diagnoses, and prior and concomitant therapies will be summarized by cohort either by descriptive statistics or categorical tables.

8.2.6 Multiplicity

This is an estimation study. The estimation of ORR and associated 95% confidence intervals of ORR will be provided. No multiplicity adjustment will be applied in subjects with PD-L1 (+) mTNBC of Cohorts A, overall population (all comers) of Cohort A and in subjects with PD-L1 strong (+) mTNBC.

There are also no hypotheses for other parameters of DOR, DCR, PFS, and OS or for Cohort B.

8.2.7 Sample Size and Power Calculations

The trial has a planned sample size of up to approximately N=285 subjects

- N = ~160: 2L+ overall population (all comers; Cohort A)
    - Would expect N=93 PD-L1 (+) subjects based on 58% prevalence
    - Would expect N=135 PD-L1 (+) subjects if PD-L1 (-) patients are discontinued at interim analysis
- N = ~45: expansion for the 2L+ PD-L1 strong (+) population (Cohort C)
    - N ~ 55 expected for total PD-L1 strong (+) population (Cohort A subgroup + Cohort C)
- N = ~80: 1L PD-L1 (+) subjects (Cohort B)

The study is for estimation.

Table 11 Summary of Sample Size Calculation

Line of Therapy	Population	Cohort	N	Number of Observed Responders	ORR Estimates	95% A-C CI of ORR (%)
2L+	Overall population	A	160	24	15.0%	(10.2,21.4)
	PD-L1 (+)	A	93	16	17.2%	(10.8, 26.2)
	PD-L1 (+)	A	135	21	15.6%	(10.3, 22.7)
	PD-L1 strong (+)	A+ C	55	11	20.0%	(11.4,32.5)
1L	PD-L1 (+)	B	80	24	30.0%	(21.0,40.8)

Details underlying the above summary calculations follow below.

ORR in the PD-L1 (+) and overall population in Cohort A

It is expected that ~160 subjects in Cohort A will be enrolled for investigating the association between PD-L1 protein expression by IHC and antitumor activity of pembrolizumab as monotherapy for mTNBC (Details in Biomarker Analysis SAP).

Similarly for the ORR in the PD-L1 (+) in Cohort A, if PD-L1 (-) is not futile at the futility analysis it is expected that ~93 subjects out of the ~160 enrolled subjects (~58% prevalence based on previous study) in Cohort A will have PD-L1 (+) expression. With ~93 subjects, if there are at least 16 responders observed, the lower bound of the 95% CI for ORR will be above 10%.

If PD-L1 (-) is futile, there will be with ~135 subjects in Cohort A [excluding 25 PD-L1 (-) in the futility analysis]. If there are at least 21 responders observed, the lower bound of the 95% CI for ORR will be above 10%.

Similarly for the ORR in the overall population in Cohort A, if PD-L1 (-) is not futile, there will be ~160 subjects. If there are at least 24 responders observed, the lower bound of the 95% CI for ORR will be above 10%.

Table 12 shows the two-sided 95% A-C CI of ORR with different sample size for different observed response rates.

Table 12 Two-sided 95% A-C CI of ORR with Different Sample Size

Sample Size (N)	Number of Observed Responders	ORR Estimates	95% A-C CI of ORR (%)
93	10	10.8%	(5.8,18.9)
	14	15.1%	(9.1,23.8)
	16	**17.2%**	**(10.8, 26.2)**
	19	20.4%	(13.4,29.8)
110	11	10.0%	(5.5,17.2)
	17	15.5%	(9.8,23.5)
	18	16.4%	(10.5, 24.5)
	22	20.0%	(13.5,28.5)
135	14	10.4%	(6.2,16.8)
	21	**15.6%**	**(10.3,22.7)**
	27	20.0%	(14.1,27.6)
160	16	10.0%	(6.2,15.7)
	24	**15.0%**	**(10.2,21.4)**
	32	20.0%	(14.5,26.9)
170	17	10.0%	(6.3,15.5)
	26	15.3%	(10.6,21.5)
	34	20.0%	(14.6,26.7)
180	18	10.0%	(6.3,15.3)
	27	15.0%	(10.5,21.0)
	36	20.0%	(14.8,26.5)

ORR in PD-L1 strong (+) in Cohorts A + C

There will be ~55 subjects with PD-L1 strong (+) tumors enrolled in Cohort A and Cohort C.

Table 13 shows the two-sided 95% A-C CI of ORR with 55 evaluable subjects for different observed response rates. With 55 subjects with PD-L1 strong (+) tumors, if there are at least 11 responders observed, the lower bound of the 95% A-C CI for ORR will be above 10%.

Table 13 Two-sided 95% A-C CI of ORR with 55 Evaluable Subjects

Number of Observed Responders	ORR Estimates	95% A-C CI of ORR (%)
6	10.9%	(4.7,22.2)
8	14.5%	(7.3,26.4)
9	16.4%	(8.6,28.5)
10	18.2%	(10.0,30.5)
11	**20.0%**	**(11.4,32.5)**
13	23.6%	(14.2,36.5)
14	25.5%	(15.7,38.4)

Table 14 shows the Two-sided exact 95% CI of AE Rate with 55 subjects.

Table 14 Two-sided 95% Exact CI of AE Incidence Rate with 55 Evaluable Subjects

Number of AE	AE Incidence Rate Estimates	95% CI of Incidence Rate (%)
6	10.9%	(4.1,22.2)
11	20.0%	(10.4,33.0)
17	30.9%	(19.1,44.8)
22	40.0%	(27.0,54.1)
28	50.9%	(37.1,64.6)

ORR in PD-L1 (+) Cohort B

There will be ~80 subjects with PD-L1 (+) tumors enrolled in Cohort B.

Table 15 shows the two-sided 95% CI of ORR with 80 or 100 subjects for different observed response rates.

Table 15 Two-sided 95% A-C CI of ORR with 80 or 100 Subjects

Sample Size (N)	Number of Observed Responders	ORR Estimates	95% CI of ORR (%)
80	12	15%	(8.6,24.6)
	16	20%	(12.6,30.1)
	20	25%	(16.7,35.6)
	24	**30%**	**(21.0,40.8)**
	28	35%	(25.4,45.9)
	32	40%	(30.0,51.0)
	36	45%	(34.6,55.9)
100	15	15%	(9.2,23.4)
	20	20%	(13.3,29.0)
	25	25%	(17.5,34.4)
	30	30%	(21.9,39.6)
	35	35%	(26.3,44.8)
	40	40%	(30.9,49.8)
	45	45%	(35.6,54.8)

Table 16 shows the Two-sided exact 95% CI of AE Rate with 80 subjects.

Table 16 Two-sided 95% Exact CI of AE Incidence Rate with 80 Evaluable Subjects

Number of AE	AE Incidence Rate Estimates	95% CI of Incidence Rate (%)
8	10.0%	(4.4,18.8)
16	20.0%	(11.9,30.4)
24	30.0%	(20.3,41.3)
32	40.0%	(29.2,51.6)
40	50.0%	(38.6,61.4)

8.2.8 Subgroup Analyses and Effect of Baseline Factors

Subgroup analyses are planned for the efficacy analyses in the classification variables:

- Age category (≤50 vs. >50 years)
- Menopausal status
- PD-L1 IHC expression [PD-L1 strong (+), PD-L1 (+), PD-L1 (-) and overall]
- Previous Chemotherapy(2/3 L vs. 4L+)
- Liver metastases (Presence vs. Absence)

8.2.9 Interim Analyses

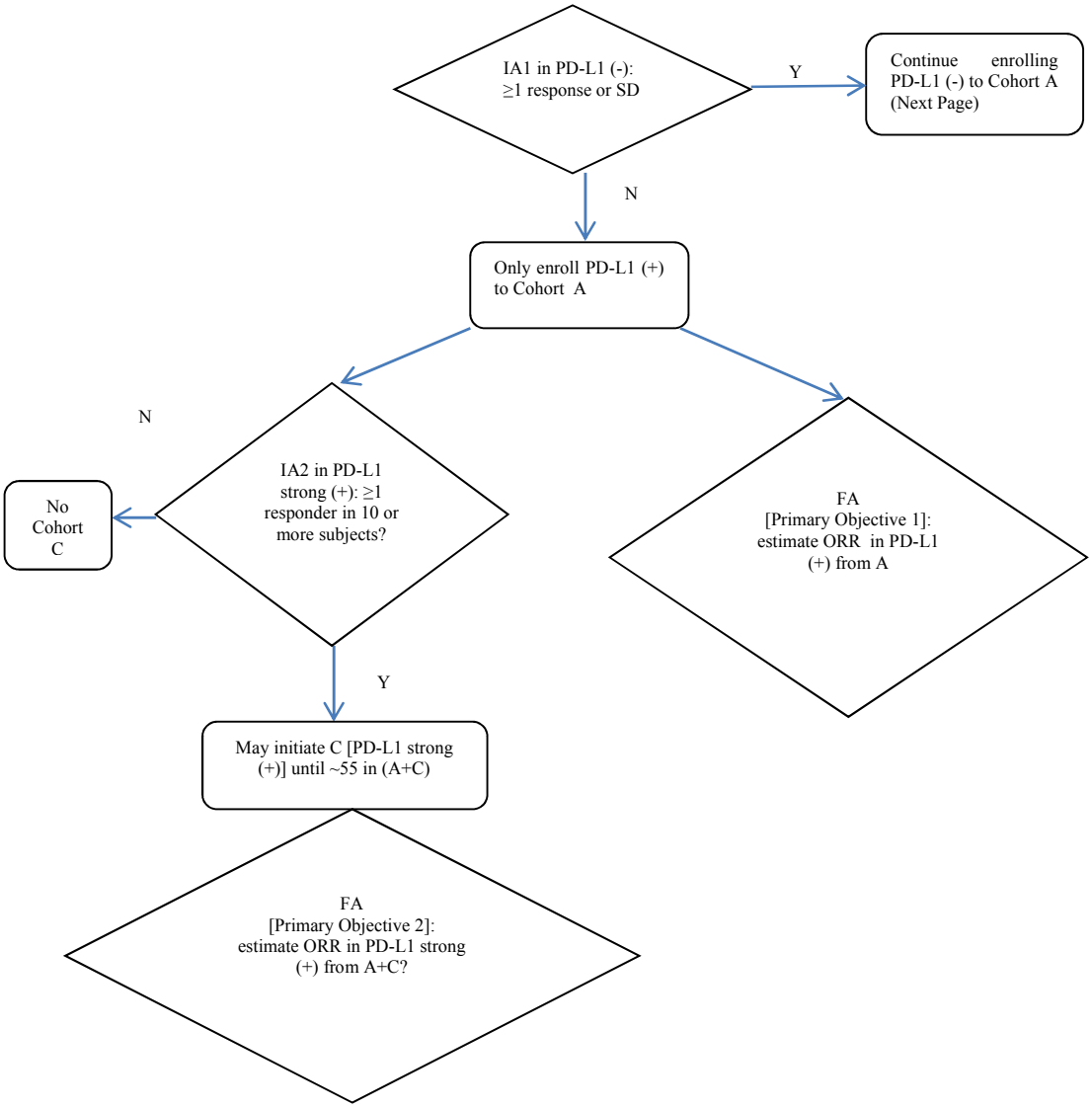
There are two interim analyses planned in this study. For Cohort A in Part 1, a futility analysis will be performed for subjects with PD-L1 (-) tumors and an interim analysis for potential efficacy expansion will be performed for subjects with PD-L1 strong (+) tumors in this cohort.

The PD-L1 strong (+) population (10 or more subjects depending on the prevalence of PD-L1 strong (+) tumors in the 2L+ population from Cohort A) may be expanded by continuing enrollment of subjects with PD-L1 strong (+) tumors into Cohort C, if at least one responder is observed in this subpopulation from Cohort A. The combined sample size of up to ~55 subjects with PD-L1 strong (+) tumors from Cohorts A and C is driven by the primary efficacy estimation for subjects with PD-L1 strong (+) tumors (with futility bound accounted for the IA in this subpopulation).

The detailed process is described as below:

1. Enrollment will begin independent of tumor PD-L1 status.
2. A futility analysis will start when the first ~25 subjects with PD-L1 (-) tumors are evaluable through response, progression or 18-week tumor imaging, whichever comes first. The purpose of this interim analysis is to check treatment futility for subjects with PD-L1 (-) tumors.
3. If the futility boundary is not crossed, that is at least one subject with response or stable disease is observed in subjects with PD-L1 (-) tumors, the trial enrollment will continue as planned. If the futility boundary is crossed for subjects with PD-L1 (-) tumors, then such subjects may be excluded from further enrollment in the trial. That is, the trial will continue to only enroll subjects with PD-L1 (+) tumors until there are 160 subjects in total.
4. An efficacy futility interim will also be performed for the PD-L1 strong (+) subpopulation of Cohort A, and enrollment of Cohort C for PD-L1 strong (+) may be initiated if one or more responders are observed in at least 10 subjects from Cohort A.

Figure 4 illustrates the study diagram for decision making (a study decision tree).


IA1 in PD-L1 (-): ≥1 response or SD
Y
Continue enrolling PD-L1 (-) to Cohort A (Next Page)
N
Only enroll PD-L1 (+) to Cohort A
N
IA2 in PD-L1 strong (+): ≥1 responder in 10 or more subjects?
No Cohort C
FA [Primary Objective 1]: estimate ORR in PD-L1 (+) from A
Y
May initiate C [PD-L1 strong (+)] until ~55 in (A+C)
FA [Primary Objective 2]: estimate ORR in PD-L1 strong (+) from A+C?

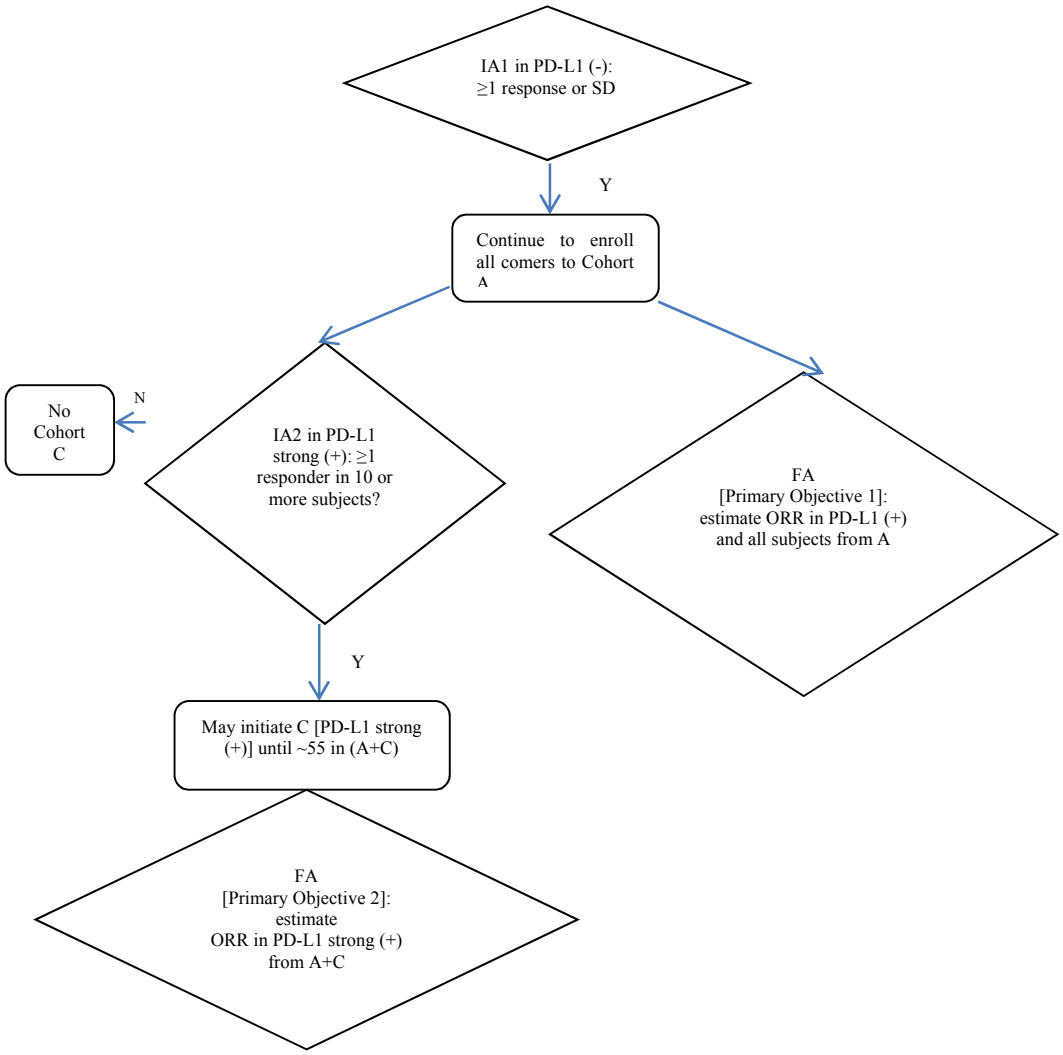


Figure 4 Decision Tree

Interim Analysis for Futility (IA1)

An interim futility check will be performed for the PD-L1 (-) population in Cohort A. Enrollment of PD-L1 (-) population will be stopped, if futility bound is reached. At least one subject without disease progression among the 25 subjects is needed for the further enrollment of subjects with PD-L1 (-) tumors. Table 17 lists the probability of stopping for futility at different true response rate in PD-L1 (-) based on different stopping rules.

Table 17 Probability of Futility under Different True Response Rate[§] in PD-L1 (-)

Response Rate[§] in PD-L1 (-)	Probability of Futility in PD-L1 (-)	
	Rule of ≥ 1 Responder or SD	Rule of ≥ 2 Responders or SD
1%	77.8%	97.4%
2%	60.3%	91.1%
5%	27.7%	64.2%
8%	12.4%	39.4%
10%	7.2%	27.1%

[§]Response rate: the proportion of responders (CR and PR) or subjects with stable disease.

Interim Analysis to Initiate Cohort C Expansion (IA 2)

IA2 (Cohort A) will be performed when at least 10 subjects with PD-L1 strong (+) tumors are evaluable through response, progression or 18-week scan, whichever comes first. One or more responses need to be observed in order to expand enrollment to additional subjects with PD-L1 strong (+) tumors (up to ~55 subjects in Cohorts A and C combined). Table 18 shows the probability to initiate Cohort C under different true ORR in PD-L1 strong (+) subpopulation in Cohort A based on the rule of one or more responders.

Table 18 Probability to Initiate Cohort C under Different True ORR in PD-L1 Strong (+)

ORR in PD-L1 Strong (+)	Probability to Initiate Cohort C
10%	65.1%
15%	80.3%
18%	86.3%
20%	89.3%
25%	94.4%
30%	97.2%

8.2.10 Compliance (Medication Adherence)

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

8.2.11 Extent of Exposure

Extent of Exposure for a subject is defined as number of cycles in which the subject receives the study medication infusion. Summary statistics will be provided on Extent of Exposure for ASaT population.

8.2.12 Other Analyses

8.2.12.1 Biomarker Analyses

Biomarker endpoints including exploring the association between PD-L1 protein expression by IHC and response to pembrolizumab as monotherapy for mTNBC to define the biomarker cut-point for mTNBC will be analyzed in a separate SAP by biomarker group.

8.2.12.2 Other Exploratory Analysis

The association between LDH and efficacy response to pembrolizumab as monotherapy for mTNBC may be explored.

9.0 LABELING, PACKAGING, STORAGE AND RETURN OF CLINICAL SUPPLIES

9.1 Investigational Product

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

Clinical Supplies will be provided by the Sponsor as summarized in Table 19.

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

Table 19 Product Descriptions

Product Name & Potency	Dosage Form
pembrolizumab 100 mg / 4mL	Solution for Infusion

9.2 Packaging and Labeling Information

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

All supplies will be provided open label. Pembrolizumab will be provided as non-kitted single vials or as single vials in a kit box.

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 7.1.3.6 – Future Biomedical Research 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 patients 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. [insert: 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. **OR** Buccal swab specimens will be collected inside the cheek with no associated venipuncture to obtain the specimen. Therefore, there will not be an additional risk for the subject.]

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.

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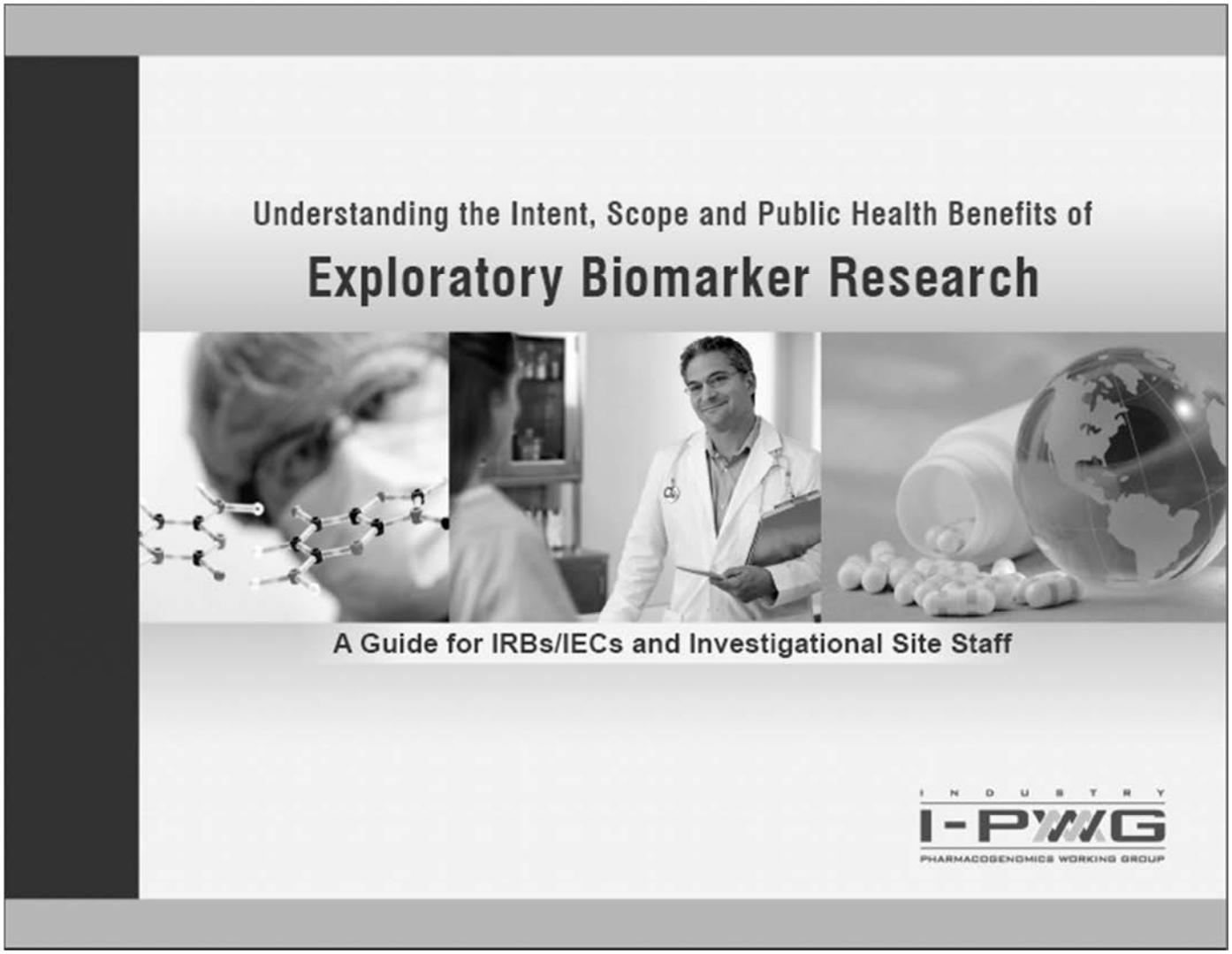
12.3 Understanding the Intent, Scope and Public Health Benefits of Exploratory Biomarker Research: A Guide for IRBs/IECs and Investigational Site Staff



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

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

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

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

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

2. Why is Biomarker Research Important?

Importance to Patients and Public Health

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

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

Importance to Drug Development

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

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

3. Importance of Biomarkers to Regulatory Authorities

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

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

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

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

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

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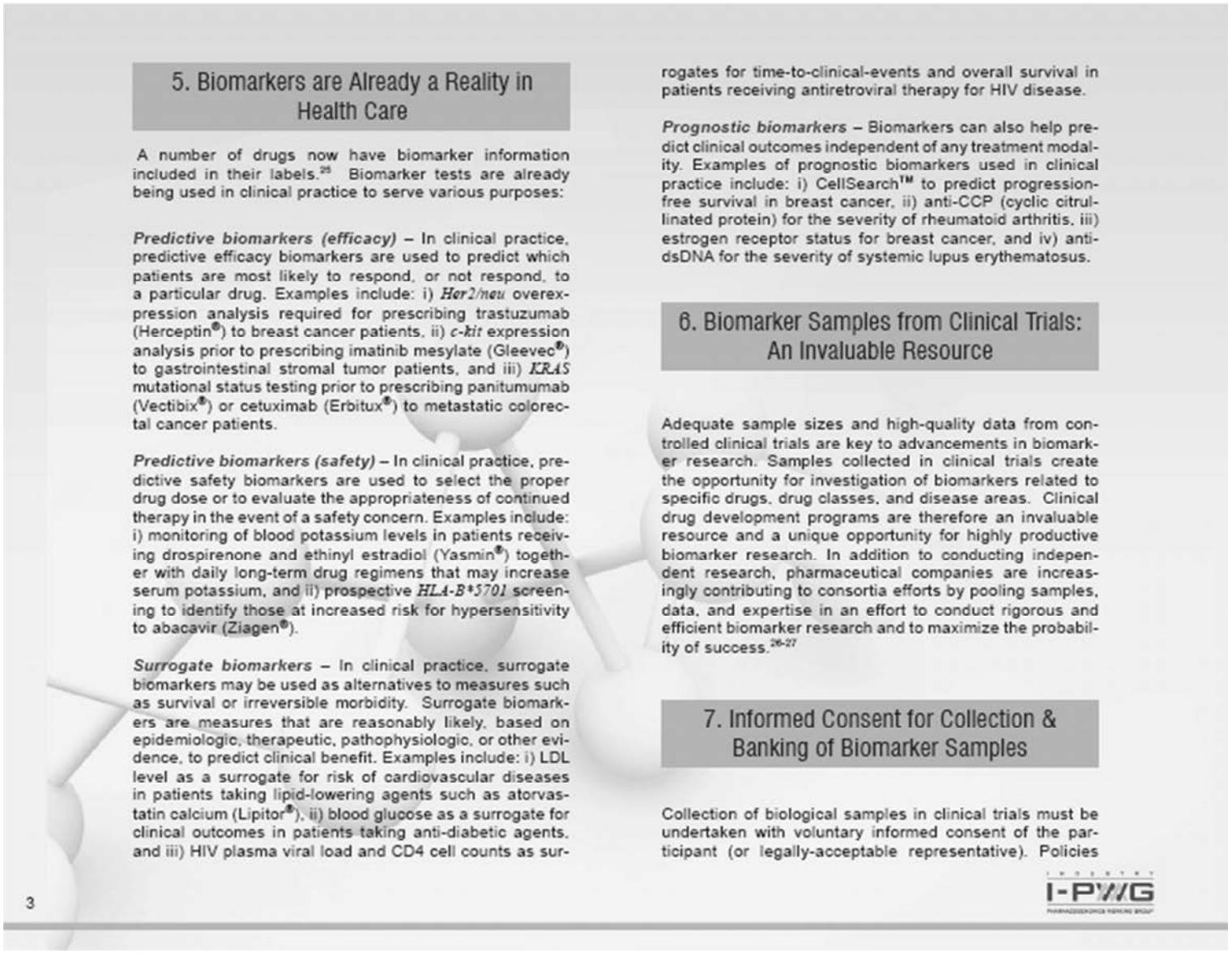

5. Biomarkers are Already a Reality in Health Care

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

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

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

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

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

6. Biomarker Samples from Clinical Trials: An Invaluable Resource

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

7. Informed Consent for Collection & Banking of Biomarker Samples

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

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

Optional vs. Required Subject Participation

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

Consent for Future Research Use

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

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

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

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

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

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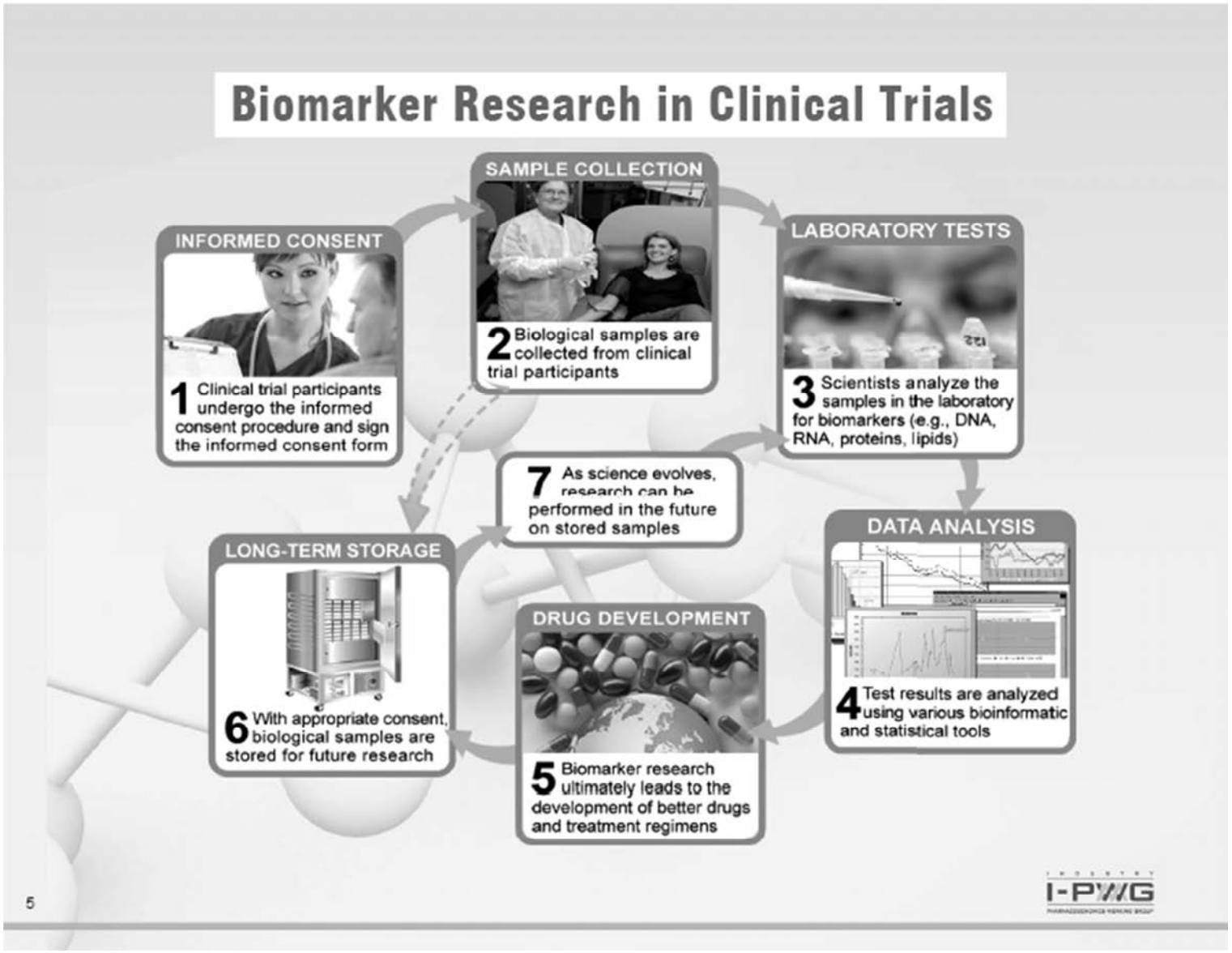
Biomarker Research in Clinical Trials
SAMPLE COLLECTION
2 Biological samples are collected from clinical trial participants
INFORMED CONSENT
1 Clinical trial participants undergo the informed consent procedure and sign the informed consent form
LABORATORY TESTS
3 Scientists analyze the samples in the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

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

9. Return of Research Results to Study Participants

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

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

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

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

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

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

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

10. Benefits and Risks Associated with Biomarker Research

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

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

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

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

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

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

11. Privacy, Confidentiality, and Patient Rights

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

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

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

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

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

12.Where to Get More Information?

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

13. What is I-PWG?

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

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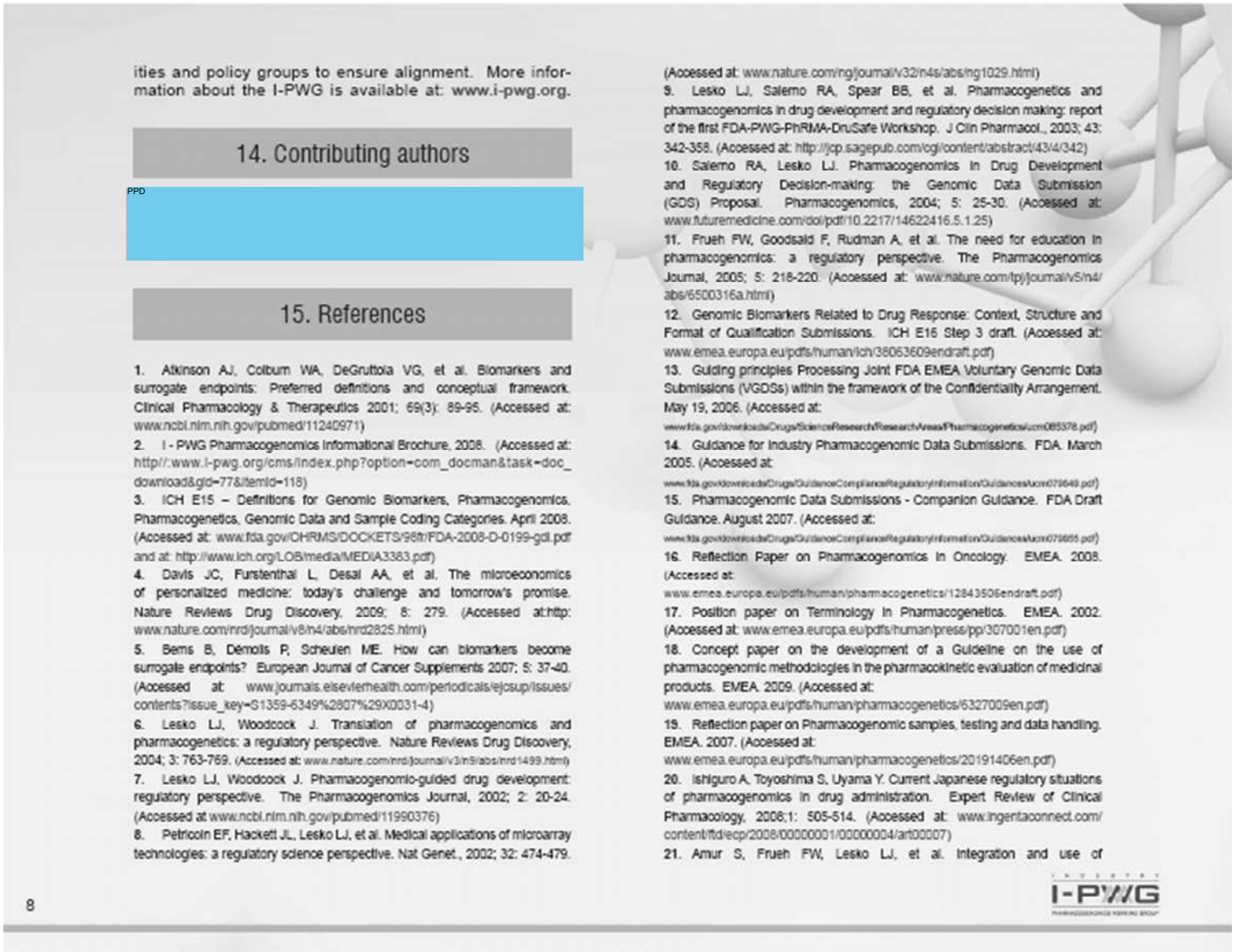

ities and policy groups to ensure alignment. More information about the I-PWG is available at: www.i-pwg.org.

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www.i-pwg.org

12.4 ECOG Performance Status

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

12.5 Abbreviations

Abbreviation/Term	Definition
1L	First Line
AE	Adverse Event
ADA	Anti-Drug Antibodies
AJCC	American Joint Committee on Cancer
ALT	Alanine Aminotransferase
AP	Alkaline Phosphatase
aPTT	Activated Partial Thromboplastin Time
AR	Androgen Receptor
ASCO	American Society of Clinical Oncology
AST	Aspartate Aminotransferase
β-hCG	β-human Chorionic Gonadotropin
BRCA	Breast Cancer 1
CBC	Complete Blood Count
CD8+	Cluster of Differentiation 8 positive
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
CTCs	Circulating Tumor Cells
CTCAE	Common Toxicity Criteria for Adverse Events
CTLA-4	Cytotoxic T-Lymphocyte-Associated Antigen-4
DIC	Disseminated Intravascular Coagulation
DKA	Diabetic Ketoacidosis
DNA	Deoxyribonucleic acid
DRFS	Distant Recurrence-Free Survival
ECG	Electrocardiogram
ECI	Events of Clinical Interest
ECOG	Eastern Cooperative Oncology Group
EDC	Electronic Data Capture
eCRFs	Electronic Case Report Forms
EGFR	Epidermal Growth Factor Receptor
EMT	Epithelial-to-Mesenchymal Transition
ER	Estrogen Receptor
ERC	Ethics Review Committee
EU	European Union
FAS	Full Analysis Set
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
FGFR	Fibroblast Growth Factor Receptor
FISH	Fluorescent In-Situ Hybridization
FNA	Fine Needle Aspirate
GCP	Good Clinical Practice
GFR	Glomerular Filtration Rate
GI	Gastrointestinal
HBsAg	Hepatitis B surface Antigen
HCV	Hepatitis C Virus
H&E	Hematoxylin and Eosin
HER2	Human Epidermal Growth Factor Receptor 2
HGFR	Hepatocyte Growth Factor Receptor
HIV	Human Immunodeficiency Virus
HPV	Human Papilloma Virus
HR	Hormone Receptor
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IDO1	Indoleamine 2,3-DiOxygenase 1
IgC	Immunoglobulin Constant
IHC	Immunohistochemistry
INR	International Normalized Ratio
irAEs	Immune-related Adverse Events
IRB	Institutional Review Board
ITIM	Immunoreceptor Tyrosine-based Inhibition Motif
ITSM	Immunoreceptor Tyrosine-based Switch Motif
IV	Intravenous
IVRS	Interactive Voice Response System
IWRS	Integrated Web Response System
Kg	Kilogram
KM	Kaplan-Meier
KN	KEYNOTE
mAb	Monoclonal Antibody
MAPKK	Mitogen-Activated Protein Kinase Kinase
mcL	Microliters
Mg	Milligram
Mg/kg	Milligram per Kilogram
mL	milliliter
MRI	Magnetic Resonance Imaging
mRNA	Messenger Ribonucleic Acid
MSD	Merck Sharp & Dohme Corp., a subsidiary of Merck & Co.,

Abbreviation/Term	Definition
	Inc.
NA or N/A	Not Applicable
NCI	National Cancer Institute
NGS	Next Generation Sequencing
NK	Natural Killer
NMR	Nuclear Magnetic Resonance
NSAID	Non-Steroidal Anti-inflammatory Drug
NSCLC	Non-Small Cell Lung Cancer
ORR	Objective Response Rate
OS	Overall Survival
OTC	Over-the-counter
PD	Progressive Disease
PD-1	Programmed Death Receptor-1
PD-L1	Programmed Death - Ligand 1
PD-L2	Programmed Death - Ligand 2
PFS	Progression-Free Survival
PGt	Pharmacogenetic
PI3K	PhosphoInositide-3-Kinase
PIN	Personal Identification Number
PK	Pharmacokinetic
PK-PD	Pharmacokinetic-Pharmacodynamic
PKCθ	Protein Kinase C theta
PO	Oral Administration
PR	Progesterone Receptor
PR	Partial Response
PS	Performance Status
PT	Prothrombin Time
PTEN	Phosphatase and TEnsin Homolog
Q3W	Every 3 Weeks
Q2W	Every 2 Weeks
RECIST	Response Evaluation Criteria in Solid Tumors
RNA	Ribonucleic Acid
SAE	Serious Adverse Events
SAP	Statistical Analysis Plan
SD	Stable Disease
SGOT	Serum Glutamic Oxaloacetic Transaminase
SGPT	Serum Glutamic Pyruvic Transaminase
SHP-1	Src-Homology 2 domain-containing phosphatase-1
SHP-2	Src-Homology 2 domain-containing phosphatase-2
SIM	Site Imaging Manual
SOC	Standard of Care
SOP	Standard Operating Procedures
T3	Total thriiodothyronine

Abbreviation/Term	Definition
T4	Free tyroxine
TCGA	The Cancer Genome Atlas
T1DM	Type-1 Diabetes Mellitus
TILs	Tumor-Infiltrating Lymphocytes
TPC	Treatment of Physician's Choice
Tregs	Regulatory T Cells
TSH	Thyroid Stimulating Hormone
ULN	Upper Limit of Normal
V-type	Ig Variable-type
WBC	White Blood Cell
WES	Whole Exome Sequencing
WGS	Whole Genome Sequencing
ZAP70	Zeta-chain-Associated Protein kinase 70

13.0 SIGNATURES

13.1 Sponsor's Representative

TYPED NAME	
TITLE	
SIGNATURE	
DATE SIGNED	

13.2 Investigator

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

TYPED NAME	
TITLE	
SIGNATURE	
DATE SIGNED	

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SUPPLEMENTAL STATISTICAL ANALYSIS PLAN (SSAP)

1. INTRODUCTION

This supplemental SAP (sSAP) is a companion document to the protocol. In addition to the information presented in the protocol SAP which provides the principal features of confirmatory analyses for this trial, this supplemental SAP provides additional statistical analysis details/data derivations and documents modifications or additions to the analysis plan that are not "principal" in nature and result from information that was not available at the time of protocol finalization.

2. SUMMARY OF CHANGES

Changes are based on the protocol amendment 01.

- Increased the subject number in Cohort B (1L, PD-L1+) from ~40 to ~80.
- Updated primary efficacy objectives to indicate that estimation will be utilized instead of hypothesis testing. The sections of statistical methods, multiplicity, sample size and power calculation and interim analysis were updated to align with this change.
- Updated PD-L1 blinding and other standard language.
- Removed subgroup analysis by BRAC1/2 status, specified Previous chemotherapy subgroups as 2/3 L vs. 4L+ and added subgroup of liver metastases
- Added an exploratory endpoint on the association between LDH and response to pembrolizumab as monotherapy for mTNBC and corresponding analysis
- Added biomarker analysis methods

3. ANALYTICAL AND METHODOLOGICAL DETAILS

3.1 Statistical Analysis Plan Summary

This section contains a brief summary of the statistical analyses for this trial. Full detail is in the Statistical Analysis Plan (SAP) (Sections 3.2 through 3.12).

In addition, a separate analysis plan document will be issued prior to biomarker unblinding for each of the following laboratory procedures and assessments: (1) Biomarkers (detailed in Protocol Section 7.1.3.4 and 7.1.3.5) and their association with antitumor efficacy and (2) Pharmacokinetic and pharmacodynamics evaluation (detailed in Protocol Section 7.1.3.3)

Study Design Overview	A Phase II Clinical Trial of Pembrolizumab as Monotherapy in Subjects with Metastatic Triple-Negative Breast Cancer (mTNBC)
Treatment Assignment	Treatment assignment is open label.
Analysis Populations	Efficacy: All Subjects as Treated (ASaT) Safety: All Subjects as Treated (ASaT)
Primary Endpoint(s)	Overall Response Rate (ORR)

Statistical Methods for Key Efficacy Analyses	ORR estimation
	• 2L+ population
	  ○ PD-L1 (+) population (Cohort A)
	  ○ Overall population (Cohort A)
	  ○ PD-L1 strong (+) population (Cohorts A+C)
	• 1L population (Cohort B)
	• Counts and percentages
	• 95% Agresti-Coull confidence intervals

Statistical Methods for Key Safety Analyses	Counts and percentages of AEs will be provided. Confidence intervals for rates of AEs of clinical interest will be computed using the exact binomial method.

Interim Analyses	• Futility analysis for 2L+ subjects (Cohort A) with PD-L1 (-) tumors based on no progression
	  ○ ~25 PD-L1 (-) subjects
	  ○ If no response or stable disease, continue 2L+ population (Cohort A) in PD-L1 (+) patients only
	• Evaluation of expansion to cohort C for PD-L1 strong (+) population based on ORR.
	  ○ ~10 patients evaluable through response, progression or 18-week scan, whichever comes first.
	  ○ Cohort C to start if ≥ 1 responses observed
	The final analysis of Cohorts A and C combined is to be completed when subjects are evaluable through response, progression or 18-week scan, whichever comes first.

Multiplicity	This is an estimation study. No multiplicity adjustment will be applied.
Sample Size and Power	The planned sample size is up to approximately 285 subjects. • ~160 subjects in the 2L+ overall population (Cohort A) • ~93/160 2L+ subjects (~58%) expected to be PD-L1 (+), if PD-L1 (-) is not futile at the futility analysis; ~135 2L+ subjects expected to be PD-L1 (+), if PD-L1 (-) is discontinued after the futility analysis • ~55 PD-L1 strong (+) subjects (Cohort C **and** PD-L1 strong (+) subgroup from Cohort A) • ~80 PD-L1 (+) first line subjects (Cohort B)

3.2 Responsibility for Analyses/In-House Blinding

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

This trial is being conducted as an open-label non-randomized single-arm clinical trial for each cohort, i.e., subjects, investigators, and SPONSOR personnel will be aware of subject treatment assignments after each subject is enrolled and treatment is assigned. The investigator and 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 in Cohort A. A designated Sponsor team (may include unblinded Sponsor statisticians, unblinded Sponsor statistical programmers, unblinded Sponsor clinical scientists, , unblinded clinical directors, and unblinded data management personnel) will have access to the subject-level PD-L1 results in Cohort A for the purpose of data review and will have no other responsibilities associated with the study. A summary of PD-L1 biomarker prevalence and biomarker cutoff analysis will be provided by the unblinded statistician. Biomarker cutoff analysis will inform the team about the outcome of the interim analyses and whether or not the pre-specified go/no go decision criteria are met. The estimation of tumor efficacy, e.g. ORR, DOR and DCR, etc. based on RECIST 1.1 by the central imaging vendor may be provided by another unblinded Sponsor statistician while the trial is ongoing.

The Clinical Biostatistics department will generate the allocation schedule for study treatment assignment. Allocation will be implemented in an interactive voice response system (IVRS).

3.3 Hypotheses/Estimation

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

3.4 Analysis Endpoints

The efficacy and safety endpoints that will be evaluated are listed below, followed by the descriptions of the derivations of selected endpoints.

3.4.1 Efficacy Endpoints

The primary efficacy endpoint is overall response rate (ORR), defined as the proportion of subjects in the analysis population who have complete response (CR) or partial response (PR), based on RECIST 1.1 by the central imaging vendor at any time during the study. As supportive analyses, ORR will also be evaluated by a) site investigator and local radiology review based on RECIST 1.1 and b) irRECIST by the central imaging vendor.

Secondary efficacy endpoints include:

- Duration of response (DOR), defined as the time from first documented evidence of CR or PR until disease progression or death due to any cause, whichever occurs first, for subjects who demonstrate CR or PR, based on RECIST 1.1 by the central imaging vendor.
- Disease control rate (DCR), defined as the percentage of subjects who have achieved confirmed CR or PR or have demonstrated SD for at least 24 weeks prior to any evidence of progression, based on RECIST 1.1 by the central imaging vendor.
- Progression-free survival (PFS), defined as the time from first dose of study medication to the first documented disease progression or death due to any cause, whichever comes first, based on RECIST 1.1 by the central imaging vendor.

- Overall survival (OS), defined as the time from first dose of study medication to death due to any cause.

As exploratory endpoints, DOR and DCR and PFS will also be evaluated based on a) RECIST 1.1 by study site and local radiology review and b) irRECIST by the central imaging vendor.

3.4.2 Safety Endpoints

A description of safety measures is provided in Protocol Section 4.2.3.2 Safety Endpoints and Section 7.

Safety and tolerability will be assessed by clinical review of all relevant parameters including adverse events (AEs), laboratory tests, and vital signs. Safety parameters to be analyzed include, but are not limited to, AEs, SAEs, fatal AEs, and laboratory changes. Furthermore, specific events will be collected and designated as events of clinical interest (ECIs) as described in Protocol Section 7.2.3.2.

3.4.3 Biomarker Endpoints

A separate biomarker SAP will be provided for the following endpoints/analyses.

- The association between PD-L1 protein expression by IHC and antitumor activity to pembrolizumab as monotherapy for mTNBC.
- The association between antitumor activity of pembrolizumab in mTNBC and efficacy/resistance biomarkers, utilizing tumor and blood specimens obtained before/after treatment and at disease progression.
- The performance comparison of PD-L1 assessment by IHC in newly-obtained vs. archived tumor samples.

3.4.4 Pharmacokinetic Endpoints

Pharmacokinetic parameters and the presence of anti-drug antibodies, following IV administration of 200 mg pembrolizumab Q3W as monotherapy in subjects with mTNBC (details see Protocol Section 4.2.3.4.)

3.4.5 Other Endpoints

Other endpoints include association between genetic variation and response to the treatment(s) administered, variation across the human genome for the association with clinical data (details see Protocol Sections 4.2.3.5 and 4.2.3.6.) and the association between LDH and efficacy response to pembrolizumab as monotherapy for mTNBC.

3.5 Analysis Populations

3.5.1 Efficacy Analysis Populations

The All-Subjects-as-Treated (ASaT) population, which consists of as all enrolled subjects who receive at least one dose of study medication with measurable metastatic disease at baseline, will serve as the primary population for the analyses of efficacy data in this trial.

Details on the approach to handling missing data for efficacy analyses are provided in Section 3.6 Statistical Methods.

3.5.2 Safety Analysis Populations

The All-Subjects-as-Treated (ASaT) population will be used for the analysis of safety data. 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.

3.6 Statistical Methods

3.6.1 Statistical Methods for Efficacy Analyses

Efficacy of pembrolizumab as 2L+ monotherapy for mTNBC will be evaluated primarily in PD-L1 (+) and overall population (all comers) in Cohort A, and also in subjects with PD-L1 strong (+) tumors from Cohorts A and C combined. . Cohort A will be evaluated for association between PD-L1 biomarker expression and antitumor activity.

The primary efficacy endpoints are ORR based on RECIST 1.1 by the central imaging vendor in subjects with PD-L1 (+) mTNBC of Cohorts A, overall population (all comers) of Cohort A and in subjects with PD-L1 strong (+) mTNBC. The point estimate, 95% Agresti-Coull confidence interval (as determined by the upper and lower 97.5% one-sided confidence bounds) will be provided based on normal approximation for the binomial distribution. Subjects without response data will be counted as non-responders.

Similarly, a supportive analysis to the primary method, ORR based on RECIST 1.1 by study site investigator and local radiology review will also be performed in the same fashion.

For the secondary endpoint of DCR, similar estimation methods used for ORR will be applied.

For the secondary endpoint of DOR, the definitions are the following:

For subjects who demonstrate CR or PR, duration of response is defined as the time from first documented evidence of CR or PR until disease progression or death due to any cause, whichever occurs first.

Subjects who are alive, have not progressed, have not initiated new anti-cancer treatment, and have not been determined to be lost to follow-up are considered ongoing responders at the time of analysis.

Censoring rules for DOR are summarized in Table 1.

Table 1 Censoring Rules for DOR

Situation	Date of Progression or Censoring	Outcome
No progression nor death, no new anti-cancer therapy initiated	Last adequate disease assessment	Censor (non-event)
No progression nor death, new anti-cancer therapy initiated	Last adequate disease assessment before new anti-cancer therapy initiated	Censor (non-event)
after ≥ 2 missed adequate disease assessments	Last adequate disease assessment prior to the after ≥ 2 missed adequate disease assessments	Censor (non-event)
Death or progression after ≤ 1 missed adequate disease assessments	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.		

For DOR, PFS and OS, Kaplan-Meier (KM) curves, median estimates, and survival at 6 and 12 months based on the KM curves (95% CI is based on Greenwood's formula) will be provided as appropriate. Subjects without efficacy evaluation data or without survival data will be censored at Day 1. The restricted mean survival time (RMST) for DOR will also be provided as a supportive analysis. Similar estimation methods will be applied to the efficacy analyses for the subjects with PD-L1 (+) mTNBC in Cohort B.

Table 2 summarizes the key efficacy analyses for primary and secondary endpoints in this study.

Table 2 Analysis Strategy for Primary/Secondary Efficacy Endpoints in Cohorts A and C

Endpoint/Variable (Description, Time Point)	Statistical Method	Analysis Population	Missing Data Approach
Primary:			
ORR, based on RECIST1.1 by the central imaging vendor,	95% Agresti-Coull CI	ASaT - PD-L1 (+) - overall - PD-L1 strong (+)	Subjects with missing data are considered non-responders
Secondary:			
Response duration (DOR) Based on RECIST1.1 o by the central imaging vendor o by study site investigator and local radiology review	Summary statistics using Kaplan-Meier method	All responders - PD-L1 (+) - overall - PD-L1 strong (+)	Non-responders are excluded in analysis
ORR Based on RECIST1.1 o by study site investigator and local radiology review	Agresti-Coull 95% CI	ASaT - PD-L1 (+) - overall - PD-L1 strong (+)	Subjects with missing data are considered non-responders
DCR Based on RECIST1.1 o by the central imaging vendor o by study site investigator and local radiology review	Agresti-Coull 95% CI	ASaT - PD-L1 (+) - overall - PD-L1 strong (+)	Subjects with missing data are considered non-responders
Progression-free survival (PFS) Based on RECIST1.1 o by the central imaging vendor o by study site investigator and local radiology review	Summary statistics using Kaplan-Meier method	ASaT - PD-L1 (+) - overall - PD-L1 strong (+)	Censored at last assessment
Overall survival (OS)	Summary statistics using Kaplan-Meier method	ASaT - PD-L1 (+) - overall - PD-L1 strong (+)	Censored at last assessment
95% confidence interval is determined by the upper and lower 97.5% one-sided confidence bounds.			

Similar efficacy methods will be applied to Cohort B for subjects with PD-L1 (+) tumors receiving pembrolizumab as 1L monotherapy for mTNBC.

3.6.2 Statistical Methods for Safety Analyses

Safety and tolerability will be assessed by clinical review of all relevant parameters including adverse experiences (AEs), laboratory tests, and vital signs by PD-L1 status within cohort and total (combining across Cohorts A-C). Summary statistics (counts, percentage, mean, standard deviation, etc.) will be provided for the safety endpoints as appropriate. The

confidence interval for the incidence rate of Grade 2 or higher adverse events with an immune etiology and the incidence rate of Grade 4/5 AEs will be provided as appropriate.

3.6.3 Summaries of Baseline Characteristics, Demographics, and Other Analyses

Demographic and Baseline Characteristics

Baseline characteristics will be assessed by the use of tables and/or graphs for each cohort. No statistical hypothesis tests will be performed on these characteristics. The number and percentage of subjects screened, treated, primary reasons for screening failure, and discontinuation will be displayed. Demographic variables (e.g., age, region), baseline characteristics, primary and secondary diagnoses, and prior and concomitant therapies will be summarized by cohort either by descriptive statistics or categorical tables.

Biomarker Analyses

The evaluation of a general positive association between CPS and ORR will be investigated via standard logistic regression as well as generalized additive models. The potential to achieve a cut-off greater than CPS = 1% for defining a PD-L1 strongly positive population will involve a review of how the positive predictive value (PPV, response rate in those above a cut-off), negative predictive value (NPV, response rate in those below the cut-off), and fraction of patients defined as strongly positive change as a function of increasing cut-offs and whether there is evidence for a relative improvement in clinical utility relative to the 1% CPS cut-off. A PD-L1 strongly positive cut-off that maintains high NPV (e.g. near or above 90%) while achieving meaningful enrichment of response and largely capturing patients showing durable clinical benefit is sought. The profiles of PPV, NPV, and the percentage of patients above a given cut-off along with intervals quantifying the uncertainty in those profiles will be estimated as a function of potential cut-offs. Receiver operating characteristic curve analysis will also be used to understand the sensitivity and specificity profile and examine cut-offs that might be suggested based on the ROC curve and their appropriateness with regard to PPV and NPV. CPS ranges for any promising cut-offs will also have to be gauged in the context of practical implementation and interpretation by pathologists in clinical practice.

Exploratory Analyses

The association between LDH and efficacy response to pembrolizumab as monotherapy for mTNBC may be explored.

3.7 Interim Analyses

There are two interim analyses planned in this study. For Cohort A in Part 1, a futility analysis will be performed for subjects with PD-L1 (-) tumors and an interim analysis for potential efficacy expansion will be performed for subjects with PD-L1 strong (+) tumors in this cohort.

The PD-L1 strong (+) population (10 or more subjects depending on the prevalence of PD-L1 strong (+) tumors in the 2L+ population from Cohort A) may be expanded by continuing enrollment of subjects with PD-L1 strong (+) tumors into Cohort C, if at least one responder is observed in this subpopulation from Cohort A. The combined sample size of up to ~55

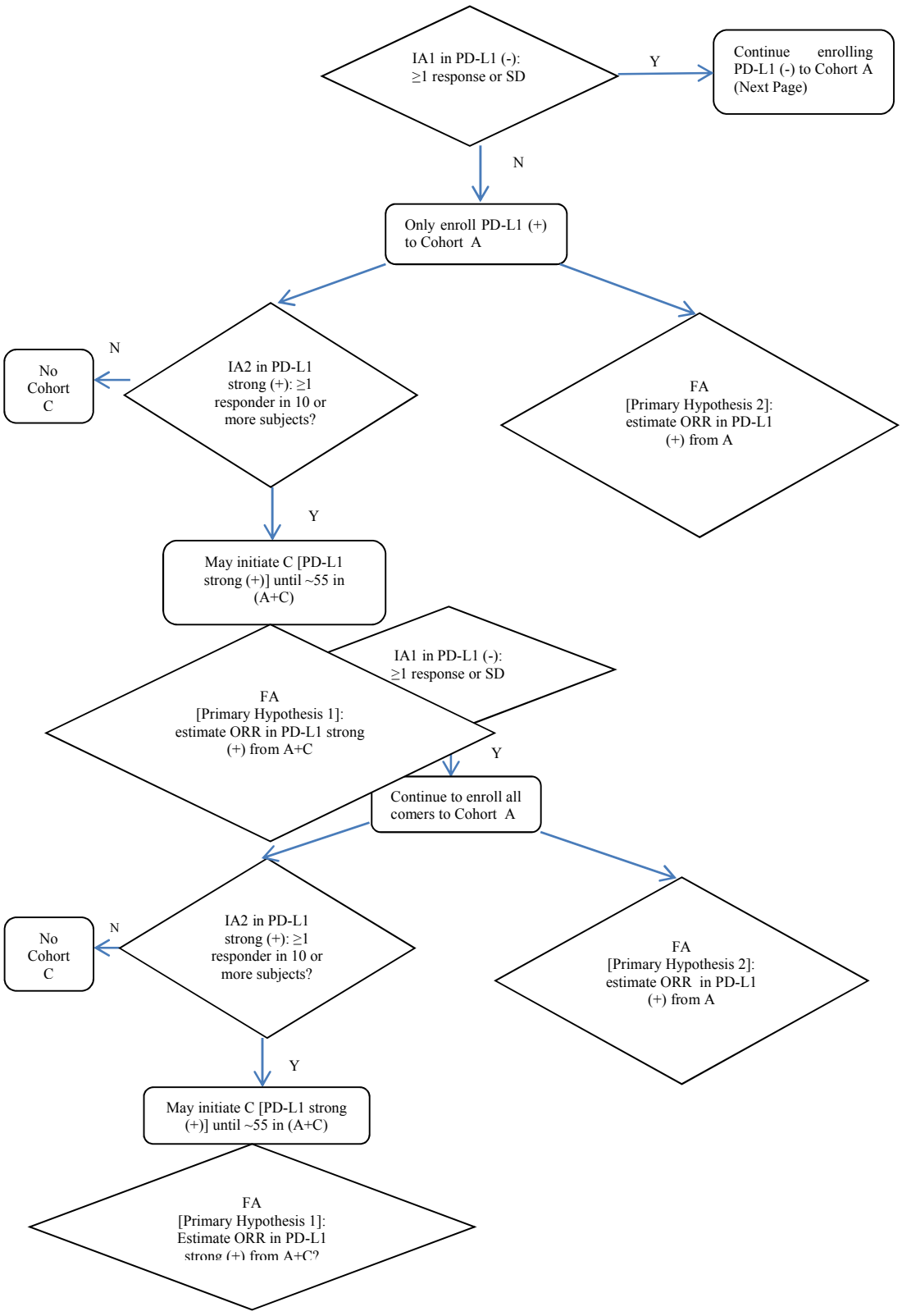
subjects with PD-L1 strong (+) tumors from Cohorts A and C is driven by the primary efficacy hypothesis for subjects with PD-L1 strong (+) tumors (with futility bound accounted for the IA in this subpopulation).

The detailed process is described as below:

1. Enrollment will begin independent of PD-L1 tumor status.
2. A futility analysis will start when the first ~25 subjects with PD-L1 (-) tumors are evaluable through response, progression or 18-week tumor imaging, whichever comes first. The purpose of this interim analysis is to check treatment futility for subjects with PD-L1 (-) tumors.
3. If the futility boundary is not crossed, that is at least one subject with response or stable disease is observed in subjects with PD-L1 (-) tumors, the trial enrollment will continue as planned. If the futility boundary is crossed for subjects with PD-L1 (-) tumors, then such subjects may be excluded from further enrollment in the trial. That is, the trial will continue to only enroll subjects with PD-L1 (+) tumors until there are 160 subjects in total.
4. An efficacy futility interim will also be performed for the PD-L1 strong (+) subpopulation of Cohort A, and enrollment of Cohort C for PD-L1 strong (+) may be initiated if one or more responders are observed in at least 10 subjects from Cohort A.

Figure 1 illustrates the study diagram for decision making (a study decision tree).

Figure 1 Decision Tree



Interim Analysis for Futility (IA1)

An interim futility check will be performed for the PD-L1 (-) population in Cohort A. Enrollment of PD-L1 (-) population will be stopped, if futility bound is reached. At least one subject without disease progression among the 25 subjects is needed for the further enrollment of subjects with PD-L1 (-) tumors. Table 3 lists the probability of stopping for futility at different true response rate in PD-L1 (-) based on different stopping rules.

Table 3 Probability of Futility under Different True Response Rate[§] in PD-L1 (-)

Response Rate[§] in PD-L1 (-)	**Probability of Futility in PD-L1 (-)**	
	Rule of ≥ 1 Responder or SD	**Rule of ≥ 2 Responders or SD**
1%	77.8%	97.4%
2%	60.3%	91.1%
5%	27.7%	64.2%
8%	12.4%	39.4%
10%	7.2%	27.1%

[§]Response rate: the proportion of responders (CR and PR) or subjects with stable disease.

Interim Analysis to Initiate Cohort C Expansion (IA 2)

IA2 (Cohort A) will be performed when at least 10 subjects with PD-L1 strong (+) tumors are evaluable through response, progression or 18-week scan, whichever comes first. One or more responses need to be observed in order to expand enrollment to additional subjects with PD-L1 strong (+) tumors (up to ~55 subjects in Cohorts A and C combined). Table 4 shows the probability to initiate Cohort C under different true ORR in PD-L1 strong (+) subpopulation in Cohort A based on the rule of one or more responders.

Table 4 Probability to Initiate Cohort C under Different True ORR in PD-L1 Strong (+)

ORR in PD-L1 Strong (+)	Probability to Initiate Cohort C
10%	65.1%
15%	80.3%
18%	86.3%
20%	89.3%
25%	94.4%
30%	97.2%

3.8 Multiplicity

This is an estimation study. The estimation of ORR and associated 95% confidence intervals of ORR will be provided. No multiplicity adjustment will be applied in ubjects with PD-L1 (+) mTNBC of Cohorts A, overall population (all comers) of Cohort A and in subjects with PD-L1 strong (+) mTNBC.

There are also no hypotheses for other parameters of DOR, DCR, PFS, and OS or for Cohort B.

3.9 Sample Size and Power Calculations

The trial has a planned sample size of up to approximately N=285 subjects

- N = ~160: 2L+ overall population (all comers; Cohort A)
  - Would expect N=93 PD-L1 (+) subjects based on 58% prevalence
  - Would expect N=135 PD-L1 (+) subjects if PD-L1 (-) patients are discontinued at interim analysis
- N = ~45: expansion for the 2L+ PD-L1 strong (+) population (Cohort C)
  - N ~ 55 expected for total PD-L1 strong (+) population (Cohort A subgroup + Cohort C)
- N = ~80: 1L PD-L1 (+) subjects (Cohort B)

The study is for estimation.

Table 5 Summary of Sample Size Calculation

Line of Therapy	Population	Cohort	N	Number of Observed Responders	ORR Estimates	95% A-C CI of ORR (%)
2L+	Overall population	A	160	24	15.0%	(10.2,21.4)
	PD-L1 (+)	A	93	16	17.2%	(10.8, 26.2)
	PD-L1 (+)	A	135	21	15.6%	(10.3, 22.7)
	PD-L1 strong (+)	A+ C	55	11	20.0%	(11.4,32.5)
1L	PD-L1 (+)	B	80	24	30.0%	(21.0,40.8)

Details underlying the above summary calculations follow below.

ORR in the PD-L1 (+) and overall population in Cohort A

It is expected that ~160 subjects in Cohort A will be enrolled for investigating the association between PD-L1 protein expression by IHC and antitumor activity of pembrolizumab as monotherapy for mTNBC (Details in Biomarker Analysis SAP).

Similarly for the ORR in the PD-L1 (+) in Cohort A, if PD-L1 (-) is not futile at the futility analysis it is expected that ~93 subjects out of the ~160 enrolled subjects (~58% prevalence based on previous study) in Cohort A will have PD-L1 (+) expression. With ~93 subjects, if there are at least 16 responders observed, the lower bound of the 95% CI for ORR will be above 10%.

If PD-L1 (-) is futile, there will be with ~135 subjects in Cohort A [excluding 25 PD-L1 (-) in the futility analysis]. If there are at least 21 responders observed, the lower bound of the 95% CI for ORR will be above 10%.

Similarly for the ORR in the overall population in Cohort A, if PD-L1 (-) is not futile, there will be ~160 subjects. If there are at least 24 responders observed, the lower bound of the 95% CI for ORR will be above 10%.

Table 6 shows the two-sided 95% A-C CI of ORR with different sample size for different observed response rates.

Table 6 Two-sided 95% A-C CI of ORR with Different Sample Size

Sample Size (N)	Number of Observed Responders	ORR Estimates	95% A-C CI of ORR (%)
93	10	10.8%	(5.8,18.9)
	14	15.1%	(9.1,23.8)
	16	**17.2%**	**(10.8, 26.2)**
	19	20.4%	(13.4,29.8)
110	11	10.0%	(5.5,17.2)
	17	15.5%	(9.8,23.5)
	18	16.4%	(10.5, 24.5)
	22	20.0%	(13.5,28.5)
135	14	10.4%	(6.2,16.8)
	21	**15.6%**	**(10.3,22.7)**
	27	20.0%	(14.1,27.6)
160	16	10.0%	(6.2,15.7)
	24	**15.0%**	**(10.2,21.4)**
	32	20.0%	(14.5,26.9)
170	17	10.0%	(6.3,15.5)
	26	15.3%	(10.6,21.5)
	34	20.0%	(14.6,26.7)
180	18	10.0%	(6.3,15.3)
	27	15.0%	(10.5,21.0)
	36	20.0%	(14.8,26.5)

ORR in PD-L1 strong (+) in Cohorts A + C

There will be ~55 subjects with PD-L1 strong (+) tumors enrolled in Cohort A and Cohort C.

Table 7 shows the two-sided 95% A-C CI of ORR with 55 evaluable subjects for different observed response rates. With 55 subjects with PD-L1 strong (+) tumors, if there are at least 11 responders observed, the lower bound of the 95% A-C CI for ORR will be above 10%.

Table 7 Two-sided 95% A-C CI of ORR with 55 Evaluable Subjects

Number of Observed Responders	ORR Estimates	95% A-C CI of ORR (%)
6	10.9%	(4.7,22.2)
8	14.5%	(7.3,26.4)
9	16.4%	(8.6,28.5)
10	18.2%	(10.0,30.5)
11	**20.0%**	**(11.4,32.5)**
13	23.6%	(14.2,36.5)
14	25.5%	(15.7,38.4)

Table 8 shows the Two-sided exact 95% CI of AE Rate with 55 subjects.

Table 8 Two-sided 95% Exact CI of AE Incidence Rate with 55 Evaluable Subjects

Number of AE	AE Incidence Rate Estimates	95% CI of Incidence Rate (%)
6	10.9%	(4.1,22.2)
11	20.0%	(10.4,33.0)
17	30.9%	(19.1,44.8)
22	40.0%	(27.0,54.1)
28	50.9%	(37.1,64.6)

ORR in PD-L1 (+) Cohort B

There will be ~80 subjects with PD-L1 (+) tumors enrolled in Cohort B.

Table 9 shows the two-sided 95% CI of ORR with 80 or 100 subjects for different observed response rates.

Table 9 Two-sided 95% A-C CI of ORR with 80 or 100 Subjects

Sample Size (N)	Number of Observed Responders	ORR Estimates	95% CI of ORR (%)
80	12	15%	(8.6,24.6)
	16	20%	(12.6,30.1)
	20	25%	(16.7,35.6)
	24	**30%**	**(21.0,40.8)**
	28	35%	(25.4,45.9)
	32	40%	(30.0,51.0)
	36	45%	(34.6,55.9)
100	15	15%	(9.2,23.4)
	20	20%	(13.3,29.0)
	25	25%	(17.5,34.4)
	30	30%	(21.9,39.6)
	35	35%	(26.3,44.8)
	40	40%	(30.9,49.8)
	45	45%	(35.6,54.8)

Table 10 shows the Two-sided exact 95% CI of AE Rate with 80 subjects.

Table 10 Two-sided 95% Exact CI of AE Incidence Rate with 80 Evaluable Subjects

Number of AE	AE Incidence Rate Estimates	95% CI of Incidence Rate (%)
8	10.0%	(4.4,18.8)
16	20.0%	(11.9,30.4)
24	30.0%	(20.3,41.3)
32	40.0%	(29.2,51.6)
40	50.0%	(38.6,61.4)

3.10 Subgroup Analyses and Effect of Baseline Factors

Subgroup analyses are planned for the efficacy analyses in the classification variables:

- Age category (≤50 vs. >50 years)
- Menopausal status
- PD-L1 IHC expression(PD-L1 strong (+), PD-L1 (+), PD-L1 (-) and overall)
- Previous Chemotherapy (2/3 L vs. 4L+)
- Liver metastases (Presence vs. Absence)

3.11 Compliance (Medication Adherence)

A day within the study will be considered an On-Therapy day, if the subject receives the study medication infusion. The number of Days on Therapy is the total number of days from the first day of study medication to the date of the last dose of study medication.

Summary statistics for the number of Days on Therapy will be provided by treatment group for the FAS population.

3.12 Extent of Exposure

Extent of Exposure for a subject is defined as number of cycles in which the subject receives the study medication infusion. Summary statistics will be provided on Extent of Exposure for ASaT population.