

Official Protocol Title:	A Phase II Study of Pembrolizumab (MK-3475) as Monotherapy in Subjects with Previously Treated Locally Advanced Unresectable or Metastatic (Stage IV) Mismatched Repair Deficient or Microsatellite Instability-High Colorectal Carcinoma (KEYNOTE-164)
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TITLE:

A Phase II Study of Pembrolizumab (MK-3475) as Monotherapy in Subjects with Previously Treated Locally Advanced Unresectable or Metastatic (Stage IV) Mismatched Repair Deficient or Microsatellite Instability-High Colorectal Carcinoma (KEYNOTE-164)

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DOCUMENT HISTORY

Document	Date of Issue	Overall Rationale
Amendment 08	13-NOV-2019	To allow participants access to an extension study.
Amendment 07	03-JAN-2018	Alignment of dose modification language with the most current label and safety information for pembrolizumab.
Amendment 06	13-OCT-2017	Following FDA approval of pembrolizumab in MMR deficient or MSI-H mCRC, addition of 3 cohorts to continue to study safety and efficacy of immunotherapies for the MSI-H mCRC population. The study will now add pembrolizumab in combination with anti- Lymphocyte-activation gene 3 (LAG-3), MK-4280.
Amendment 05/ France-specific amendment	06-MAR-2017	Alignment with France-specific template requirements
Amendment 04	04-JAN-2017	To allow additional follow-up analysis to be performed that would provide improved data maturity and to change the timing of Cohort A interim analysis due to rapid enrolled.

Document	Date of Issue	Overall Rationale
Amendment 03	24-MAR-2016	Addition of a second cohort (Cohort B) of 60 subjects to evaluate pembrolizumab 200 mg Q3W in subjects with colorectal cancer (CRC) who have undergone 1 line of systemic treatment (fluoropyrimidine + oxaliplatin or fluoropyrimidine + irinotecan +/- anti-VEGF/EGFR monoclonal antibody). The first cohort will be designated Cohort A.
Amendment 02	19-OCT-2015	To further clarify prior treatments a subject should have received in order to be eligible for participation in the study.
Amendment 01	08-JUL-2015	To reflect routine clinical practice and allow enrollment flexibility when defining previous treatments.
Original Protocol	21-MAY-2015	Not Applicable

SUMMARY OF CHANGES

PRIMARY REASON(S) FOR THIS AMENDMENT:

Section Number (s)	Section Title(s)	Description of Change (s)	Rationale
1.0 2.2 5.10	Trial Summary: Duration of participation Trial Diagram Beginning and End of the Trial	Addition of text to allow enrollment in an extension study to continue protocol-defined assessments and treatment.	To allow participants access to an extension study.

ADDITIONAL CHANGE(S) FOR THIS AMENDMENT:

Section Number (s)	Section Title (s)	Description of Change (s)	Rationale
1.0 2.1 5.8	Trial Summary: Duration of participation Trial Design Subject Withdrawal/Discontinuation Criteria	Replace <i>withdraw</i> in the discontinuation criteria "investigator's decision to <i>withdraw</i> the subject" with <i>discontinue</i> .	Alignment with program standards

Section Number (s)	Section Title (s)	Description of Change (s)	Rationale
Throughout	Multiple Sections	<p>Changed timing of imaging schedule from Q9W to “The first on-study imaging will be performed at 9 weeks (63 days \pm 7 days) from date of allocation. Subsequent imaging will be performed every 9 weeks (Q9W; 63 days \pm 7 days) for the first 12 months, then every 12 weeks (Q12W; 84 days, \pm 7 days) thereafter, or more frequently if clinically indicated.</p> <p>Changed timing of post-treatment follow-up and survival follow-up visits from every 9 weeks to every 12 weeks.</p>	Reduce subject burden and alignment with extension study
5.5.2	Prohibited Concomitant Medications	Bullet for Systemic glucocorticoids revised	Clarity and to alignment with program standards - AEs with immunological etiology are no longer routinely collected as ECIs

Section Number (s)	Section Title (s)	Description of Change (s)	Rationale
5.8	Subject Withdrawal/Discontinuation Criteria	Deletion of: noncompliance with trial treatment or procedure requirements.	Alignment with program standards
7.1.6.3.1	Safety Follow-up	Deletion of text defining the time windows for collection of AEs/SAEs information.	The deleted text introduces a conflict in the reporting of AEs/SAEs for pembrolizumab requested by Merck Global Safety.
7.2.3.2	Events of Clinical Interest	Deletion of timings for collection of ECI. Deletion of reference to irAE	Remove repetition and alignment with program standards - AEs with immunological etiology are no longer routinely collected as ECIs
Throughout	N/A	Minor editorial changes	Correction of typographical/formatting errors and consistency.

1.0 TRIAL SUMMARY

Abbreviated Title	A Phase II Study of Pembrolizumab in Previously Treated Subjects with Mismatched Repair Deficient or Microsatellite Instability-High Colorectal Carcinoma
Trial Phase	Phase II
Clinical Indication	Locally Advanced Unresectable or Metastatic (Stage IV) Mismatched Repair Deficient or Microsatellite Instability - High Colorectal Carcinoma
Trial Type	Interventional
Type of control	No treatment control
Route of administration	Intravenous (IV)
Trial Blinding	Unblinded Open-label
Treatment Groups	Pembrolizumab (MK-3475) 200 mg IV every 3 weeks (Q3W)
Number of trial subjects	Approximately 120 subjects will be enrolled.
Estimated duration of trial	The Sponsor estimates that the trial will require approximately 24 months from the time the first subject signs the informed consent until the last subject's last study-related phone call or visit.
Duration of Participation	<p>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 of up to 28 days, eligible subjects will receive pembrolizumab beginning on Day 1 of each 3-week dosing cycle.</p> <p>Treatment with pembrolizumab will continue until progressive disease (PD), unacceptable adverse events (AEs), intercurrent illness that prevents further administration of treatment, investigator's decision to discontinue the subject, subject withdraws consent, pregnancy of the subject, noncompliance with trial treatment or procedure requirements, subject receives 35 treatments (approximately 2 years) of pembrolizumab, or administrative reasons requiring cessation of treatment. Subjects who stop pembrolizumab as a result of obtaining a confirmed complete response (CR) or those subjects who stop after receiving 35 trial treatments may be eligible, at the discretion of the investigator, for an additional 17 trial treatments (approximately 1 year) after experiencing PD if they meet the criteria for re-treatment; this will be designated as the Second Course Treatment Phase. Subjects who discontinue for reasons other than PD will have post-treatment follow-up for disease status until PD, initiating a non-study cancer treatment, withdrawing consent, or becoming lost to follow-up. All subjects will be followed for overall survival (OS) until death, withdrawal of consent, or the end of the study.</p> <p>After the end of treatment, each subject will be followed for 30 days for AE monitoring. Serious adverse events (SAE) and events of clinical interest (ECI) will be collected for 90 days after the end of treatment or for 30 days after the end of treatment if the subject initiates new anticancer therapy, whichever is earlier.</p> <p>Once the participant has achieved the study objective or the study has ended, the participant is discontinued from this study and may be enrolled in an extension study to continue protocol-defined assessments and treatment.</p>

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

2.0 TRIAL DESIGN

2.1 Trial Design

This is a single arm, multi-cohort, open-label, multi-site trial of pembrolizumab in previously treated subjects who have locally advanced unresectable or metastatic (Stage IV) Mismatched Repair (MMR) Deficient or Microsatellite- Instability (MSI) high colorectal carcinoma (CRC). MSI, a form of genomic instability, occurs through the insertion or deletion of repeating nucleotides during DNA replication and failure of the mismatch repair system to correct errors in nucleotide repeat markers (Refer to section 4.2.3.3 for further details). Subjects will be required to have at least one measurable lesion by Response Evaluation Criteria in Solid Tumors (RECIST 1.1) for response assessment and had to have been previously treated with standard therapies, which must include fluoropyrimidine, oxaliplatin, and irinotecan (for Cohort A), and at least one line of systemic standard of care therapy: fluoropyrimidine + oxaliplatin or fluoropyrimidine + irinotecan +/- anti-vascular endothelial growth factor (VEGF)/ epidermal growth factor regulator (EGFR) monoclonal antibody (for Cohort B). Subjects who have withdrawn from standard treatment due to unacceptable toxicity warranting discontinuation of that treatment and precluding retreatment with the same agent before progression of disease will also be eligible. Regimens given with adjuvant intent will be counted as treatment for metastatic disease if the patient's disease had progressed within 6 months following treatment. Tumor tissue samples, while optional in Cohort A, will be obtained from all subjects enrolled into Cohort B. Blood will be collected for biomarker studies; plasma for circulating tumor DNA will be collected for Cohort B only. The enrollment of subjects and the data analysis will be performed separately for each Cohort.

Approximately 60 subjects will be enrolled in Cohort A and approximately 60 subjects will be enrolled in Cohort B to receive single agent pembrolizumab 200 mg IV Q3W.

The primary objective of this trial is to determine the objective response rate (ORR) of pembrolizumab given as monotherapy. Beginning with screening, all imaging assessments will be submitted for central imaging vendor review and will be evaluated using RECIST 1.1 for determining eligibility and assessment of response. The first on-study imaging will be performed at 9 weeks (63 days \pm 7 days) from date of allocation. Subsequent imaging will be performed every 9 weeks (Q9W; 63 days \pm 7 days) for the first 12 months, then every 12 weeks (Q12W; 84 days, \pm 7 days) thereafter, or more frequently if clinically indicated. RECIST 1.1 will be used by the site for treatment decisions until first radiologic evidence of PD. Following the first evidence of radiologic PD, treatment decisions may be made by the adaption of RECIST 1.1 as described in Section 7.1.4.1.5.1 termed immune-related RECIST (irRECIST) to accommodate for the tumor response patterns seen with pembrolizumab treatment (e.g., tumor flare). For a clinically stable subject with first radiologic evidence of PD it is at the discretion of the site investigator to continue treating the subject with pembrolizumab until PD is confirmed at least 4 weeks from the date of the first tumor imaging suggesting PD. If radiologic PD is confirmed by the subsequent tumor imaging the

subject should be discontinued from treatment unless, in the opinion of the investigator, the subject is achieving a clinically meaningful benefit; an exception to continue treatment may be considered following consultation with the Sponsor.

Subjects will continue to be treated with pembrolizumab until PD, unacceptable AEs, intercurrent illness that prevents further administration of treatment, investigator's decision to discontinue the subject, subject withdraws consent, pregnancy of the subject, noncompliance with trial treatment or procedure requirements, administrative reasons, or the subject has received 35 trial treatments (approx. 2 years) with pembrolizumab. Subjects who discontinue treatment for reasons other than PD will have post-treatment follow-up visits for disease status until PD, initiating a non-study cancer treatment, withdrawing consent, or becoming lost to follow-up. All subjects will be followed for OS until death, withdrawal of consent or the end of the study, whichever comes first.

Subjects who attain confirmed CR (assessed by the site) by 2 tumor imaging assessments at least 4 weeks apart and who have received at least 8 treatments (approximately 6 months) with pembrolizumab may discontinue treatment at the discretion of the investigator after receiving at least 2 treatments beyond the initial determination of a CR. Subjects who stop pembrolizumab after receiving 35 trial treatments for reasons other than PD or intolerability or who stopped after attaining a CR may be eligible for retreatment with up to an additional 17 treatments (approx. 1 year) after they have experienced radiographic PD. The decision to retreat will be at the discretion of the investigator only if no other cancer treatment was administered since the last dose of pembrolizumab, the subject still meets the parameters listed in the retreatment criteria (Section 7.1.6.2.1), and the trial remains open.

Adverse events will be monitored throughout the trial and graded in severity according to the guidelines outlined in the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 (Section 12.6). After the end of treatment, each subject will be followed for 30 days for AE monitoring. SAEs and ECIs 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.

There is one interim analysis planned in this study for Cohort A and no interim analyses planned for Cohort B. See Section 8.7 for details about the timing and purpose of the interim analysis. Enrollment will not be paused when interim analysis is conducted. Results will be reviewed by study team.

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 is depicted in [Figure 1](#) below.

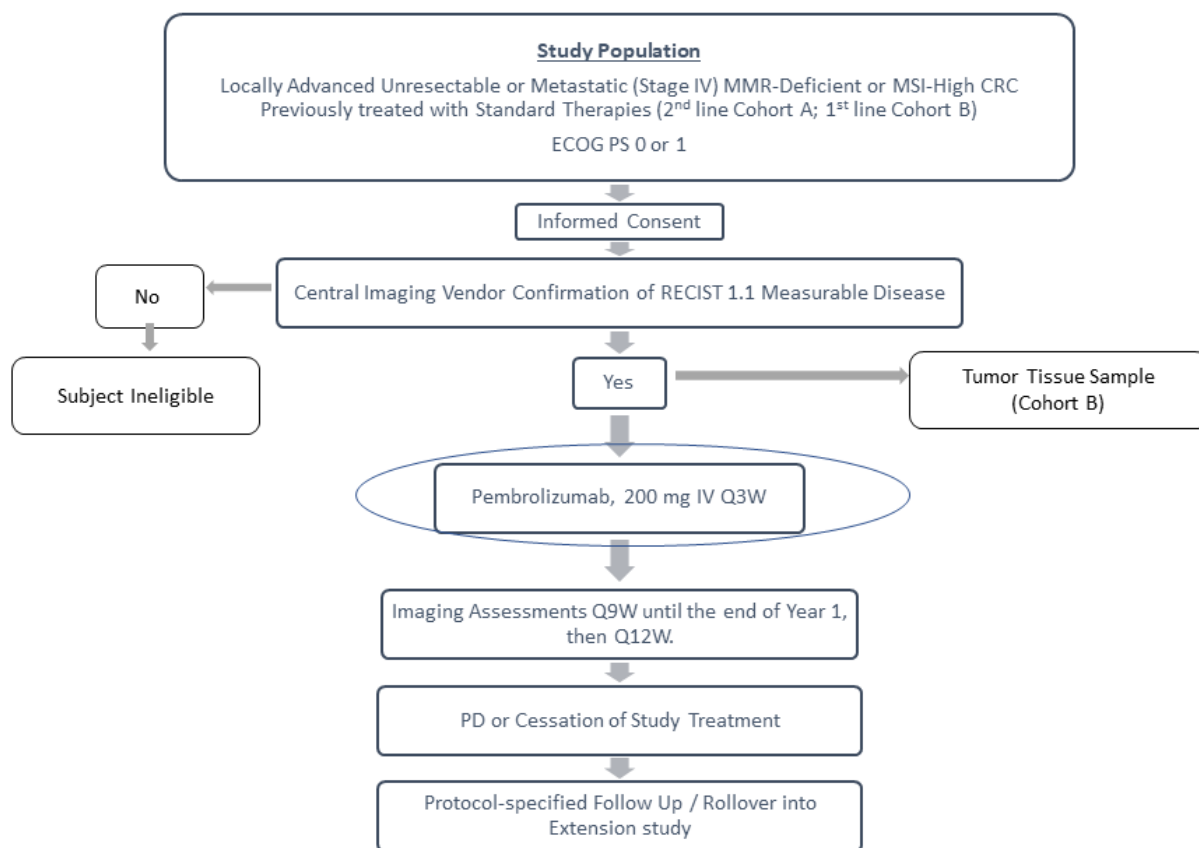


Figure 1 Trial Diagram

3.0 OBJECTIVE(S) & HYPOTHESIS(ES)

3.1 Primary Objective(s) & Hypothesis(es)

(1) **Objective (Cohort A):** To evaluate the ORR per RECIST 1.1 assessed by central imaging vendor of the 200 mg Q3W dose of pembrolizumab in subjects with locally advanced unresectable or metastatic MMR deficient or MSI high CRC and who have been previously treated with standard of care therapies, which must include fluoropyrimidine, oxaliplatin, and irinotecan.

Hypotheses: The ORR based on RECIST 1.1 assessed by central imaging vendor in subjects with locally advanced unresectable or metastatic MMR deficient or MSI high CRC is greater than 15%.

(2) **Objective (Cohort B):** To estimate the ORR per RECIST 1.1 assessed by central imaging vendor of the 200 mg Q3W dose of pembrolizumab in subjects with locally advanced unresectable or metastatic MMR deficient or MSI high CRC and who have been previously treated with at least one line of systemic standard of care therapy

(fluoropyrimidine + oxaliplatin or fluoropyrimidine + irinotecan +/- anti-VEGF/EGFR monoclonal antibody).

3.2 Secondary Objective(s) & Hypothesis(es)

In both Cohort A and Cohort B separately:

- (1) **Objective:** To determine safety and tolerability of pembrolizumab.
- (2) **Objective:** To evaluate Duration of Response (DOR), Disease Control Rate (DCR) and Progression-free Survival (PFS) per RECIST 1.1 assessed by central imaging vendor and Overall Survival (OS).

3.3 Other Tertiary and Exploratory Objectives

For Cohorts A and B separately:

- (1) **Objective:** To evaluate ORR, DOR, DCR and PFS per RECIST 1.1 assessed by investigator.
- (2) **Objective:** To evaluate ORR, DOR, DCR and PFS per irRECIST 1.1 assessed by central imaging vendor.
- (3) **Objective:** To identify molecular (genomic, metabolic, and/or proteomic) biomarkers that may be indicative of clinical response/resistance, safety, pharmacodynamic activity, and/or the mechanism of action of pembrolizumab.

4.0 BACKGROUND & RATIONALE

4.1 Background

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

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

4.1.1 Pharmaceutical and Therapeutic Background

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 favorable prognosis in various malignancies [2] [3] [4] [5] [6]. In particular, the presence of CD8⁺ T-cells and the ratio of CD8⁺ effector T-cells / FoxP3⁺ regulatory T-cells seems to correlate with improved prognosis and long-term survival in many solid malignancies, such as ovarian, colorectal, and pancreatic cancer; hepatocellular carcinoma; malignant melanoma; and renal cell carcinoma. Tumor-infiltrating lymphocytes can be expanded ex vivo and reinfused, inducing durable objective tumor responses in cancers such as melanoma [7] [8].

The PD-1 receptor-ligand interaction is a major pathway hijacked by tumors to suppress immune control. 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 Ig superfamily member related to cluster of differentiation 28 (CD28) and cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) that has been shown to negatively regulate antigen receptor signaling upon engagement of its ligands (PD-L1 and/or PD L2) [9] [10].

The structure of murine PD-1 has been resolved [11]. PD-1 and family members are type I transmembrane glycoproteins containing an Ig variable-type (IgV-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 and an immunoreceptor tyrosine-based switch motif. Following T-cell stimulation, PD 1 recruits the tyrosine phosphatases SHP-1 and SHP-2 to the immunoreceptor tyrosine-based switch motif within its cytoplasmic tail, leading to the dephosphorylation of effector molecules such as CD3 zeta (CD3 ζ), protein kinase C-theta (PKC θ) and zeta-chain associated protein kinase (ZAP70), which are involved in the CD3 T-cell signaling cascade [9] [12] [13] [14]. The mechanism by which PD-1 down modulates T-cell responses is similar to, but distinct from that of CTLA-4, because both molecules regulate an overlapping set of signaling proteins [15] [16].

Because of higher mutational load (and thus potentially more neo-antigens) than MSS tumors, MSI high colorectal tumors have vigorous immune microenvironment. Although there have been inconsistent observations about the expression of PD-L1 in MSI high colorectal cancer [17] [18]. MSI high colorectal cancer has been considered as a good candidate for immune checkpoint inhibitors including anti PD-1/ PD-L1 antibodies [18] [19].

4.1.2 Pre-clinical and Clinical Trials

4.1.2.1 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 leads ultimately to tumor rejection, either as a mono-therapy or in combination with other

treatment modalities. Anti-mouse PD-1 or anti-mouse PD-L1 antibodies have demonstrated anti-tumor responses as a mono-therapy in models of squamous cell carcinoma, pancreatic carcinoma, MEL and colorectal carcinoma. Blockade of the PD-1 pathway effectively promoted CD8+ T-cell infiltration into the tumor and the presence of IFN- γ , granzyme B and perforin, indicating that the mechanism of action involved local infiltration and activation of effector T-cell function in vivo [7] [8] [20] [21] [22] [23]. Experiments have confirmed the in vivo efficacy of PD-1 blockade as a mono-therapy as well as in combination with chemotherapy in syngeneic mouse tumor models (see the Investigator's Brochure [IB]).

4.1.2.2 Ongoing Clinical Trials

Clinical trials have demonstrated pembrolizumab monotherapy efficacy in subjects with many different indications including advanced melanoma, non-small cell lung cancer (NSCLC), head and neck cancer, bladder cancer, Hodgkin's lymphoma, triple-negative breast cancer, gastric adenocarcinoma, and MSI-H cancers.

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

4.2 Rationale

4.2.1 Rationale for the Trial and Selected Subject Population

Colorectal cancer is a heterogeneous disease arising through different pathways including the chromosomal instability (CIN) pathway, the MSI pathway, and CpG island methylator phenotype (CIMP) [24]. MSI CRC comprises approximately 15% of sporadic CRC and 5% of Stage IV CRC, whereas microsatellite stable (MSS) CRC comprises the remainder [19] [25]. MSI status plays a role as a predictive factor of chemosensitivity [26] and MSI status test is recommended in both National Comprehensive Cancer Network (NCCN) and European Society for Medical Oncology (ESMO) guidelines [27] [28]. The lack of efficacy with standard 5-fluorouracil (5-FU) based adjuvant chemotherapies in MSI high CRC have been reported [26] [29]. In stage III MSI high CRC, irinotecan-containing regimen demonstrated improved outcomes compared to 5-FU/leucovorin alone [30]. However, the prognosis of MSI high Stage IV patients was worse than MSS patients with the irinotecan-containing regimens [31].

In early stage CRC, favorable prognosis with MSI high patients has been reported [26] [29]. The survival benefit of MSI high CRC has been explained with prognostic effect of tumor-infiltrating T-cell subsets (CD3+, CD8+, CD45RO+ and FOXP3+) [32]. The strong association between MSI status and CD45RO+-cell density supports stimulated host immune response in MSI high CRC, which may offer one explanation for favorable prognosis and attenuated response to cytotoxic chemotherapy [32].

A recent study reported that once there is a recurrence the prognostic advantage is lost as the median OS after recurrence in stage II disease is 1.6 versus 2.2 years (MSI high vs MSS,

respectively; hazard ratio (HR) 1.00, 95% confidence interval (CI), 0.68-1.48; $p > 0.99$), and after Stage III disease is 1.2 versus 1.6 years (MSI high vs. MSS, respectively; HR 1.00, 95% CI, 0.85-1.17; $p > 0.99$) [33]. The same group reported that there is actually a disadvantage in having deficient mismatch repair (dMMR) status. Five percent of the primary tumors of 3063 patients, pooled from four phase III first-line studies in metastatic CRC (mCRC), were found to be dMMR. The median PFS and OS were significantly worse for patients with MSI high compared with proficient MSS tumors (PFS: 6.2 vs. 7.6 months; HR 1.33, 95% CI, 1.12-1.57; $p = 0.001$; OS: 13.6 vs. 16.8; HR 1.35, 95% CI, 1.13-1.61; $p = 0.001$) [24].

The prognosis of patients with metastatic CRC who have progressed on all standard therapies is very poor. Despite a minimal improvement in PFS and OS, regorafenib was recently approved for the treatment in this patient population [34]. Progression-free survival and OS for patients treated with regorafenib versus placebo was 1.9 vs. 1.7 months (HR 0.49, 95% CI 0.4-0.58; $p < 0.0001$) and OS was 6.4 versus 5.0 months (HR 0.77, 95% CI 0.64-0.94; one-sided $p = 0.0052$), respectively. Novel and effective therapies that are capable of producing durable responses are desperately needed in this patient population [34].

There have been several reports about increased tumor-specific neo-antigens in MSI high CRC [18] [35], suggesting potential benefit from immunotherapy. However, there have been inconsistent observations about the expression of PD-L1 in MSI high CRC [17] [18].

Pembrolizumab monotherapy in MSI high and MSS CRC patients was evaluated in KN016 study. The data for KN016, in an article by Le et al., was presented at the American Society of Clinical Oncology (ASCO) 2015 conference held on 30-May-2015 [36]. The trial accrued 11 MSI high and 21 MSS CRC patients. All CRC patients received >2 prior chemotherapy regimens (median=4) except for one MMR-proficient patient who had received one chemotherapeutic and one (non-PD1-based) immunotherapeutic regimens. The patients received pembrolizumab 10mg/kg every 2 weeks. Radiologic assessments were made using RECIST 1.1 and immune-related response criteria (irRC) at 12 weeks and then every 8 weeks. There were no treatment-related serious adverse events. Treatment-related adverse events are listed in the article for KN016. A total of 4/10 (40%) MSI high CRC patients achieved a confirmed RECIST 1.1 partial response (PR), whereas there were no MSS CRC patients achieved PR with pembrolizumab monotherapy. In the patients with MSI high colorectal cancer, median PFS and median OS were not reached. In contrast, the patients with MSS cancers achieved a PFS of only 2.2 months (95% CI, 1.4 to 2.8) and median OS of 5.0 months (95% CI, 3.0 to not estimable).

At the annual Society of Immunotherapy of Cancer meeting, Le et al. updated results for this cohort; as of September 2015, the ORR for patients with MMR-deficient colorectal cancer (N=20) was 55% with a DCR of 90%. Responses were durable with the median PFS and OS not reached as of October 2015, with a median follow up time of 37 weeks (range, 11 to 93 weeks). The results of KN016 suggest that MSI status predicts clinical benefit of immune checkpoint blockade with pembrolizumab, and patients with MSI-H CRC may experience durable benefit from the treatment. The recent update from KN-016, especially demonstrates the durability of responses, and strongly indicates that pembrolizumab might offer clinical benefits to patients in an earlier treatment line setting (i.e. patients who were previously

treated with one line of standard of care therapy). As such, Cohort B of this study is designed to evaluate the anticancer activity of pembrolizumab in a population of subjects who have undergone less prior treatment than those in Cohort A.

4.2.2 Rationale for Dose Selection/Regimen

4.2.2.1 Rationale for Fixed Dose Pembrolizumab

The planned dose of pembrolizumab for this trial is 200 mg every 3 weeks (Q3W). Based on the totality of data generated in the Keytruda development program, 200 mg Q3W is the appropriate dose of pembrolizumab across all indications and regardless of tumor type. As outlined below, this dose is justified by:

- Clinical data from eight randomized studies demonstrating flat dose- and exposure-efficacy relationships from 2 mg/kg Q3W to 10 mg/kg every two weeks (Q2W),
- Clinical data showing meaningful improvement in benefit-risk including overall survival at 200 mg Q3W across multiple indications, and
- Pharmacology data showing full target saturation in both systemic circulation (inferred from pharmacokinetic [PK] data) and tumor (inferred from physiologically based pharmacokinetic [PBPK] analysis) at 200 mg Q3W

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

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

Finally, population PK analysis of pembrolizumab, which characterized the influence of body weight and other subject covariates on exposure, has shown that the fixed-dosing

provides similar control of PK variability as weight-based dosing, with considerable overlap in the distribution of exposures from the 200 mg Q3W fixed dose and 2 mg/kg Q3W dose. Supported by these PK characteristics and given that fixed-dose has advantages of reduced dosing complexity and reduced potential of dosing errors, the 200 mg Q3W fixed-dose was selected for evaluation across all pembrolizumab protocols.

4.2.3 Rationale for Endpoints

4.2.3.1 Efficacy Endpoints

4.2.3.1.1 Primary Endpoint

The primary efficacy objective of this study is to evaluate the anti-tumor activity of pembrolizumab in subjects with locally advanced unresectable or metastatic (Stage IV) MMR deficient or MSI-high CRC. Objective response rate (ORR) will be used as the primary endpoint per RECIST 1.1 assessed by the central imaging vendor.

4.2.3.1.2 Secondary Endpoints

The secondary efficacy objectives of this study are to evaluate DOR, DCR, and PFS per RECIST 1.1 as assessed by the central imaging vendor, and OS in subjects with locally advanced unresectable or metastatic (Stage IV) MMR deficient or MSI-high CRC.

4.2.3.1.3 Tertiary and Exploratory Endpoints

The exploratory efficacy objectives of this study are to evaluate ORR, DOR, and PFS per RECIST 1.1 as assessed by the investigator; and to evaluate the ORR, DOR, DCR, and PFS per irRECIST as assessed by the central imaging vendor in subjects with locally advanced unresectable or metastatic (Stage IV) MMR deficient or MSI-high CRC.

4.2.3.1.3.1 Immune-related RECIST

RECIST 1.1 will be adapted to account for the unique tumor response characteristics seen with treatment of pembrolizumab. Immunotherapeutic agents such as pembrolizumab may produce antitumor effects by potentiating endogenous cancer-specific immune responses. The response patterns seen with such an approach may extend beyond the typical time course of responses seen with cytotoxic agents, and can manifest a clinical response after an initial increase in tumor burden or even the appearance of new lesions. RECIST may not provide an accurate response assessment of immunotherapeutic agents such as pembrolizumab. Immune-related RECIST (irRECIST) is RECIST 1.1 adapted as described below to account for the unique tumor response seen with immunotherapeutics. Following site identification of PD, irRECIST will be used by site investigators to assess tumor response and progression, and make treatment decisions.

If radiologic imaging by the site identifies PD by RECIST 1.1, subject management and tumor assessment will shift to irRECIST. Imaging should be repeated ≥ 4 weeks later in

order to confirm PD with the option of continuing treatment per below while awaiting radiologic confirmation of progression.

If repeat imaging shows <20% increase in tumor burden compared to nadir, stable or improved previous new lesion (if identified as cause for initial PD), and stable/improved non-target disease (if identified as cause for initial PD), PD is not confirmed. Treatment may continue and subsequently follow regular imaging schedule.

If repeat imaging confirms PD (irPD) due to any of the scenarios listed below, subjects will be discontinued from study therapy (exception noted in Section 7.1.4.1.5.1).

In determining whether or not the tumor burden has increased or decreased, site study team should consider all target lesions as well as non-target lesions.

Scenarios where PD is confirmed at repeat imaging:

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

In subjects who have initial evidence of radiological PD by the site, it is at the discretion of the site investigator whether to continue a subject on study treatment until repeat imaging is obtained (irRECIST subject management). This clinical judgment decision should be based on the subject's overall clinical condition, including performance status, clinical symptoms, and laboratory data. Subjects may receive study treatment while waiting for confirmation of PD if they are clinically stable as 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

When feasible, subjects should not be discontinued until progression is confirmed. This allowance to continue treatment despite initial radiologic progression takes into account the observation that some subjects can have a transient tumor flare in the first few months after the start of immunotherapy, but with subsequent disease response. Subjects that are deemed clinically unstable are not required to have repeat imaging for confirmation of PD.

4.2.3.2 Safety Endpoints

The safety objective of this trial is to characterize the safety and tolerability of pembrolizumab in subjects with MMR deficient or MSI-high CRC. The primary safety analysis will be based on subjects who experienced toxicities as defined by CTCAE, v4.0 (Section 12.6). 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 Biomarkers

4.2.3.3.1 MSI Status Testing

MSI, a form of genomic instability, occurs through the insertion or deletion of repeating nucleotides during DNA replication and failure of the mismatch repair system to correct errors in nucleotide repeat markers. MMR proteins or MSI loci testing for CRC is clinically indicated as per NCCN, ESMO, and ASCO guidelines [27] [28] [37]. MMR- or MSI status is, respectively, determined by examining either CRC tumor 1) protein expression by immunohistochemistry of 4 MMR enzymes (MLH1/MSH2/MSH6/PMS2) or 2) 3-5 tumor microsatellite loci using PCR-based assay.

Tumors are classified as MSI high when at least 2 allelic shifts among the 3-5 analyzed microsatellite markers are detected by PCR or absence of at least 1 of 4 mismatch repair proteins expression is detected by IHC.

4.2.3.3.2 Planned Exploratory Biomarker Research

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

Germline (blood) genetic analyses (eg, single-nucleotide polymorphism [SNP] analyses, whole exome sequencing, whole genome sequencing)

This research will evaluate whether genetic variation within a clinical trial population correlates with response to the treatment(s) under evaluation. If genetic variation is found to predict efficacy or AEs, the data might inform optimal use of therapies in the patient

population. Furthermore, it is important to evaluate germline DNA variation across the genome in order to interpret tumor-specific DNA mutations.

Genetic (DNA) analyses from tumor

The application of new technologies, such as next generation sequencing, has provided scientists the opportunity to identify tumor-specific DNA changes (ie, mutations, methylation status, microsatellite instability). Key molecular changes of interest to immune-oncology drug development include the mutational burden of tumors and the clonality of T-cells in the tumor microenvironment. Increased mutational burden (sometimes referred to as a 'hyper-mutated' state) may generate neo-antigen presentation in the tumor microenvironment. To conduct this type of research, it is important to identify tumor-specific mutations that occur across all genes in the tumor genome. Thus, genome-wide approaches may be used for this effort. Note that in order to understand tumor-specific mutations; it is necessary to compare the tumor genome with the germline genome.

Tumor and blood RNA analyses

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

Proteomics and IHC using blood or tumor

Tumor and blood samples from this trial may undergo proteomic analyses (eg, PD-L1 IHC). PD-L1 protein level in tumor sections, assessed by IHC, has been shown to correlate with response to pembrolizumab in patients with NSCLC, and an in vitro diagnostic (IVD) device has been developed for use with pembrolizumab in NSCLC. Preliminary data indicates that this association may also be true in additional cancer types (ie, triple negative breast cancer, head and neck, and gastric). Additional tumor or blood-derived proteins may also correlate with response to immunotherapeutics. Therefore, tumor tissue may be subjected to proteomic analyses using a variety of platforms that could include but are not limited to immunoassays and liquid chromatography/mass spectrometry. This approach could identify novel protein biomarkers that could aid in patient selection for pembrolizumab therapies.

Other blood-derived biomarkers

In addition to expression on the tumor tissue, PD-L1 and other tumor derived proteins can be shed from tumor and released into the blood. Assays such as enzyme-linked immunosorbent assay (ELISA) measure such proteins in serum. Correlation of expression with response to pembrolizumab therapy may identify new approaches for predictive biomarkers in blood,

representing a major advance from today's reliance on assessing tumor biomarkers. This research would serve to develop such assays for future clinical use.

4.2.3.4 Future Biomedical Research

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

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

4.3 Benefit/Risk

Subjects in clinical trials generally cannot expect to receive direct benefit from treatment during participation, as clinical 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 Subject Inclusion Criteria

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

1. Be willing and able to provide written informed consent for the trial. The subject may also provide consent for Future Biomedical Research. However, the subject may participate in the main trial without participating in Future Biomedical Research.
2. Be male or female subjects who are ≥ 18 years of age on the day of signing the informed consent.

3. Locally confirmed MMR deficient or MSI-h CRC (refer to Section 4.2.3.3.1 for details).
4. Have a histologically proven locally advanced unresectable or metastatic (Stage IV) CRC.
5. Have been previously treated with standard therapies, which must include, for Cohort A, fluoropyrimidine, oxaliplatin, and irinotecan, and for Cohort B, at least one line of systemic standard of care therapy: fluoropyrimidine + oxaliplatin or fluoropyrimidine + irinotecan +/- anti-VEGF/EGFR monoclonal antibody.
 - Subjects who have withdrawn from standard treatment due to unacceptable toxicity warranting discontinuation of that treatment and precluding retreatment with the same agent before progression of disease will also be eligible.
 - Regimens given with adjuvant intent will be counted as treatment for metastatic disease if the patient's disease had progressed within 6 month following treatment.
6. Have an ECOG performance status of 0 or 1.
7. Have a life expectancy of greater than 3 months.
8. Provide an archival or newly obtained tumor tissue sample (Cohort B) (refer to Section 7.1.3.2.5).
9. Have at least one measurable lesion by RECIST 1.1 as determined by central review for response assessment.

Note: The same imaging modality, acquisition and technical parameters should be used throughout the study unless clinically contraindicated (please refer to the Site Imaging Manual)

10. Female subjects of childbearing potential should have a negative urine or serum pregnancy test within 72 hours prior to receiving the first dose of study medication. If the urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required.
11. Female subjects of childbearing potential (Section 5.7.2) must be willing to use an adequate method of contraception as outlined in Section 5.7.2 – Contraception, for the course of the study through 120 days after the last dose of study medication.

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

12. Male subjects of childbearing potential (Section 5.7.2) must agree to use an adequate method of contraception as outlined in Section 5.7.2 – Contraception, starting with the first dose of study therapy through 120 days after the last dose of study therapy.

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

13. Demonstrated adequate organ function as defined in [Table 1](#). All screening labs should be performed within 10 days of treatment initiation.

Table 1 Adequate Organ Function Lab Values

System	Laboratory Value
Hematological	
Absolute neutrophil count (ANC)	$\geq 1,500/\text{mcL}$
Platelets	$\geq 100,000/\text{mcL}$
Hemoglobin	$\geq 9 \text{ g/dL}$ or $\geq 5.6 \text{ mmol/L}$ without transfusion or EPO dependency within 7 days.
Renal	
Creatinine OR Measured or calculated ^a creatinine clearance (GFR can also be used in place of creatinine or CrCl)	$\leq 1.5 \text{ X}$ upper limit of normal (ULN) OR $\geq 60 \text{ mL/min}$ for subject with creatinine levels $> 1.5 \text{ X}$ institutional ULN
Hepatic	
Total bilirubin	$\leq 1.5 \text{ X ULN}$ OR Direct bilirubin $\leq \text{ULN}$ for subjects with total bilirubin levels $> 1.5 \text{ ULN}$
AST (SGOT) and ALT (SGPT)	$\leq 2.5 \text{ X ULN}$ OR $\leq 5 \text{ X ULN}$ for subjects with liver metastases
Albumin	$\geq 2.5 \text{ g/dL}$
Coagulation	
International Normalized Ratio (INR) or Prothrombin Time (PT)	$\leq 1.5 \text{ X ULN}$ unless subject is receiving anticoagulant therapy as long as PT or PTT is within therapeutic range of intended use of anticoagulants
Activated Partial Thromboplastin Time (aPTT)	$\leq 1.5 \text{ X ULN}$ 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.	

Subjects who did not meet entry criteria for enrollment in Cohort A may be rescreened for Cohort B only after consultation with the SPONSOR.

5.1.2 Subject Exclusion Criteria

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

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

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 (e.g. 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 known active central nervous system (CNS) metastases and/or carcinomatous meningitis. Subjects with previously treated brain metastases may participate provided they have stable brain metastases [without evidence of progression by imaging [confirmed by magnetic resonance imaging (MRI) if MRI was used at prior imaging, or confirmed by computed tomography (CT) imaging if CT used at prior imaging] for at least four weeks prior to the first dose of trial treatment; also, any neurologic symptoms must have returned to baseline], have no evidence of new or enlarging brain metastases, and have not used steroids for brain metastases for at least 7 days prior to trial treatment. This exception does not include carcinomatous meningitis, as subjects with carcinomatous meningitis are excluded regardless of clinical stability.
5. Has had prior monoclonal antibody (mAb), chemotherapy, targeted small molecule therapy, or radiation therapy within 2 weeks prior to study Day 1 or who has not recovered (i.e., \leq Grade 1 or at baseline) from adverse events due to a previously administered agent.

Note: Subjects with \leq Grade 2 neuropathy or \leq Grade 2 alopecia 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 received prior therapy with an anti-PD-1, anti-PD-L1, or anti-PD-L2 agent.
7. Has a known additional malignancy that is progressing or requires active treatment. Exceptions include basal cell carcinoma of the skin or squamous cell carcinoma of the skin that has undergone potentially curative therapy or in situ cervical cancer.
8. Has received a live vaccine within 30 days of planned start of study therapy.

Note: The killed virus vaccines used for seasonal influenza vaccines for injection are allowed; however intranasal influenza vaccines (e.g., FluMist®) are live attenuated vaccines, and are not allowed.

9. 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.
10. Has a known history of Human Immunodeficiency Virus (HIV) (HIV 1/2 antibodies).
11. Has known active Hepatitis B (e.g., HBsAg reactive) or Hepatitis C (e.g., HCV RNA [qualitative] is detected).
12. Has known history of, or any evidence of interstitial lung disease or active, non-infectious pneumonitis.
13. Has an active infection requiring systemic therapy.
14. Has known psychiatric or substance abuse disorders that would interfere with cooperation with the requirements of the trial.
15. Is pregnant or breastfeeding, or expecting to conceive 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.

5.2 Trial Treatment(s)

The treatment to be used in this trial is outlined below in [Table 2](#).

Table 2 Trial Treatment

Study Treatment	Dose/Potency	Dose Frequency	Route of Administration	Regimen	Use
Pembrolizumab (MK-3475)	200 mg	Q3W	IV Infusion	Day 1 of each 21-day cycle	experimental

All products indicated in [Table 2](#) will be provided centrally by the Sponsor or locally by the trial site, subsidiary or designee, depending on local country operational or regulatory requirements.

Trial treatment for Cycle 1 should begin within 3 days of allocation. However, every effort should be made to begin trial treatment on the day of allocation.

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

5.2.1 Dose Selection/Modification

5.2.1.1 Dose Selection (Preparation)

The rationale for selection of the dose 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 and Toxicity Management Guidelines for Pembrolizumab

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

AEs associated with pembrolizumab exposure may represent an immunologic etiology. These immune-related AEs (irAEs) may occur shortly after the first dose or several months after the last dose of pembrolizumab treatment and may affect more than one body system simultaneously. Therefore, early recognition and initiation of treatment is critical to reduce complications. Based on existing clinical trial data, most irAEs were reversible and could be managed with interruptions of pembrolizumab, administration of corticosteroids and/or other supportive care. For suspected irAEs, ensure adequate evaluation to confirm etiology or exclude other causes. Additional procedures or tests such as bronchoscopy, endoscopy, skin biopsy may be included as part of the evaluation. Based on the severity of irAEs, withhold or permanently discontinue pembrolizumab and administer corticosteroids. Dose modification and toxicity management guidelines for irAEs associated with pembrolizumab are provided in [Table 3](#).

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

General instructions:				
<ol style="list-style-type: none"> 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	<ul style="list-style-type: none"> • Administer corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper 	<ul style="list-style-type: none"> • 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	<ul style="list-style-type: none"> • Administer corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper 	<ul style="list-style-type: none"> • 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 \geq 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	<ul style="list-style-type: none"> Administer corticosteroids (initial dose of 0.5- 1 mg/kg prednisone or equivalent) followed by taper 	<ul style="list-style-type: none"> 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	<ul style="list-style-type: none"> 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	<ul style="list-style-type: none"> Initiate insulin replacement therapy for subjects with T1DM Administer anti-hyperglycemic in subjects with hyperglycemia 	<ul style="list-style-type: none"> Monitor subjects for hyperglycemia or other signs and symptoms of diabetes.
Hypophysitis	Grade 2	Withhold	<ul style="list-style-type: none"> Administer corticosteroids and initiate hormonal replacements as clinically indicated. 	<ul style="list-style-type: none"> 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	<ul style="list-style-type: none"> Treat with non-selective beta-blockers (eg, propranolol) or thionamides as appropriate 	<ul style="list-style-type: none"> Monitor for signs and symptoms of thyroid disorders.
	Grade 3 or 4	Withhold or permanently discontinue ¹		
Hypothyroidism	Grade 2-4	Continue	<ul style="list-style-type: none"> Initiate thyroid replacement hormones (eg, levothyroxine or liothyroine) per standard of care 	<ul style="list-style-type: none"> Monitor for signs and symptoms of thyroid disorders.
Nephritis and Renal dysfunction	Grade 2	Withhold	<ul style="list-style-type: none"> Administer corticosteroids (prednisone 1-2 mg/kg or equivalent) followed by taper. 	<ul style="list-style-type: none"> 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	<ul style="list-style-type: none">Based on severity of AE administer corticosteroids	<ul style="list-style-type: none">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	<ul style="list-style-type: none">Based on type and severity of AE administer corticosteroids	<ul style="list-style-type: none">Ensure adequate evaluation to confirm etiology and/or exclude other causes
	Grade 3	Withhold or discontinue based on the type of event. Events that require discontinuation include and not limited to: Guillain-Barre Syndrome, encephalitis		
	Grade 4 or recurrent Grade 3	Permanently discontinue		
1. Withhold or permanently discontinue pembrolizumab is at the discretion of the investigator or treating physician.				
NOTE: For subjects with Grade 3 or 4 immune-related endocrinopathy where withhold of pembrolizumab is required, pembrolizumab may be resumed when AE resolves to ≤ Grade 2 and is controlled with hormonal replacement therapy or achieved metabolic control (in case of T1DM).				

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

Pembrolizumab may cause severe or life-threatening infusion-reactions including severe hypersensitivity or anaphylaxis. Signs and symptoms usually develop during or shortly after drug infusion and generally resolve completely within 24 hours of completion of infusion. Dose modification and toxicity management guidelines on pembrolizumab associated infusion reaction are provided in [Table 4](#).

Table 4 Pembrolizumab Infusion Reaction Dose modification and Treatment Guidelines

NCI CTCAE Grade	Treatment	Premedication at Subsequent Dosing
Grade 1 Mild reaction; infusion interruption not indicated; intervention not indicated	Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator.	None
Grade 2 Requires therapy or infusion interruption but responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDs, narcotics, IV fluids); prophylactic medications indicated for ≤ 24 hr	<p>Stop Infusion.</p> <p>Additional appropriate medical therapy may include but is not limited to:</p> <p>IV fluids</p> <p>Antihistamines</p> <p>NSAIDs</p> <p>Acetaminophen</p> <p>Narcotics</p> <p>Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator.</p> <p>If symptoms resolve within 1 hour of stopping drug infusion, the infusion may be restarted at 50% of the original infusion rate (e.g. from 100 mL/hr to 50 mL/hr). Otherwise dosing will be held until symptoms resolve and the subject should be premedicated for the next scheduled dose.</p> <p>Subjects who develop Grade 2 toxicity despite adequate premedication should be permanently discontinued from further study drug treatment</p>	<p>Subject may be premedicated 1.5h (\pm 30 minutes) prior to infusion of pembrolizumab with:</p> <p>Diphenhydramine 50 mg po (or equivalent dose of antihistamine).</p> <p>Acetaminophen 500-1000 mg po (or equivalent dose of analgesic).</p>

NCI CTCAE Grade	Treatment	Premedication at Subsequent Dosing
Grades 3 or 4 Grade 3: Prolonged (i.e., not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae (e.g., renal impairment, pulmonary infiltrates) Grade 4: Life-threatening; pressor or ventilatory support indicated	Stop Infusion. Additional appropriate medical therapy may include but is not limited to: Epinephrine** IV fluids Antihistamines NSAIDs Acetaminophen Narcotics Oxygen Pressors Corticosteroids Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator. Hospitalization may be indicated. **In cases of anaphylaxis, epinephrine should be used immediately. Subject is permanently discontinued from further study drug treatment.	No subsequent dosing
Appropriate resuscitation equipment should be available at the bedside and a physician readily available during the period of drug administration. For further information, please refer to the Common Terminology Criteria for Adverse Events v4.0 (CTCAE) at http://ctep.cancer.gov		

Other allowed dose interruption for pembrolizumab

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

5.2.2 Timing of Dose Administration

Cycle 1 Day 1 treatment with pembrolizumab should begin on the day of allocation, but no later than 3 days from the date the subject is allocated to study treatment. However, every effort should be made to begin trial treatment on the day of allocation.

For all additional cycles of pembrolizumab, treatment may be administered up to 3 days before or 3 days after the scheduled Day 1 of each cycle due to administrative reasons per the investigator's judgment.

All study treatments will begin on Day 1 of each cycle after all pre-dose study procedures and 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.

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 the preparation of the pembrolizumab infusion fluid and administration of infusion solution.

All trial treatments will be administered on an outpatient basis.

5.2.3 Trial Blinding/Masking

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

5.3 Randomization or Treatment Allocation

Assignment of the treatment/allocation number will occur centrally using an interactive voice response system/integrated web response system (IVRS/IWRS). All enrolled subjects will be allocated to receive pembrolizumab 200 mg IV Q3W as monotherapy in an unblinded fashion.

5.4 Stratification

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

5.5 Concomitant Medications/Vaccinations (Acceptable and 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.

Palliative and supportive care is permitted during the course of the trial for underlying medical conditions and management of symptoms. Surgery for tumor control or symptom management is not permitted during the study. Palliative radiotherapy is permitted to a

single lesion if considered medically necessary by the treating physician as long as the lesion is NOT a RECIST 1.1 defined target lesion and is NOT administered for tumor control. Trial therapy should be held during the course of palliative radiotherapy and should be resumed no earlier than the next scheduled administration of trial therapy. The specifics of the radiation treatment, including the location, will be recorded.

All concomitant medications received within 28 days prior to the first dose of trial treatment and up to 30 days after the last dose of trial treatment should be recorded. All concomitant medications received within 28 days prior to the first dose of retreatment should also be recorded. Concomitant medications administered more than 30 days after the last dose of trial treatment should be recorded for SAEs and ECIs as defined in Section 7.2

5.5.2 Prohibited Concomitant Medications

Subjects are prohibited from receiving the following therapies during the Screening 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: Palliative radiation therapy to a symptomatic solitary non-target lesion or to the brain may be allowed after consultation with the Sponsor.

- 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, chickenpox, yellow fever, rabies, BCG, and typhoid (oral) vaccines. The killed virus vaccines used for seasonal influenza vaccines for injection are allowed. However, intranasal influenza vaccines (e.g. FluMist®) are live attenuated vaccines, and are not allowed.
- Systemic glucocorticoids for any purpose other than to modulate symptoms from an AE of suspected immunologic etiology. The use of physiologic doses of corticosteroids may be approved after consultation with the Sponsor.
 - *Note: Inhaled steroids are allowed for the management of asthma*
 - *Note: Use of prophylactic corticosteroids to avoid allergic reactions (e.g., to IV contrast 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 discontinued from study treatment. Subjects may receive other medications or treatments that the investigator deems to be medically necessary.

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

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

5.6 Rescue Medications & Supportive Care

5.6.1 Supportive Care Guidelines for Pembrolizumab

Subjects should receive appropriate supportive care measures as deemed necessary by the treating investigator. Suggested supportive care measures for the management of adverse events with potential immunologic etiology are outlined along with the dose modification guidelines in Section 5.2.1.2, [Table 3](#). Where appropriate, these guidelines include the use of oral or 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 to pembrolizumab, the investigator does not need to follow the treatment guidance. Refer to [Table 3](#) in Section 5.2.1.2 for guidelines regarding dose modification and supportive care.

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

5.7 Diet/Activity/Other Considerations

5.7.1 Diet

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

5.7.2 Contraception

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

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

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

- (1) postmenopausal (defined as at least 12 months with no menses without an alternative medical cause; in women < 45 years of age a high follicle stimulating hormone (FSH)

level in the postmenopausal range may be used to confirm a post-menopausal state in women not using hormonal contraception or hormonal replacement therapy. In the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.);

OR

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

OR

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

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

(1) practice abstinence[†] from heterosexual activity;

OR

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

Acceptable methods of contraception are[‡]:

Single method (one of the following is acceptable):

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

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

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

[†]Abstinence (relative to heterosexual activity) can be used as the sole method of contraception if it is consistently employed as the subject's preferred and usual lifestyle and if considered acceptable by local regulatory agencies and ERCs/IRBs. Periodic abstinence

(e.g., calendar, ovulation, sympto-thermal, post-ovulation methods, etc.) and withdrawal are not acceptable methods of contraception.

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

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

For countries or sites that follow the Clinical Trial Facilitation Group (CTFG) guidance, please use the following:

Pembrolizumab may have adverse effects on a fetus in utero. Furthermore, it is not known if these therapies have transient adverse effects on the composition of sperm. Therefore, non-pregnant, non-breastfeeding women may only be enrolled if they are willing to follow the CTFG Guidance (Final Version 2014-09-15, Sections 4.1 and 4.2) for highly effective birth control as outlined below, or are considered to be 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. Subjects should use birth control methods that can achieve a failure rate of less than 1% per year when used consistently and correctly and are considered as highly effective birth control methods. Such methods include:

- Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation:
 - Oral
 - Intravaginal
 - Transdermal
- Progestogen-only hormonal contraception associated with inhibition of ovulation:
 - Oral
 - Injectable
 - Implantable
- Intrauterine device (IUD)
- Intrauterine hormone-releasing system (IUS)
- Bilateral tubal occlusion
- Vasectomised partner
- Sexual abstinence

Subjects should start using birth control from study Visit 1 throughout the study period up to 180 days after the last dose of study therapy.

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 must be reported to the Sponsor and followed as described in Section 7.2.2 (Reporting of Pregnancy and Lactation to the Sponsor).

5.7.4 Use in Nursing Women

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

5.8 Subject Withdrawal/Discontinuation Criteria

Subjects may withdraw consent at any time for any reason or be dropped from the trial at the discretion of the investigator should any untoward effect occur. In addition, a subject may be withdrawn by the investigator or the Sponsor if enrollment into the trial is inappropriate, the trial plan is violated, or for administrative and/or other safety reasons. Specific details regarding discontinuation or withdrawal procedures; including specific details regarding withdrawal from Future Biomedical Research, are provided in Section 7.1.5 – 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 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 PD (irPD) as outlined in Section 7.1.4.1 (exception if Sponsor approves treatment continuation)
- Unacceptable adverse experiences as described in Section 7.2
- Any progression or recurrence of any malignancy, or any occurrence of another malignancy that requires active treatment
- Recurrent Grade 2 pneumonitis
- Intercurrent illness that prevents further administration of treatment
- Investigator's decision to discontinue the subject
- The subject has a confirmed positive serum pregnancy test
- Administrative reasons
- Completed 35 treatments with pembrolizumab
 - *Note: 35 treatments (approx. 2 years) are calculated from the first dose. Subjects who stop pembrolizumab after receiving 35 treatments may be eligible for retreatment if they progress after stopping study treatment provided they meet the requirements detailed in Section 7.1.6.2.1. Subjects may be retreated in the Second Course Phase with up to 17 (approx. 1 year) additional trial treatments.*

The End of Treatment and Follow-up Visit procedures are listed in Section 7.1.6.3 and the Trial Flow Chart and Section 6.0. After the end of treatment, each subject will be followed for a minimum of 30 days for AE monitoring (SAEs and ECIs will be collected for up to 90 days after the end of treatment as described in Section 7.2.3.1). Subjects who discontinue for reasons other than PD will have post-treatment follow-up for disease status until PD, initiating a non-study cancer treatment, withdrawing consent or becoming lost to follow-up. After documented PD each subject will be followed for OS until death, withdrawal of consent, or the end of the study, whichever occurs first.

5.8.1 Discontinuation of Study Therapy after Complete Response

Discontinuation of treatment may be considered for subjects who have attained a confirmed CR (assessed by the site) that have received at least 8 trial treatments (approx. 6 months) of pembrolizumab and had at least 2 treatments with pembrolizumab beyond the date when the

initial CR was declared. Subjects who stop then experience radiographic disease progression may be eligible for up to 17 additional treatments (approx. 1 year) with pembrolizumab in 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 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 7.1.6.2.1. Response or progression in this Second Course Phase will not count towards 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 ends when fewer than 25% of subjects are evaluable for OS or all subjects have discontinued trial treatment (including retreatment), whichever occurs earlier.

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

5.11 Clinical Criteria for Early Trial Termination

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

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

1. Quality or quantity of data recording is inaccurate or incomplete
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 Flow Chart for Initial Treatment Phase with Pembrolizumab

Trial Period:	Screening Phase	Treatment Cycles								End of Treatment	Post-treatment		
Treatment Cycle/Title:	Screening (Visit 1)	1	2	3	4	5	6	7	8 to 35	Discon	Safety Follow-up	Follow-up Visits	Survival Follow-up ^a
										At Time of Discon	30 Days from Last Dose	Every 12 Weeks ⁿ	Every 12 Weeks
Scheduling Window (Days) ^b	-28 to -1		± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 7	± 7	± 7
Administrative Procedures													
Informed Consent	X												
Informed Consent for Future Biomedical Research (optional)	X												
Inclusion/Exclusion Criteria	X												
Subject Identification Card	X												
Demographics and Medical History	X												
Prior and Concomitant Medication Review	X	X	X	X	X	X	X	X	X	X	X		
Clinical Procedures/Assessments													
Review Adverse Events	X	X	X	X	X	X	X	X	X	X	X	X	
Full Physical Examination	X									X			
Directed Physical Examination		X	X	X	X	X	X	X	X				
Height, Weight, and Vital Signs (T,P,RR,BP) ^c	X	X	X	X	X	X	X	X	X	X			
12-Lead Electrocardiogram	X												
ECOG Performance Status	X ^e	X	X	X	X	X	X	X	X	X			
Post-study Anticancer Therapy Status											X	X	X
Survival Status ^a		←-----→											X
Trial Treatment Administration													
Pembrolizumab Administration		X ^b	X	X	X	X	X	X	X				
LOCAL Laboratory Assessments													
Pregnancy Test - Urine or Serum β-hCG	X ^d		X	X	X	X	X	X	X	X	X		
PT/INR and aPTT	X ^e												
CBC with Differential ^f	X ^e		X	X	X	X	X		X ^f	X	X		
Chemistry Panel ^f	X ^e		X	X	X	X	X		X ^f	X	X		
Urinalysis	X ^e												
T3 (or FT3), FT4, and TSH ^f	X		X		X		X		X ^f	X	X		

Trial Period:	Screening Phase	Treatment Cycles								End of Treatment	Post-treatment		
Treatment Cycle/Title:	Screening (Visit 1)	1	2	3	4	5	6	7	8 to 35	Discon At Time of Discon	Safety Follow-up 30 Days from Last Dose	Follow-up Visits Every 12 Weeks ⁿ	Survival Follow-up ^a Every 12 Weeks
Serum Tumor Markers ^g	X ^e	X	X	X	X	X	X	X	X	X			
CENTRAL Laboratory Assessments													
Blood for Genetics ^h		X											
Plasma for circulating tumor DNA (Cohort B only)(optional)		X		X						X			
Correlative Blood Samples (DNA and RNA) ⁱ		X	X	X						X			
Tumor Tissue Collection													
Archival or Newly Obtained Tumor Tissue ^m	X ^m									X			
Efficacy Measurements													
Tumor Imaging ^k	X ^j	X ^k								X ^l		X	

- a. Subjects that experience site assessed PD or start a new anti-cancer therapy should be followed approximately Q12W 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).
- b. Cycle 1 treatment must be given within 3 days of allocation. The window for each visit is ± 3 days unless otherwise noted.
- c. Height will be measured at Visit 1 only.
- d. For women of reproductive potential, a serum or urine pregnancy test should be performed within 72 hours prior to each dose of trial treatment and 30 days post last dose of study treatment.
- e. ECOG Performance Status and Laboratory tests for screening are to be performed within 10 days prior to the first dose of trial treatment.
- f. After Cycle 1, lab samples can be collected up to 72 hours prior to the scheduled time point. Thyroid function tests to be performed every other cycle. CBC and Chemistry to be performed every cycle through Cycle 6 and then every other cycle thereafter.
- g. Serum tumor markers (CEA) should be collected at screening (baseline) and every Cycle until treatment discontinuation; may be collected up to 72 hours prior to the scheduled time point.
- h. 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. Leftover extracted DNA will be stored for future biomedical research if the subject signs the ICF for FBR. Details for collection can be found in Section 7.1.3.2 Central Laboratory Assessments.
- i. Whole blood samples for correlative studies should be collected pre-dose on Day 1 of Cycle 1, Cycle 2, and Cycle 3, and again at treatment discontinuation.
- j. Screening tumor imaging will be performed within 28 days prior to allocation. Confirmation of measurable disease by the central imaging vendor is required prior to subject allocation.
- k. The first on-study imaging time point will be performed 9 weeks (63 days ± 7 days) from date of allocation. Subsequent imaging will be performed Q9W (63 days ± 7 days) for the first 12 months, then Q12W (84 days, ± 7 days) thereafter, or more frequently if clinically indicated. Imaging timing should be calculated from the date of allocation, should follow calendar days, and should not be adjusted for delays in cycle starts.
- l. In subjects who discontinue study therapy without confirmed PD by the site per irRECIST, tumor imaging should be performed at the time of treatment discontinuation (± 4 weeks). If previous tumor imaging was obtained within 4 weeks prior to the date of discontinuation, then additional tumor imaging at treatment discontinuation is not required.
- m. Submitting tumor tissue for exploratory analysis is optional for Cohort A, but required for Cohort B, and should be submitted only after the samples have been evaluated at the local site laboratory for MSI/MMR status. Note: In subjects for whom newly obtained samples cannot be obtained (e.g., inaccessible and/or patient safety concern) and for whom no archived tissue is available, eligibility must be discussed with the Sponsor prior to enrollment. Leftover tumor tissue will be stored for future biomedical research for subjects who sign the Future Biomedical Research (FBR) consent. A tumor biopsy at treatment discontinuation is highly encouraged for all subjects in Cohort B, but not mandatory.
- n. The Follow-up Visits should occur approximately Q12W (after treatment discontinuation) to review AEs and post-treatment anti-cancer therapy status. However, to minimize subject burden, if the time window for this visit does not align with the timing for the continued tumor imaging (also occurring Q12W), the first Follow-up Visit may be performed earlier than scheduled to align these two visits. The imaging schedule should not be adjusted. All subsequent Follow-up Visits should occur Q12W as scheduled.

6.2 Flow Chart for Second Course Phase with Pembrolizumab (Retreatment)

Trial Period:	Treatment Cycles								End of Treatment	Post-treatment		
Treatment Cycle/Title:	1	2	3	4	5	6	7	8 to 17	Discon	Safety Follow-up	Follow Up Visits	Survival Follow-Up ^a
									At Time of Discon	30 Days from Last Dose	Every 12 Weeks ^h	Every 12 Weeks
Scheduling Window (Days) ^b		± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 7	± 7	± 7
Administrative Procedures												
Eligibility Criteria	X											
Concomitant Medication Review	X	X	X	X	X	X	X	X	X	X		
Clinical Procedures/Assessments												
Review Adverse Events	X	X	X	X	X	X	X	X	X	X	X	
Full Physical Examination	X								X			
Directed Physical Examination		X	X	X	X	X	X	X				
Weight, and Vital Signs (T,P,RR,BP)	X	X	X	X	X	X	X	X	X			
ECOG Performance Status	X	X	X	X	X	X	X	X	X			
Post-study anticancer Therapy Status										X	X	X
Survival Status ^a	←-----→											X
Trial Treatment Administration												
Pembrolizumab	X	X	X	X	X	X	X	X				
LOCAL Laboratory Assessments												
Pregnancy Test – Urine or Serum β-hCG ^e	X	X	X	X	X	X	X	X	X	X		
PT/INR and aPTT	X ^d											
CBC with Differential ^e	X ^d	X	X	X	X	X		X	X	X		
Chemistry Panel ^e	X ^d	X	X	X	X	X		X	X	X		
Urinalysis	X ^d											
T3, FT4, and TSH ^e	X		X		X		X	X ^e	X	X		
Efficacy Measurements												
Tumor Imaging	X ^f	←-----X ^f -----→							X ^g		X	

- a. After the start of new anti-cancer treatment or PD the subject should be followed approximately Q12W 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).
- b. In general, the window for each visit is ± 3 days unless otherwise noted.
- c. For women of reproductive potential, a urine or serum pregnancy test should be performed within 72 hours prior to each dose of study treatments and 30 days post last dose of study treatment.
- d. Laboratory tests for determining eligibility are to be performed within 10 days prior to the first retreatment dose of pembrolizumab
- e. After Cycle 1, lab samples can be collected up to 72 hours prior to the scheduled time point. Thyroid function tests to be performed every other cycle. CBC and Chemistry, to be performed every cycle through Cycle 6 and then every other cycle thereafter.
- f. Tumor imaging should be performed within 28 days prior to restarting treatment with pembrolizumab and continue to be performed every 12 weeks (84 ± 7 days) after the first dose of retreatment, or more frequently if clinically indicated.
- g. 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 additional tumor imaging at treatment discontinuation isn't mandatory.
- h. The Follow-up Visits should occur approximately Q12W (after treatment discontinuation and completion of 17 cycles) to review AEs and post-treatment anti-cancer therapy status. However, to minimize subject burden, if the time window for this visit does not align with the timing for the continued tumor imaging (also occurring Q12W), the first Follow -up Visit may be performed earlier than scheduled to align these two visits. The imaging schedule should not be adjusted. All subsequent Follow -up Visits should occur Q12W as scheduled.

7.0 TRIAL PROCEDURES

7.1 Trial Procedures

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

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

7.1.1 Administrative Procedures

7.1.1.1 Informed Consent

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

7.1.1.1.1 General Informed Consent

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

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

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

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

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

7.1.1.1.2 Consent and Collection of Specimens for Future Biomedical Research

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

7.1.1.2 Inclusion/Exclusion Criteria

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

7.1.1.3 Subject Identification Card

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

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

7.1.1.4 Medical History

A medical history will be obtained by the investigator or qualified designee. Medical history will include all active conditions, and any condition diagnosed within the prior 10 years that are considered to be clinically significant by the investigator. Disease details regarding the subject's CRC will be recorded separately and not listed as medical history.

Please note that if the subject has lost at least 15 lbs. (6.8 kg) over the three months prior to screening, "weight loss" should be entered as an active condition on the Medical History. As well, any autoimmune disorders, regardless of onset date, should be recorded.

7.1.1.5 Disease Details

The investigator or qualified designee will obtain prior and current details regarding the subject's colorectal carcinoma.

7.1.1.6 Prior and Concomitant Medications Review

7.1.1.6.1 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 of first dose of trial treatment.

Prior anti-cancer treatment for colorectal carcinoma will be recorded separately and not listed as a prior medication.

7.1.1.6.1.1 Prior Treatment Details for Colorectal Carcinoma

The investigator or qualified designee will review all prior anti-cancer treatments including systemic treatments, radiation and surgeries.

7.1.1.6.2 Concomitant Medications

The investigator or qualified designee will record medication, if any, taken by the subject during the trial from the time of signing the informed consent form until the Safety Follow-up Visit. In addition, new medications started within 28 days prior to the first dose of the Second Course Phase through the Second Course Safety Follow-up Visit should be recorded.

All medications related to reportable SAEs and ECIs should be recorded as defined in Section 7.2

7.1.1.7 Assignment of Screening Number

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

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

Specific details on the screening visit requirements (screening/rescreening) are provided in Section 7.1.6.1.

7.1.1.8 Assignment of Treatment/Randomization Number

All eligible subjects will be allocated, by non-random assignment, and will receive an allocation number. The allocation number identifies the subject for all procedures occurring after treatment allocation. Once an allocation number is assigned to a subject, it can never be re-assigned to another subject.

A single subject cannot be assigned more than 1 allocation number.

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

Interruptions from the protocol specified treatment for greater than 12 weeks between pembrolizumab doses for non-drug-related or administrative reasons require consultation between the investigator and the Sponsor and written documentation of the collaborative decision on subject management.

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

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

7.1.2 Clinical Procedures/Assessments

7.1.2.1 Adverse Event Monitoring

The investigator or qualified designee will assess each subject to evaluate for potential new or worsening AEs as specified in the Trial Flow Chart and more frequently if clinically indicated. Adverse events will be graded and recorded throughout the trial and during the follow-up period according to NCI CTCAE Version 4.0 (see Section 12.6). Toxicities will be characterized in terms regarding seriousness, causality, toxicity grading, and action taken with regard to trial treatment.

All AEs of unknown etiology associated with pembrolizumab exposure should be evaluated to determine if it is possibly an ECI of a potentially immunologic etiology (termed immune-related adverse events, or irAEs); see Section 5.2.1 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 physical exam during the screening period. Clinically significant abnormal findings should be recorded as medical history. Additional full physical exams should be performed as specified in the Trial Flow Chart-Section 6.0. 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-Section 6.0, 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 Height, Weight, and Vital Signs

The investigator or qualified designee will take vital signs at screening, prior to the administration of each dose of trial treatment, and at treatment discontinuation as specified in the Trial Flow Chart- Section 6.0.

Vital signs should include temperature, pulse, respiratory rate, blood pressure, height, and weight.

7.1.2.4 12-Lead Electrocardiogram

A standard 12-lead electrocardiogram (ECG) will be performed one time during screening using local standard procedures. 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 Performance Status

The investigator or qualified designee will assess Eastern Cooperative Oncology Group (ECOG) PS (see Section 12.5) 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 – Section 6.0.

7.1.2.6 Post-study 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.

7.1.3 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.

Refer to the Trial Flow Chart – Section 6.0 for the schedule of laboratory assessments.

7.1.3.1 Local Laboratory Assessments

Table 5 Laboratory Assessments

Hematology	Chemistry	Urinalysis	Other
Hematocrit	Albumin	Specific gravity	TSH
Hemoglobin	Alkaline phosphatase	Microscopic exam, if abnormal results are noted	Pregnancy test ^a
Platelet count	Lactate dehydrogenase (LDH)	Urine pregnancy test ^a	Tumor markers (CEA)
Red blood count	Alanine aminotransferase (ALT)	Protein	Total triiodothyronine (T3) or Free T3 ^d
White blood cell count (total and differential) ^e	Aspartate aminotransferase (AST)	Glucose	Free thyroxine (FT4)
Absolute neutrophil count ^f	Bicarbonate or Carbon dioxide ^c	Blood	PT(INR)
Absolute lymphocyte count ^f	Calcium		aPTT
	Chloride		
	Creatinine		
	Glucose		
	Potassium		
	Sodium		
	Total bilirubin		
	Direct bilirubin, if total bilirubin is elevated above the upper limit of normal		
	Total protein		
	Blood urea nitrogen/Urea ^b		

a. Perform on women of childbearing potential only. Serum pregnancy test is preferred but urine test can be considered if serum not appropriate.
b. Blood Urea Nitrogen is preferred; if not available urea may be tested.
c. If these tests are not done as part of standard of care in your region, then these tests do not need to be performed.
d. T3 is preferred; if not available free T3 may be tested. If the local laboratory is unable to perform either of these tests the site should submit the sample to the central laboratory for testing; details are provided in the procedure manual.
e. Report % or absolute results per standard of practice. Report the results in the same manner throughout the study.
f. Results should be calculated per local standard of practice.

Laboratory tests for screening should be performed within 10 days prior to the first dose of trial treatment. Subjects eligible for retreatment with pembrolizumab should have lab test

performed within 10 days prior to the first dose of trial treatment in the Second Course Phase. After Cycle 1, in both the Initial Treatment Phase and the Second Course Phase, pre-dose laboratory safety tests can be conducted up to 72 hours prior to dosing.

Laboratory test results must be reviewed by the investigator or qualified designee and found to be acceptable prior to administration of each dose of trial treatment. 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.

7.1.3.1.1 Serum/Urine β -hCG

All women who are being considered for participation in the trial, and who are not surgically sterilized or postmenopausal, must be tested for pregnancy within 72 hours of each cycle of trial treatment and 30 days post the last dose of study treatment. If a urine test is positive or not evaluable a serum test will be required. Subjects must be excluded/discontinued from the study in the event of a positive or borderline-positive test result.

The results of the pregnancy testing will not be recorded.

7.1.3.2 Central Laboratory Assessments

Sample collection timing, storage and shipment instructions for the Central Laboratory Assessments will be provided in the procedure manual.

7.1.3.2.1 Pharmacokinetic/Pharmacodynamic Evaluations

The accumulation of robust PK and ADA data has allowed for the adequate characterization the clinical pharmacology of pembrolizumab across indications. Therefore, upon approval of Amendment 7 each site is to stop the collection of PK and ADA samples for all subjects. Blood samples for PK and ADA collected prior to Amendment 7 may be stored. Analysis will be performed only if required.

7.1.3.2.2 Planned Genetic Analysis Sample Collection

Whole blood should be drawn prior to treatment at the Cycle 1 visit for planned analysis of the association between genetic variants in DNA and drug response. If there is either a documented law or regulation prohibiting collection, or if the IRB/IEC does not approve the collection of the sample for these purposes, then this sample will not be collected at that site. If the sample is collected, leftover extracted DNA will be stored for FBR if the subject signs the FBR consent. If the planned genetic analysis is not approved, but FBR is approved and consent is given, this sample will be collected for the purpose of FBR.

7.1.3.2.3 Plasma Sample for Circulating Tumor DNA Study

A plasma sample will be collected prior to treatment at the Cycle 1, Cycle 3, and discontinuation visits for planned analysis of circulating tumor DNA.

7.1.3.2.4 Blood Collections for Correlative Studies

Additional biomarker research to identify factors important for pembrolizumab therapy will also be pursued. Analysis will include, but may not be limited to, the subset of tests mentioned in Section 4.2.3.3.2.

If the subject signs the FBR consent, leftover DNA and RNA that would ordinarily be discarded at the end of the main study will be retained for FBR.

7.1.3.2.5 Tumor Tissue Collection

Submitting tumor tissue is optional for Cohort A, but required for Cohort B of this study. Newly obtained tissue (≤ 60 days prior to first dose of study treatment) from primary tumor is encouraged if it is accessible and not a contraindication due to subject safety concerns; otherwise, archival tumor tissue from primary tumor is accepted. Tumor tissue obtained by fine needle aspiration will be inadequate and not acceptable.

A tumor biopsy at treatment discontinuation is highly encouraged for all subjects in Cohort B. The Sponsor may use tumor tissue that is submitted for exploratory analyses to identify factors important for pembrolizumab therapy (see Section 4.2.3.3.2). Analyses will include, but may not be limited to, the subset of tests mentioned in Section 4.2.3.3.2.

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

7.1.3.3 Future Biomedical Research Sample Collection

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

- Leftover DNA for future research
- Leftover archival or newly obtained tumor tissue
- Leftover RNA testing

7.1.4 Efficacy Measurements

7.1.4.1 Tumor Imaging and RECIST Assessment

The process for image collection and transmission to the central imaging vendor can be found in the Site Imaging Manual (SIM). Tumor imaging should be performed by CT (preferred). Magnetic resonance imaging (MRI) should only be used when CT is contraindicated or for imaging in the brain, but the same imaging technique should be used in a subject throughout the trial. CT imaging is the more commonly used modality and is preferred for the majority of subjects. An MRI can be utilized if clinically appropriate. Imaging should include the chest, abdomen, and pelvis at baseline and all subsequent follow up time points; additional details are in the Site Imaging Manual (SIM).

Confirmation of measurable disease based on RECIST 1.1 will be completed by the central imaging vendor prior to subject allocation. All tumor imaging including scheduled and unscheduled images should be submitted to the central imaging vendor for evaluation and should be submitted in a timely fashion.

7.1.4.1.1 Initial Tumor Imaging

Initial tumor imaging at screening must be performed within 28 days prior to the date of allocation. The site study team must review screening images to confirm the subject has measurable disease per RECIST 1.1. The screening images must be submitted immediately to the central imaging vendor for confirmation of measurable disease per RECIST 1.1.

Tumor imaging performed as part of routine clinical management are acceptable for use as initial tumor imaging if they are of diagnostic quality, include all anatomy as described in the SIM, and performed within 28 days prior to the date of allocation.

7.1.4.1.2 Tumor Imaging During Trial

The first on study imaging assessment should be performed at 9 weeks (63 days \pm 7 days) from the date of allocation. Subsequent tumor imaging should be performed Q9W (63 days \pm 7 days) for the first year, and then Q12W (84 days \pm 7 days) thereafter, or more frequently if clinically indicated until PD. Imaging should not be delayed for delays in cycle starts or extension of pembrolizumab cycle intervals.

Per RECIST 1.1, partial or complete response should be confirmed by a repeat tumor imaging assessment 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 (i.e. 9 weeks for the first year, or 12 weeks thereafter), whichever is clinically indicated. Subjects will then return to regular scheduled imaging Q9W in the first year, Q12W thereafter, starting with the next scheduled imaging time point. Subjects who obtain a confirmation imaging assessment do not need to undergo scheduled tumor imaging if it is <4 weeks later and may wait until the next scheduled imaging time point.

Per irRECIST (Section 4.2.3.1.3.1), if radiologic imaging identifies PD, tumor assessment should be repeated \geq 4 weeks later in order to confirm PD with the option of continuing treatment while awaiting radiologic confirmation of progression. Subjects who obtain confirmation tumor imaging do not need to undergo scheduled tumor imaging if it is <4 weeks later and may wait until the next scheduled imaging time point if clinically stable.

Imaging should continue to be performed until disease progression by RECIST 1.1 (unless the site investigator chooses to manage the patient by irRECIST which would then be irPD), the start of new anti-cancer treatment, withdrawal of consent, death, or notification by the Sponsor, whichever occurs first. Disease progression may be confirmed at least 4 weeks after the first tumor imaging indicating PD disease in clinically stable subjects.

If the subject is clinically stable as per Section 4.2.3.1.3.1, it is the discretion of the PI to continue to treat and image the subject at least 4 weeks after the first tumor imaging indicating PD by RECIST 1.1 by the site. irRECIST would then be followed by the study site to determine if the follow-up tumor imaging confirms PD (irPD). Subjects who have unconfirmed PD may continue on treatment and follow the regular imaging schedule intervals until subsequent PD (irPD) is confirmed by the site per irRECIST provided they have met the conditions detailed in Section 4.2.3.1.3.1.

7.1.4.1.3 End of Treatment and Follow-up Tumor Imaging

In subjects who discontinue trial treatment, tumor imaging should be performed at the time of treatment discontinuation (± 4 -week window). If a previous scan was obtained within 4 weeks prior to the date of discontinuation, then a scan at treatment discontinuation isn't mandatory. In subjects who discontinue trial treatment due to documented disease progression (PD or irPD for subjects managed under irRECIST), this is the final required tumor imaging.

In subjects who discontinue trial treatment without documented disease progression, every effort should be made to continue monitoring their disease status by radiologic imaging using the same imaging schedule of Q9W for the first year, Q12W thereafter to monitor disease status until the start of new anti-cancer treatment, disease progression, death, or the end of the study, whichever occurs first.

7.1.4.1.4 Second Course Phase Tumor Imaging

A scan must be performed within 28 days prior to restarting treatment with pembrolizumab. Imaging should be submitted to the central imaging vendor for retrospective analysis.

The first on study imaging assessment should be performed at 12 weeks (84 days ± 7 days) after the restart of treatment. Subsequent tumor imaging should be performed Q12W (84 days ± 7 days) or more frequently if 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.

The Follow-up Visits should occur approximately every 12 weeks (after treatment discontinuation or completion of 17 cycles) to review AEs and post-treatment anti-cancer therapy status. However, to minimize subject burden, if the time window for this visit does not align with the timing for the continued tumor imaging (also occurring every Q12W), the first Follow -up Visit may be performed earlier than scheduled to align these two visits. The imaging schedule should not be adjusted. All subsequent Follow -up Visits should occur every Q12W weeks as scheduled.

In subjects who discontinue trial treatment, tumor imaging should be performed at the time of treatment discontinuation (± 4 -week window). If a previous scan was obtained within 4

weeks prior to the date of discontinuation, then a scan at treatment discontinuation isn't mandatory.

All tumor imaging (scheduled and unscheduled) should be submitted to the central imaging vendor.

7.1.4.1.5 RECIST 1.1 Assessment of Disease

RECIST 1.1 will be applied by the central imaging vendor as the primary measure for assessment of tumor response, date of disease progression, and as a basis for all protocol guidelines related to disease status (e.g., discontinuation of study therapy).

During the follow-up period, imaging will be repeated every Q9W (63 ± 7 days) for the first year, and Q12W (84 ± 7 days) thereafter from the date of allocation until PD. See the Trial Flow Charts - Section 6.0 and Section 7.1.6.3.2 for information about the Follow-up Visits.

7.1.4.1.5.1 Immune-related RECIST (irRECIST)

As noted above, if the site has identified PD by RECIST 1.1, subject management can shift to irRECIST if clinically stable and the study site may elect to continue treatment, repeat imaging ≥ 4 weeks later and assess tumor response or confirmed progression per irRECIST (see Section 4.2.3.1.3.1 and [Table 6](#)).

Table 6 Imaging and Treatment After First Radiologic Evidence of PD

	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 local site investigator's discretion while awaiting confirmatory tumor imaging by site	Repeat tumor imaging at ≥ 4 weeks to confirm PD per physician discretion only	Discontinue treatment
Repeat tumor imaging confirms PD	No additional tumor imaging required*	Discontinue treatment**	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 local site investigator's discretion	Continue regularly scheduled tumor imaging assessments	May restart study treatment if condition has improved and/or clinically stable per local site investigator's discretion

- In determining whether or not the tumor burden has increased or decreased, local study site investigators should consider all target lesions as well as non-target lesions as per irRECIST. Subjects that are deemed clinically unstable are not required to have repeat tumor imaging for confirmation.

- For a **clinically stable** subject with first radiologic evidence of PD (i.e., **unconfirmed progression of disease**), it is at the discretion of the site investigator to continue treating the subject with the assigned treatment per protocol until progression of disease is confirmed at least 28 days from the date of the tumor imaging first suggesting PD. If radiologic progression is confirmed by subsequent tumor imaging (irPD) then the subject will be discontinued from trial treatment. If radiologic progression is not confirmed, then the subject should resume or continue trial treatment and have their next tumor imaging according to the protocol schedule of Q9W (63 days \pm 7 days) for the first year, and then Q12W thereafter.
- ***NOTE:** If a subject has confirmed radiographic progression (i.e. 2 tumor imaging assessments at least 4 weeks apart demonstrating PD per irRECIST, but the subject is achieving a clinically meaningful benefit, an exception to continue treatment may be considered following consultation with the Sponsor. If treatment is continued beyond confirmed radiographic progression, tumor imaging assessments should continue to be performed Q9W for the first year, and then Q12W thereafter, and be submitted to the central imaging vendor.
- ****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 Q9W (63 days \pm 7 days) for the first year, and then Q12W thereafter, until; the start of new anti-cancer treatment, disease progression, death, or the end of the study, whichever occurs first.

irRECIST data will be collected in the clinical database.

7.1.5 Other Procedures

7.1.5.1 Withdrawal/Discontinuation

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

When a subject discontinues/withdraws from participation in the trial, all applicable activities scheduled for the end of treatment 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 attain a CR or complete 35 trial treatments (approximately 2 years) may discontinue treatment with the option of restarting treatment if they meet the criteria specified in Section 7.1.6.2.1. After discontinuing treatment following assessment of a CR or the 35 trial treatments, subjects should return to the site for a Safety Follow-up Visit (Section 7.1.6.3.1) and then proceed to the Follow-up Period of the study (Section 7.1.6.3.2).

7.1.5.1.1 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.

7.1.5.2 Blinding/Unblinding

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

7.1.5.3 Calibration of Equipment

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

Equipment requiring calibration for this trial includes:

- Laboratory equipment – as required for inclusion labs and trial assessments
- Imaging equipment – as required for study objectives

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

7.1.6 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.

7.1.6.1 Screening

Approximately 28 days prior to treatment allocation, potential subjects will be evaluated to determine that they fulfill the entry requirements as set forth in Section 5.0. Screening procedures may be repeated.

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 of trial treatment except for the following:

- Laboratory tests and ECOG PS are to be performed within 10 days prior to the first dose of trial treatment.
- For women of reproductive potential, a serum pregnancy test will be performed within 72 hours prior to the first dose of trial treatment. A urine test may be considered if serum test is not appropriate.

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 repeat screening test if performed within the specified time frame and the inclusion/exclusion criteria is met. Subjects who are rescreened will retain their original screening number.

7.1.6.2 Treatment Period

Visit requirements are outlined in the Trial Flow Chart (Section 6.0). Specific procedure-related details are provided above in the Trial Procedures (Section 7.0)

7.1.6.2.1 Second Course Phase (Retreatment)

Subjects who stop pembrolizumab with stable disease (SD) or better may be eligible for up to 17 additional trial treatments (approximately 1 year) if they progress after stopping study treatments. Retreatment with pembrolizumab is termed the Second Course Phase and is only available if the trial 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
 - Was treated with at least 8 trial treatments (approximately 6 months) 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 after 35 trial treatments (approximately 2 years) for reasons other than disease progression or intolerability
- **AND**
 - Experienced an investigator-determined 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 [Table 1](#).
 - 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.
 - Male subject 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.
 - 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.

Subjects who enter the Second Course Phase will be retreated at the same dose frequency as when they last received pembrolizumab. Pembrolizumab will be administered for up to an additional 17 trial treatments (approximately 1 year).

Visit requirements for the second course phase are outlined in the Second Course Phase Trial Flow Chart (Section 6.2).

7.1.6.3 Post-Treatment Visits

7.1.6.3.1 Safety Follow-up Visits

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.

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

7.1.6.3.2 Follow-up Visits

Subjects who discontinue trial treatment for reasons other than disease progression will move into the Follow-up Phase and should be assessed Q9W (63 days \pm 7 days) for the first year, and then Q12W (84 days \pm 7 days) thereafter, from the date of allocation by radiologic imaging to monitor disease status. Every effort should be made to collect information regarding disease status until the start of a new anti-cancer therapy, disease progression, death, the end of the study, or if the subject begins retreatment with study treatment.

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 7.1.6.2.1 will move from the Follow-up Phase to the Second Course Phase when they experience disease progression.

7.1.6.3.3 Survival Follow-up

Subjects, who experience confirmed disease progression (by site assessment) or start a new anti-cancer therapy, will move into the Survival Follow-Up phase and should be contacted by telephone approximately Q12W to assess for survival status until death, withdrawal of consent, or the end of the study, whichever occurs first.

7.1.6.4 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 participants who do not/will not have a scheduled study visit or study contact during the sponsor defined time period will be contacted for their survival status (excluding participants that have a 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 randomization/treatment allocation must be reported by the investigator if they cause the subject to be excluded from the trial, or are the result of a protocol-specified intervention, including but not limited to washout or discontinuation of usual therapy, diet, placebo treatment or a procedure. From the time of randomization/treatment allocation through 30 days following cessation of treatment, all adverse events must be reported by the investigator. Such events will be recorded at each examination on the Adverse Event case report forms/worksheets. The reporting timeframe for adverse events meeting any serious criteria is described in Section 7.2.3.1. The investigator will make every attempt to follow all subjects with non-serious adverse events for outcome.

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

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

In this trial, an overdose is any dose higher than ≥ 1000 mg (5 times the protocol defined dose) of pembrolizumab. No specific information is available on the treatment of over dose of pembrolizumab. In the event of overdose, study treatment should be discontinued and the

subject should be observed closely for signs of toxicity. Appropriate supportive treatment should be provided if clinically indicated.

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

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

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

7.2.2 Reporting of Pregnancy and Lactation to the Sponsor

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

Pregnancies and lactations that occur after the consent form is signed but before randomization/treatment allocation must be reported by the investigator if they cause the subject to be excluded from the trial, or are the result of a protocol-specified intervention, including but not limited to washout or discontinuation of usual therapy, diet, placebo treatment or a procedure. Pregnancies and lactations that occur from the time of randomization/treatment allocation 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 7](#) for additional details regarding each of the above criteria.

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

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

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

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

7.2.3.2 Events of Clinical Interest

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

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

For the time period beginning at randomization/treatment allocation through 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).

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

7.2.4 Evaluating Adverse Events

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

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

Table 7 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 mild 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 of 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	<p>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.)</p>
	Rechallenge	<p>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.</p>
	Consistency with Trial Treatment Profile	<p>Is the clinical/pathological presentation of the AE consistent with previous knowledge regarding the Sponsor's product or drug class pharmacology or toxicology?</p>
<p>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.</p>		
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.	<p>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.</p>	
No, there is not a reasonable possibility of Sponsor's product relationship	<p>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.)</p>	

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.

8.0 STATISTICAL ANALYSIS PLAN

This section outlines the statistical analysis strategy and procedures for the study. If, after the study has begun, but prior to any final database lock, changes 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 final database lock, will be documented in a supplemental SAP (sSAP) and referenced in the Clinical Study Report (CSR) for the study. Post hoc exploratory analyses will be clearly identified in the CSR.

8.1 Statistical Analysis Plan Summary

Key elements of the statistical analysis plan are summarized in [Table 8](#). The comprehensive plan is provided in Sections 8.2 through 8.12. The analyses described in section 8 will be applied to Cohort A and Cohort B separately.

Table 8 Key Elements of the Statistical Analysis Plan

Study Design Overview	A Phase II Study of Pembrolizumab in Previously Treated Subjects with Mismatched Repair Deficient or Microsatellite-High Colorectal Carcinoma
Treatment Assignment	This is an open-label study.
Analysis Populations	All Subjects as Treated (ASaT)
Primary Endpoint(s)	ORR based on RECIST 1.1 assessed by central imaging vendor
Statistical Methods for Key Efficacy Analyses	<p>The analyses described in this section will be applied separately for Cohort A and Cohort B.</p> <p>Cohort A: The primary hypothesis will be evaluated by testing the centrally reviewed RECIST 1.1 ORR greater than 15% using Exact method based on binomial distribution.</p> <p>Cohort B: 95% CI for ORR will be calculated using Exact method based on binomial distribution.</p>
Statistical Methods for Key Safety Analyses	Count and percentage of AE will be provided.
Interim Analyses	<p>For Cohort A, an interim analysis is planned. The interim analysis is summarized below; details are provided in Section 8.7.</p> <ul style="list-style-type: none"> • Interim Analysis <ul style="list-style-type: none"> ○ Timing: To be performed when the first 40 subjects have been followed up for at least 18 weeks ○ Purpose: Efficacy analysis for primary endpoint ORR • Final Analysis <ul style="list-style-type: none"> ○ Timing: To be performed when all patients have been followed up for at least 6 months. If data is not mature, additional analysis will be performed when all patients have had longer follow-up time or have discontinued study therapy. In that case, the originally planned final analysis will be considered supportive. <p>There is no interim analysis planned for Cohort B.</p>
Multiplicity	<p>Cohort A and Cohort B will be evaluated independently.</p> <p>No multiplicity adjustment in each cohort.</p>
Sample Size and Power	<p>The overall sample size is approximately 120.</p> <p>Cohort A: The planned sample size is 60 subjects.</p> <p>For the ORR per RECIST 1.1 assessed by central imaging vendor, the trial has 93% power to demonstrate that ORR of pembrolizumab is better than 15% at an overall one-sided 2.5% alpha level, if the underlying centrally reviewed RECIST 1.1 ORR of pembrolizumab is 35%.</p> <p>Cohort B: The planned sample size is 60 subjects.</p>

8.2 Responsibility for Analyses/In-House Blinding

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

This trial is being conducted as an open-label study, i.e., subjects, investigators, and SPONSOR personnel will be aware of subject treatment assignments after each subject is enrolled and treatment is assigned.

The Clinical Biostatistics department will generate the allocation schedule.

8.3 Hypotheses/Estimation

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

8.4 Analysis Endpoints

8.4.1 Efficacy Endpoints

8.4.1.1 Primary Efficacy Endpoint

- **Objective response rate (ORR) - RECIST 1.1 assessed by central imaging vendor**

Objective response rate is defined as the proportion of the subjects in the analysis population who have a complete response (CR) or partial response (PR). Responses are based upon blinded central imaging vendor per RECIST 1.1.

8.4.1.2 Secondary Efficacy Endpoints

- **Disease Control Rate (DCR) - RECIST 1.1 assessed by central imaging vendor**

Disease control rate (DCR) is 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.

- **Duration of Response (DOR) - RECIST 1.1 assessed by central imaging vendor**

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.

- **Progression-free Survival (PFS) - RECIST 1.1 assessed by central imaging vendor**

PFS is defined as the time from first day of study treatment to the first documented disease progression or death due to any cause, whichever occurs first.

- **Overall survival (OS)**

OS is defined as the time from first day of study treatment to death due to any cause. Subjects without documented death at the time of analysis will be censored at the date of the last follow-up.

8.4.2 Safety Endpoints

The primary safety objective of this trial is to characterize the safety and tolerability of pembrolizumab in subjects with MMR deficient or MSI-high CRC. The primary safety analysis will be based on subjects who experienced toxicities as defined by CTCAE, Version 4.0 criteria (Appendix 12.6). 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

8.5 Analysis Populations

8.5.1 Efficacy Analysis Populations

The All Subjects as Treated (ASaT) population will be used for the analysis of ORR, DCR, PFS, and OS. The ASaT population consists of all subjects who received at least one dose of study treatment.

The analysis population for DOR consists of responders.

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

8.5.2 Safety Analysis Populations

The ASaT population will be used for the analysis of safety data in this study. The ASaT population consists of all allocated subjects who received at least one dose of study treatment.

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

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

8.6 Statistical Methods

8.6.1 Statistical Methods for Efficacy Analyses

This section describes the statistical methods that address the primary and secondary objectives. Efficacy for each cohort will be analyzed separately.

The primary efficacy endpoint is ORR per RECIST 1.1 assessed by central imaging vendor. In Cohort A, the point estimate, 95% confidence interval, and p-value for testing the response rate is greater than 15% will be provided using exact binomial method proposed by Clopper and Pearson (1934) [38]. In Cohort B, the point estimate and 95% confidence interval will be provided using exact binomial method proposed by Clopper and Pearson (1934) [38]. Subjects in the primary analysis population (ASaT) without ORR data will be counted as non-responder.

For DCR, the point estimate, 95% confidence interval will be provided using exact binomial method proposed by Clopper and Pearson (1934) [38]. Subjects in the analysis population (ASaT) with missing DCR are considered as disease not under control.

For DOR, Kaplan-Meier (KM) curves and median estimates from the KM curves will be provided as appropriate.

Censoring rules for DOR are summarized in [Table 9](#).

Table 9 Censoring Rules for DOR

Situation	Date of Progression or Censoring	Outcome
Neither progression nor death, no new anti-cancer therapy initiated	Last adequate disease assessment	Censor (non-event)
Neither progression nor death, new anti-cancer therapy initiated	Last adequate disease assessment before new anti-cancer therapy initiated	Censor (non-event)
Death or progression after ≥ 2 consecutive missed adequate disease assessments	Last adequate disease assessment prior to ≥ 2 missed adequate disease assessments	Censor (non-event)
Death or progression after ≤ 1 missed adequate disease assessments	PD or death	End of response (Event)
Subjects are considered to have an ongoing response if censored, alive, have not progressed, have not started a new anti-cancer therapy and have not been determined to be lost to follow-up.		

For PFS and OS endpoints, Kaplan-Meier (KM) curves and median estimates from the KM curves will be provided as appropriate.

The efficacy analysis is summarized in [Table 10](#). The efficacy analyses will be applied to Cohort A and Cohort B separately.

Table 10 Analysis Strategy for Efficacy Variables

Endpoint/Variable (Description, Time Point)	Statistical Method	Analysis Population	Missing Data Approach
Primary Endpoint and Hypothesis			
ORR (Cohort A) <ul style="list-style-type: none">RECIST 1.1, Central assessment Hypotheses: ORR per RECIST 1.1 by central imaging vendor is greater than assumed historical control (15%).	Exact method based on binomial distribution	ASaT in Cohort A	Subjects with missing data are considered non-responders
ORR (Cohort B) <ul style="list-style-type: none">RECIST 1.1, Central assessment		ASaT in Cohort B	
Secondary Endpoints			
DCR <ul style="list-style-type: none">RECIST 1.1, Central assessment	Exact method based on binomial distribution	ASaT in below populations: Cohort A Cohort B	Subjects with missing data are considered as disease not under control
DOR <ul style="list-style-type: none">RECIST 1.1, Central assessment	Summary statistics using Kaplan-Meier method	All responders in below populations: Cohort A Cohort B	Non-responders are excluded from analysis
PFS <ul style="list-style-type: none">RECIST 1.1, Central assessment	Summary statistics using Kaplan-Meier method	ASaT in below populations: Cohort A Cohort B	Censored at last assessment
OS	Summary statistics using Kaplan-Meier method	ASaT in below populations: Cohort A Cohort B	Censored at last known alive date

8.6.2 Statistical Methods for Safety Analyses

Safety and tolerability will be assessed by clinical review of all relevant parameters including adverse experiences (AEs), laboratory tests, and vital signs for each cohort separately. Count and percentage of AE will be provided.

8.6.3 Summaries of Baseline Characteristics, Demographics, and Other Analyses

The number and percentage of subjects screened, randomized, the primary reasons for screening failure, and the primary reason for discontinuation will be displayed. Demographic variables (e.g., age, gender), baseline characteristics, primary and secondary diagnoses, and

prior and concomitant therapies will be summarized either by descriptive statistics or categorical tables for all enrolled subjects.

8.7 Interim Analyses

For Cohort A, there is one interim analysis planned in this study. There is no interim analysis planned for Cohort B. In Cohort A, final analysis is to be performed 6 months after the last subject is enrolled. Subjects will continue to be followed until overall trial ends. If data is not mature at the pre-planned final analysis after all subjects have been followed up for 6 months or have discontinued study therapy, additional analyses will be performed after all patients have had longer follow-up time or have discontinued study therapy. The originally planned final analysis will then be considered as a supportive analysis.

There is one planned interim analysis in Cohort A. The purpose of the interim analysis is efficacy analysis for primary endpoint ORR in Cohort A. It was originally planned to be performed 18 weeks after the 40th subject enrolled. However, due to the rapid enrollment of the remaining subjects in Cohort A, it was decided to be conducted after all 61 subjects enrolled in Cohort A had been followed up for at least 18 weeks. With this change, the group sequential approach based on the first 40 subjects as originally planned is no longer applicable.

8.8 Multiplicity

Cohort A and Cohort B will be evaluated independently. No multiplicity adjustment in each cohort.

8.9 Sample Size and Power Calculations

Efficacy and safety for each cohort will be analyzed separately.

In this study, approximately 60 subjects for each cohort will be enrolled.

Cohort A

With a sample size of 60, the study has 93% power to reject the null hypothesis of ORR=15% with a one-sided type I error rate of 2.5% if the true ORR is 35%. The historical response rate is less than 5% in CORRECT study [39].

At alpha level of 2.5% using exact method based on binomial distribution, the boundary to demonstrate statistical success corresponds to an approximate observed ORR $\geq 26.7\%$ (16/60) at $\alpha = 2.5\%$ (one-sided).

Table 11 shows the two-sided 95% confidence interval of ORR with 60 subjects for different observed response rates.

Table 11 Two-sided 95% Confidence Interval of ORR with 60 Subjects

Number of Observed Responders	ORR Estimates	95% CI of ORR (%)
15	25%	(14.7, 37.9)
16	26.7%	(16.1, 39.7)
17	28.3%	(17.5, 41.4)
18	30%	(18.8, 43.2)

Cohort B

The historical response rate is about 20% [40] [41] [42] for subjects with locally advanced unresectable or metastatic MMR deficient or MSI high CRC and have been previously treated with at least one line of systemic standard of care therapy.

With a sample size of 60, if there are at least 19 responders observed, the lower bound of the 95% confidence interval for ORR will be above 20%.

Table 12 shows the two-sided 95% confidence interval of ORR with 60 subjects for different observed response rates.

Table 12 Two-sided 95% Confidence Interval of ORR with 60 Subjects

Number of Observed Responders	ORR Estimates	95% CI of ORR (%)
18	30%	(18.8, 43.2)
19	31.7%	(20.3, 45.0)
20	33.3%	(21.7, 46.7)
21	35%	(23.1, 48.4)

8.10 Subgroup Analyses and Effect of Baseline Factors

The estimate of the treatment effect for the primary endpoint will be estimated and plotted within each category of the following classification variables:

- Age category (≤ 65 vs. > 65 years)
- Sex (Female vs. Male)
- Race (white vs. non-white)

The consistency of the treatment effect will be assessed descriptively via summary statistics by category for the classification variables listed above.

8.11 Compliance (Medication Adherence)

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

8.12 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.

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 13](#).

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 13 Clinical Supplies

Product Name & Potency	Dosage Form
MK-3475, 25 mg/mL 4 mL	Injection

All other supplies not indicated in [Table 13](#) above will be provided centrally by the Sponsor or locally by the trial site, subsidiary or designee, depending on local country operational or regulatory requirements.

For any commercially available product that is provided by the trial site, subsidiary or designee every attempt will be made to source these supplies from a single lot/batch number. The trial site is responsible to record the lot number, manufacturer and expiry date for any locally purchased product as per local guidelines unless otherwise instructed by the Sponsor.

9.2 Packaging and Labeling Information

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

Subjects will receive open label vials for every 3 week dosing. No kitting is required.

9.3 Clinical Supplies Disclosure

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

9.4 Storage and Handling Requirements

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

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

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

9.5 Discard/Destruction/Returns and Reconciliation

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

discard and destruction is appropriate, the investigator is responsible for ensuring that a local discard/destruction procedure is documented.

9.6 Standard Policies

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

10.0 ADMINISTRATIVE AND REGULATORY DETAILS

10.1 Confidentiality

10.1.1 Confidentiality of Data

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

10.1.2 Confidentiality of Subject Records

By signing this protocol, the investigator agrees that the Sponsor (or Sponsor representative), IRB/ERC, or regulatory authority representatives may consult and/or copy trial documents in order to verify worksheet/case report form data. By signing the consent form, the subject agrees to this process. If trial documents will be photocopied during the process of verifying worksheet/case report form information, the subject will be identified by unique code only; full names/initials will be masked prior to transmission to the Sponsor.

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

10.1.3 Confidentiality of Investigator Information

By signing this protocol, the investigator recognizes that certain personal identifying information with respect to the investigator, and all subinvestigators and trial site personnel,

may be used and disclosed for trial management purposes, as part of a regulatory submissions, and as required by law. This information may include:

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

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

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

10.1.4 Confidentiality of IRB/IEC Information

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

10.2 Compliance with Financial Disclosure Requirements

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

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

10.3 Compliance with Law, Audit and Debarment

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

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

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

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

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

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

The investigator must maintain copies of all documentation and records relating to the conduct of the trial in compliance with all applicable legal and regulatory requirements. This documentation includes, but is not limited to, the protocol, worksheets/case report forms, advertising for subject participation, adverse event reports, subject source data, correspondence with regulatory authorities and IRBs/ERCs, consent forms, investigator's curricula vitae, monitor visit logs, laboratory reference ranges, laboratory certification or quality control procedures and laboratory director curriculum vitae. By signing this protocol, the investigator agrees that documentation shall be retained until at least 2 years after the last approval of a marketing application in an ICH region or until there are no pending or contemplated marketing applications in an ICH region or until at least 2 years have elapsed

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

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

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

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

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

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

10.4 Compliance with Trial Registration and Results Posting Requirements

Under the terms of the Food and Drug Administration Amendments Act (FDAAA) of 2007 and the European Medicines Agency (EMA) clinical trial Directive 2001/20/EC, the Sponsor

of the trial is solely responsible for determining whether the trial and its results are subject to the requirements for submission to <http://www.clinicaltrials.gov>, www.clinicaltrialsregister.eu or other local registries. Merck, as Sponsor of this trial, will review this protocol and submit the information necessary to fulfill these requirements. Merck entries are not limited to FDAAA or the EMA clinical trial directive mandated trials. Information posted will allow subjects to identify potentially appropriate trials for their disease conditions and pursue participation by calling a central contact number for further information on appropriate trial locations and trial site contact information.

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

10.5 Quality Management System

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

10.6 Data Management

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

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

10.7 Publications

This trial is intended for publication, even if terminated prematurely. Publication may include any or all of the following: posting of a synopsis online, abstract and/or presentation at a scientific conference, or publication of a full manuscript. The Sponsor will work with the authors to submit a manuscript describing trial results within 12 months after the last data become available, which may take up to several months after the last subject visit in some cases such as vaccine trials. However, manuscript submission timelines may be extended on OTC trials. For trials intended for pediatric-related regulatory filings, the investigator agrees to delay publication of the trial results until the Sponsor notifies the investigator that all relevant regulatory authority decisions on the trial drug have been made with regard to pediatric-related regulatory filings. Merck will post a synopsis of trial results for approved

products on www.clinicaltrials.gov by 12 months after the last subject's last visit for the primary outcome, 12 months after the decision to discontinue development, or product marketing (dispensed, administered, delivered or promoted), whichever is later.

These timelines may be extended for products that are not yet marketed, if additional time is needed for analysis, to protect intellectual property, or to comply with confidentiality agreements with other parties. Authors of the primary results manuscript will be provided the complete results from the Clinical Study Report, subject to the confidentiality agreement. When a manuscript is submitted to a biomedical journal, the Sponsor's policy is to also include the protocol and statistical analysis plan to facilitate the peer and editorial review of the manuscript. If the manuscript is subsequently accepted for publication, the Sponsor will allow the journal, if it so desires, to post on its website the key sections of the protocol that are relevant to evaluating the trial, specifically those sections describing the trial objectives and hypotheses, the subject inclusion and exclusion criteria, the trial design and procedures, the efficacy and safety measures, the statistical analysis plan, and any amendments relating to those sections. The Sponsor reserves the right to redact proprietary information.

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

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

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

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12.0 APPENDICES

12.1 Merck Code of Conduct for Clinical Trials

Merck*
Code of Conduct for Clinical Trials

I. Introduction

A. Purpose

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

B. Scope

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

II. Scientific Issues

A. Trial Conduct

1. Trial Design

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

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

2. Site Selection

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

3. Site Monitoring/Scientific Integrity

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

B. Publication and Authorship

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

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

III. Subject Protection

A. IRB/ERC review

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

B. Safety

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

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

C. Confidentiality

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

D. Genomic Research

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

IV. Financial Considerations

A. Payments to Investigators

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

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

B. Clinical Research Funding

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

C. Funding for Travel and Other Requests

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

V. Investigator Commitment

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

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

12.2 Collection and Management of Specimens for Future Biomedical Research

1. Definitions

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

2. Scope of Future Biomedical Research

The specimens collected in this trial as outlined in Section 7.1.3.3 – Future Biomedical Research Sample Collection will be used to study various causes for how subjects may respond to a drug/vaccine. Future biomedical research specimen(s) will be stored to provide a resource for future trials conducted by the Sponsor focused on the study of biomarkers responsible for how a drug/vaccine enters and is removed by the body, how a drug/vaccine works, other pathways a drug/vaccine may interact with, or other aspects of disease. The specimen(s) may be used for future assay development and/or drug/vaccine development.

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

3. Summary of Procedures for Future Biomedical Research

a. Subjects for Enrollment

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

b. Informed Consent

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

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

c. **eCRF Documentation for Future Biomedical Research Specimens**

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

d. **Future Biomedical Research Specimen Collections**

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

4. Confidential Subject Information for Future Biomedical Research

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

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

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

5. Biorepository Specimen Usage

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

6. Withdrawal From Future Biomedical Research

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

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

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

7. Retention of Specimens

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

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

8. Data Security

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

9. Reporting of Future Biomedical Research Data to Subjects

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

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

with clinical significance, the Sponsor will endeavor to make such results available through appropriate mechanisms (e.g., scientific publications and/or presentations). Subjects will not be identified by name in any published reports about this study or in any other scientific publication or presentation.

10. Future Biomedical Research Study Population

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

11. Risks Versus Benefits of Future Biomedical Research

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

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

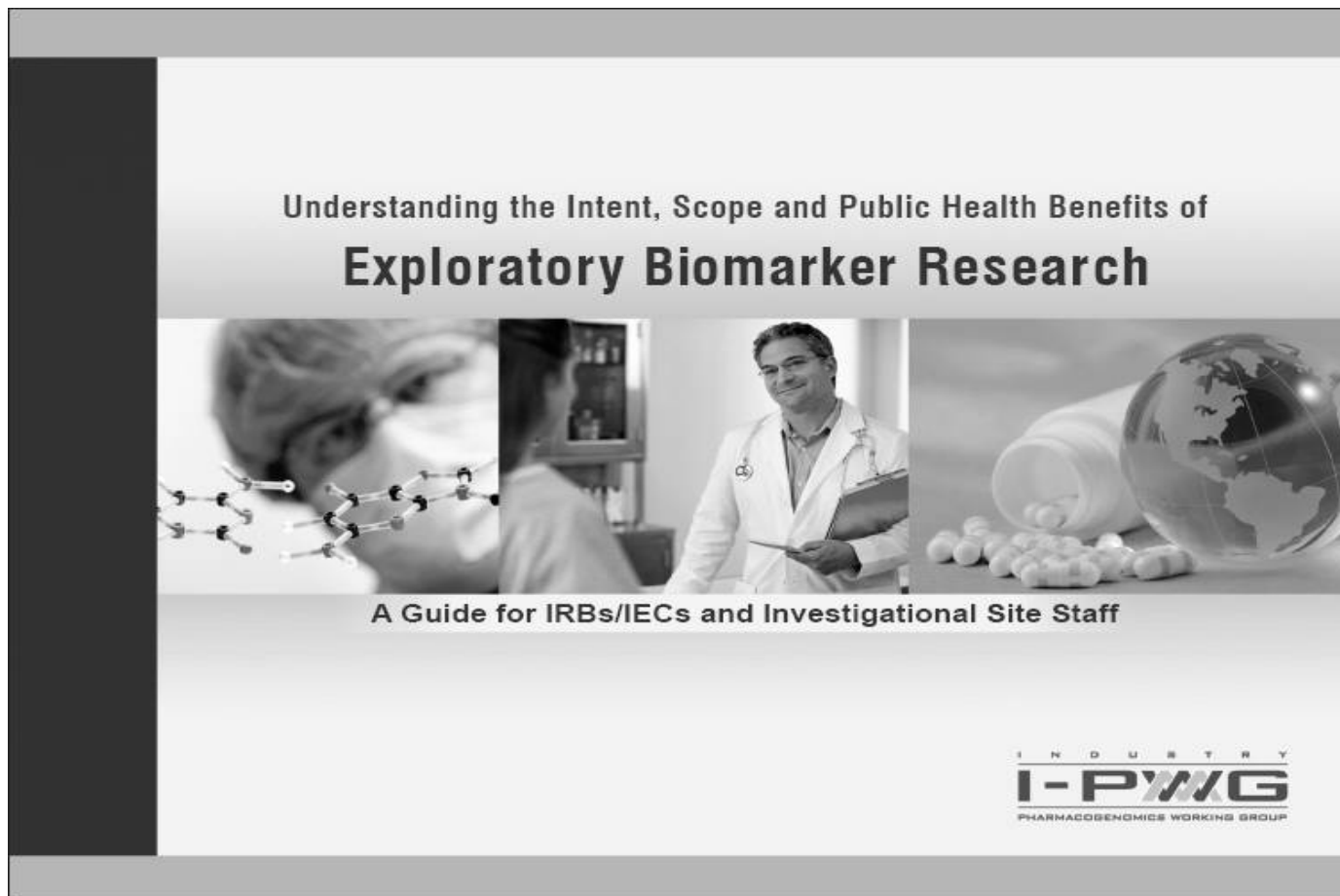
12. Questions

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

13. References

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

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



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

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

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

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

Biomarker research, including research on pharmacogenomic biomarkers, is a tool used to improve the development of pharmaceuticals and understanding of disease. It involves the analysis of biomolecules (such as DNA, RNA, proteins, and lipids), or other measurements (such as blood pressure or brain images) in relation to clinical endpoints of interest. Biomarker research can be influential across all phases of drug development, from drug discovery and preclinical evaluations to clinical development and post-marketing studies. This brochure focuses on biomarker research involving analysis of biomolecules from biological samples collected in clinical trials. Please refer to I-PWG Pharmacogenomic Informational Brochure² and ICH Guidance E15³ 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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I-PWG
INDUSTRY PHARMACOGENOMICS WORKING GROUP

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.

5. Biomarkers are Already a Reality in Health Care

A number of drugs now have biomarker information included in their labels.²⁶ 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 (Erbix®) 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*57:01* 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 sur-

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

Prognostic biomarkers – Biomarkers can also help predict clinical outcomes independent of any treatment modality. Examples of prognostic biomarkers used in clinical practice include: i) CellSearch™ 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

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.²⁹⁻³¹

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

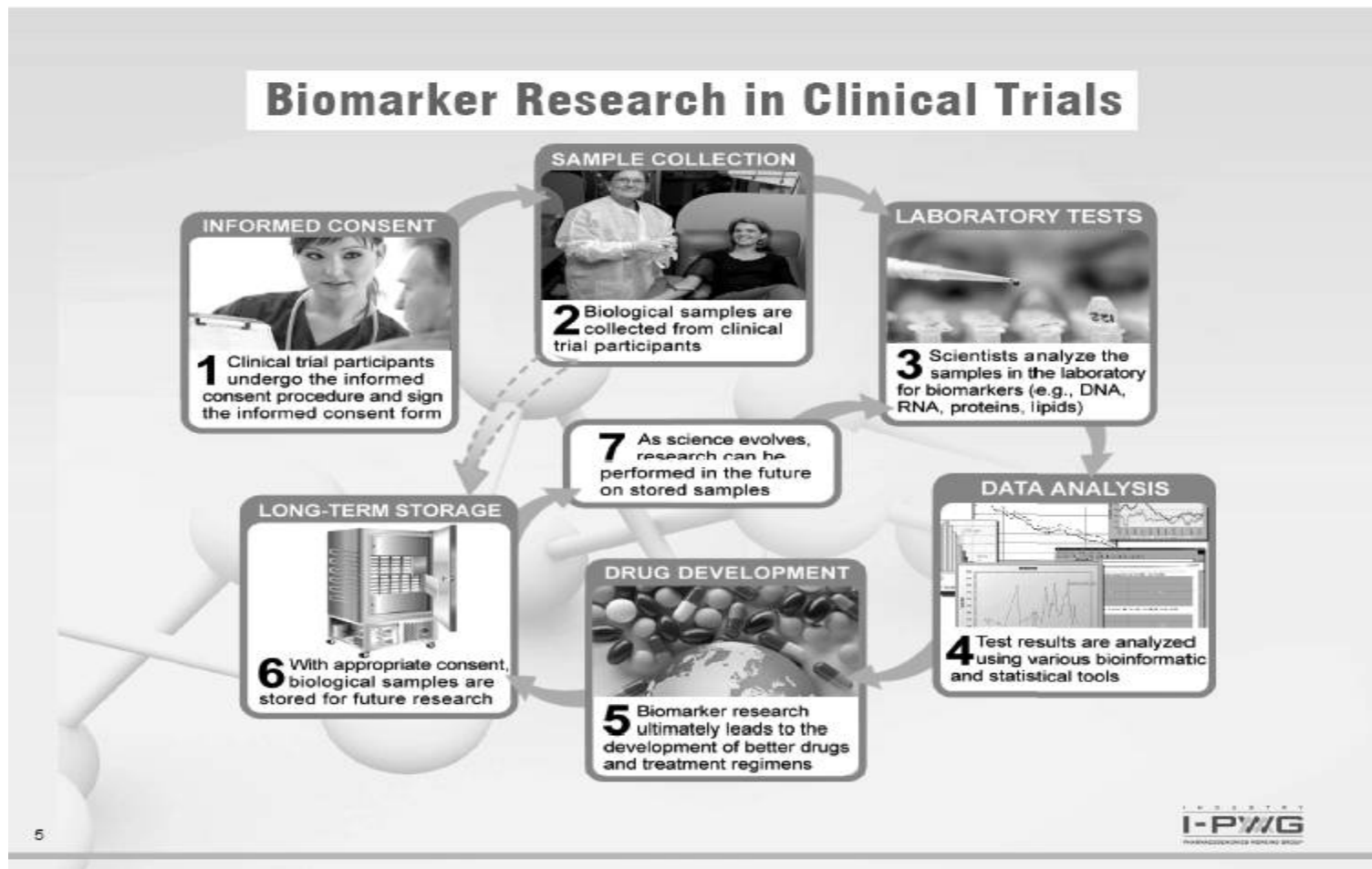
While it can be a challenge to specify the details of the research that will be conducted in the future, the I-PWG holds the view that future use of samples collected for exploratory biomarker research in clinical trials should be permissible when i) the research is scientifically sound, ii) participants 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:³⁰

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.



8. Biomarker Sample Collection in Different Countries

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

9. Return of Research Results to Study Participants

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

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

Renegar *et al.* 2006 and Article 29 Data Protection Working Party (an advisory committee to the European Commission on the European Data Protection Directive) have addressed these considerations in detail in relation to pharmacogenomic research data and provided a list of documents addressing the general issue of return of research results.³⁴⁻³⁵

10. Benefits and Risks Associated with Biomarker Research

Benefits

While it may not always directly benefit the study participant who is providing the samples, biomarker research can improve overall understanding of disease and treatment of future patients receiving therapies developed from such research. Patients are now benefiting from retrospective biomarker research conducted on samples collected from clinical trials and stored for exploratory research. One example is the recent label update to the EGFR antibody drugs cetuximab (Erbix[®]) 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

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-



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

14. Contributing authors

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12.4 Response Evaluation Criteria in Solid Tumors

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

*As published in the European Journal of Cancer [43].

12.5 ECOG Performance Status

The ECOG PS, developed by the ECOG, Robert L. Comis, MD, Group Chair, will be used.

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

12.6 Common Terminology Criteria for Adverse Events v4.0

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

12.7 List of Abbreviations

Abbreviation/Term	Definition
1L	First Line
5-FU	5-fluorouracil
AE	Adverse Event
ADA	Anti-Drug Antibodies
ALT	Alanine Aminotransferase
ANC	Absolute Neutrophil Count
aPTT	Activated Partial Thromboplastin Time
ASaT	All Subjects as Treated
ASCO	American Society of Clinical Oncology
AST	Aspartate Aminotransferase
AUC	Area Under the Curve
BCG	Bacillus Calmette-Guerin
β-hCG	Beta Human Chorionic Gonadotropin
CBC	Complete Blood Count
CI	Confidence Interval
CIMP	CPG Island Methylator Phenotype
CIN	Chromosomal Instability
CNS	Central Nervous System
CR	Complete Response
CRC	Colorectal Carcinoma
CrCl	Calculated Creatinine Clearance
CRF	Case Report Form
CSR	Clinical Study Report
CT	Computed Tomography
CTCAE	Common Toxicity Criteria for Adverse Events
CTLA-4	Cytotoxic T-Lymphocyte-Associated Antigen-4
DCR	Disease Control Rate
dMMR	Mismatch Repair Deficient
DNA	Deoxyribonucleic acid
DOR	Duration of Response
ECI	Events of Clinical Interest
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Form
eDMC	External Data Monitoring Committee
EGFR	Epidermal Growth Factor Regulator
ELISA	Enzyme-linked Immunosorbent assay
ERC	Ethics Review Committee
ESMO	European Society for Medical Oncology
FBR	Future Biomedical Research
FDA	Food and Drug Administration

Abbreviation/Term	Definition
FDAAA	Food and Drug Administration Amendments Act
FIH	First in Human
FSH	Follicle Stimulating Hormone
GCP	Good Clinical Practice
GFR	Glomerular Filtration Rate
HBsAg	Hepatitis B surface Antigen
HCV	Hepatitis C Virus
HIV	Human Immunodeficiency Virus
HR	Hazard Ratio
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
Ig	Immunoglobulin
IgV	Immunoglobulin Variable-Type
IHC	Immunohistochemistry
INR	International Normalized Ratio
irAEs	Immune-related Adverse Events
irRECIST	Immune related RECIST (Modification of RECIST 1.1)
irRC	Immune related Response Criteria
IRB	Institutional Review Board
ITIM	Immunoreceptor Tyrosine-based Inhibition Motif
ITSM	Immunoreceptor Tyrosine-based Switch Motif
IUD	Intrauterine Device
IUS	Intrauterine Hormone-releasing System
IV	Intravenous
IVRS	Interactive Voice Response System
IWRS	Integrated Web Response System
KM	Kaplan-Meier
kg	Kilogram
LDH	Lactate Dehydrogenase
mAb	Monoclonal Antibody
mCRC	Metastatic Colorectal Carcinoma
mcL	Microliters
mg	Milligram
mg/kg	Milligram per Kilogram
mL	milliliter
MMR	Mismatched Repair
MRI	Magnetic Resonance Imaging
mRNA	Messenger Ribonucleic Acid
MSD	Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc.
MSI-H	Microsatellite Instability High
NA or N/A	Not Applicable

Abbreviation/Term	Definition
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
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 cell death 1
PD-2	Programmed cell death 2
PFS	Progression Free Survival
PIN	Personal Identification Number
PK	Pharmacokinetic
PKCθ	Protein Kinase C-theta
PR	Partial Response
PT	Prothrombin Time
PS	Performance Status
Q3W	Every 3 Weeks
Q9W	Every 9 Weeks
Q12W	Every 12 Weeks
RECIST	Response Evaluation Criteria in Solid Tumors
RNA	Ribonucleic Acid
RR	Response Rate
SAE	Serious Adverse Events
SAP	Statistical Analysis Plan
SGOT	Serum Glutamic Oxaloacetic Transaminase
SGPT	Serum Glutamic Pyruvic Transaminase
SIM	Site Imaging Manual
SOP	Standard Operating Procedures
sSAP	Supplemental Statistical Analysis Plan
Tregs	Regulatory T cells
TSH	Thyroid Stimulating Hormone
ULN	Upper Limit of Normal
VEGF	Vascular Endothelial Growth Factor
ZAP70	Zeta-Chain Associated Protein Kinase

12.8 Country-specific Requirements

12.8.1 France-specific Requirements

France has country-specific requirements for the protocol which are summarized below:

Section 5.1.1 – Subject Inclusion Criteria

Subjects participating in the study in France may not be enrolled into Cohort B. They must meet the criteria for Cohort A only for enrollment.

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	

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

A second cohort of 60 subjects was added to evaluate pembrolizumab 200 mg 3QW in subjects with colorectal cancer (CRC) who have undergone 1 line of systemic treatment (fluoropyrimidine + oxaliplatin or fluoropyrimidine + irinotecan +/- anti-VEGF/EGFR monoclonal antibody). The first cohort will be designated Cohort A, the second, Cohort B.

Details and clarifications for Cohort A and B are given in the following sections: Analysis summary, details and sample size calculation for Cohort B (Section 3.1, 3.6.1, 3.6.2, 3.8, 3.9), Secondary Efficacy Endpoints (Sections 3.4.1), definition of duration of response and censoring rules (Sections 3.6.1), Interim analysis (Section 3.7).

3. ANALYTICAL AND METHODOLOGICAL DETAILS

3.1 Statistical Analysis Plan Summary

Key elements of the statistical analysis plan are summarized in Table 1. The comprehensive plan is provided in Sections 3.2 through 3.12. The analyses described in section 3 will be applied to Cohort A and Cohort B separately.

Table 1 Key Elements of the Statistical Analysis Plan

Study Design Overview	A Phase II Study of Pembrolizumab in Previously Treated Subjects with Mismatched Repair Deficient or Microsatellite-High Colorectal Carcinoma
Treatment Assignment	This is an open-label study.
Analysis Populations	All Subjects as Treated (ASaT)
Primary Endpoint(s)	ORR based on RECIST 1.1 assessed by central imaging vendor
Statistical Methods for Key Efficacy Analyses	<p>The analyses described in this section will be applied separately for Cohort A and Cohort B.</p> <p>Cohort A: The primary hypothesis will be evaluated by testing the centrally reviewed RECIST 1.1 ORR greater than 15% using Exact method based on binomial distribution.</p> <p>Cohort B: 95% CI for ORR will be calculated using Exact method based on binomial distribution.</p>
Statistical Methods for Key Safety Analyses	Count and percentage of AE will be provided.
Interim Analyses	<p>For Cohort A, an interim analysis is planned in this study. The interim analysis is summarized below; Details are provided in Section 3.7.</p> <ul style="list-style-type: none"> • Interim Analysis <ul style="list-style-type: none"> ○ [REDACTED] ○ Purpose: Efficacy analysis for primary endpoint ORR • Final Analysis <ul style="list-style-type: none"> ○ [REDACTED] • There is no interim analysis planned for Cohort B.
Multiplicity	For Cohort A, the overall type I error is controlled at 2.5% (one-sided) by group sequential approach for interim analysis and final analysis. For Cohort B, no multiplicity adjustment will be applied.
Sample Size and Power	<p>The overall sample size is approximately 120.</p> <p>Cohort A: The planned sample size is 60 subjects.</p> <p>For the ORR per RECIST 1.1 assessed by central imaging vendor, the trial has 93% power to demonstrate that ORR of pembrolizumab is better than 15% at an overall one-sided 2.5% alpha-level, if the underlying centrally reviewed RECIST 1.1 ORR of pembrolizumab is 35%.</p> <p>Cohort B: The planned sample size is 60 subjects.</p>

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 study, i.e., subjects, investigators, and SPONSOR personnel will be aware of subject treatment assignments after each subject is enrolled and treatment is assigned.

The Clinical Biostatistics department will generate the allocation schedule.

3.3 Hypotheses/Estimation

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

3.4 Analysis Endpoints

3.4.1 Efficacy Endpoints

3.4.1.1 Primary Efficacy Endpoint

- **Overall response rate (ORR) - RECIST 1.1 assessed by central imaging vendor**

Overall response rate is defined as the proportion of the subjects in the analysis population who have a complete response (CR) or partial response (PR). Responses are based upon blinded central imaging vendor per RECIST 1.1.

3.4.1.2 Secondary Efficacy Endpoints

- **Disease Control Rate (DCR) - RECIST 1.1 assessed by central imaging vendor**

Disease control rate (DCR) is 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.

- **Duration of Response (DOR) - RECIST 1.1 assessed by central imaging vendor**

For subjects who demonstrated CR or PR, response duration is defined as the time from the date of first response (CR or PR) until the date of disease progression or death.

- **Progression-free Survival (PFS) - RECIST 1.1 assessed by central imaging vendor**

PFS is defined as the time from first day of study treatment to the first documented disease progression or death due to any cause, whichever occurs first.

- **Overall survival (OS)**

OS is defined as the time from first day of study treatment to death due to any cause. Subjects without documented death at the time of the final analysis will be censored at the date of the last follow-up.

3.4.2 Safety Endpoints

The primary safety objective of this trial is to characterize the safety and tolerability of pembrolizumab in subjects MMR deficient or MSI-high CRC. The primary safety analysis will be based on subjects who experienced toxicities as defined by CTCAE, Version 4.0 criteria (Protocol Appendix 12.6). 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 Protocol Section 7.2.3.2.

3.5 Analysis Populations

3.5.1 Efficacy Analysis Populations

The All Subjects as Treated (ASaT) population will be used for the analysis of ORR, DCR, PFS, and OS. The ASaT population consists of all subjects who received at least one dose of study treatment.

The analysis population for DOR consists of responders.

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

3.5.2 Safety Analysis Populations

The All Subjects as Treated (ASaT) population will be used for the analysis of safety data in this study. The ASaT population consists of all allocated subjects who received at least one dose of study treatment.

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

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

3.6 Statistical Methods

3.6.1 Statistical Methods for Efficacy Analyses

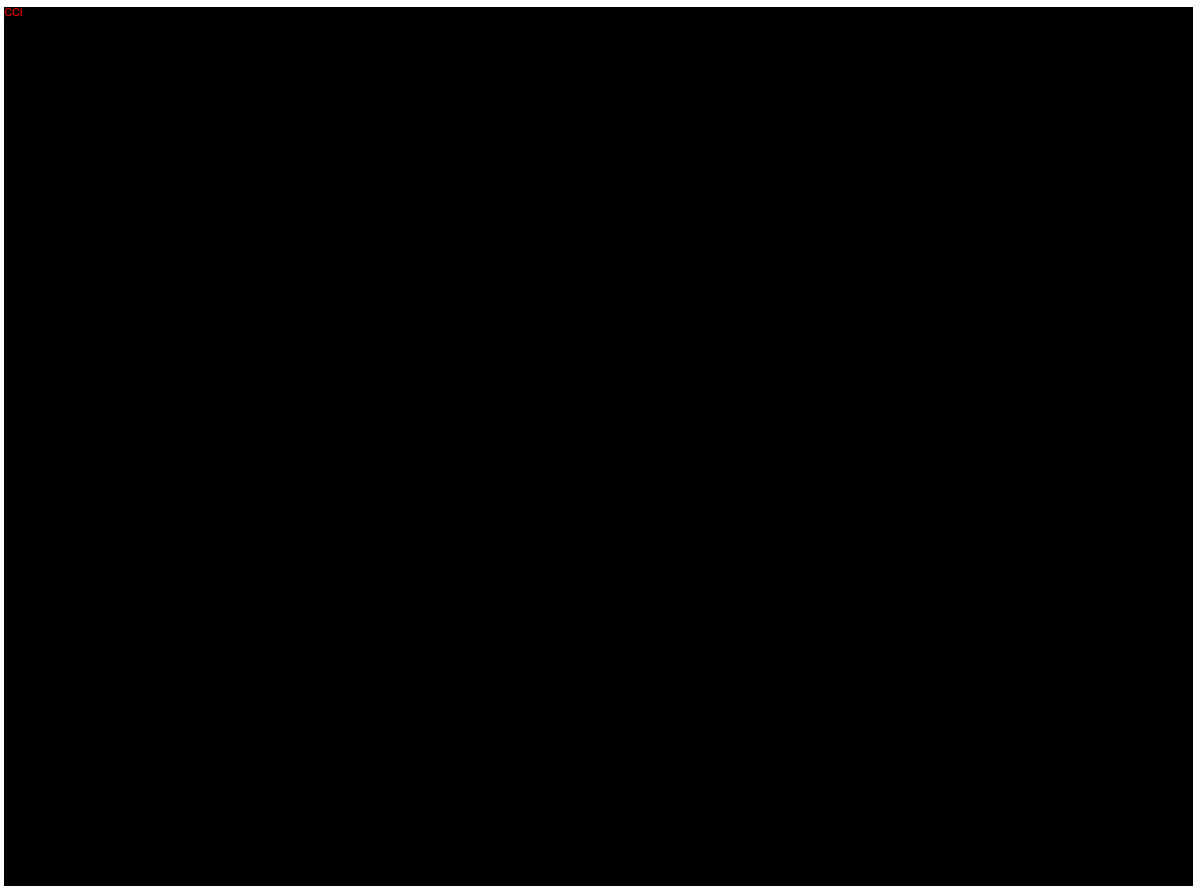
This section describes the statistical methods that address the primary and secondary objectives.

The primary efficacy endpoint is ORR per RECIST 1.1 assessed by central imaging vendor. In Cohort A, the point estimate, 95% confidence interval, and p-value for testing the response rate is greater than 15% will be provided using exact binomial method proposed by Clopper and Pearson (1934) [1]. In Cohort B, the point estimate and 95% confidence interval will be provided using exact binomial method proposed by Clopper and Pearson (1934) [1]. Subjects in the primary analysis population (ASaT) without ORR data will be counted as non-responder.

For DCR, the point estimate, 95% confidence interval will be provided using exact binomial method proposed by Clopper and Pearson (1934) [1]. Subjects in the analysis population (ASaT) with missing DCR are considered as disease not under control.

For DOR, Kaplan-Meier (KM) curves and median estimates from the KM curves will be provided as appropriate.

Censoring rules for DOR are summarized in [Table 2](#).



For PFS and OS endpoints, Kaplan-Meier (KM) curves and median estimates from the KM curves will be provided as appropriate.

The efficacy analysis is summarized in [Table 3](#) . The efficacy analyses will be applied to Cohort A and Cohort B separately.



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. Count and percentage of AE will be provided.

3.6.3 Summaries of Baseline Characteristics, Demographics, and Other Analyses

The number and percentage of subjects screened, randomized, the primary reasons for screening failure, and the primary reason for discontinuation will be displayed. Demographic variables (e.g., age, gender), baseline characteristics, primary and

secondary diagnoses, and prior and concomitant therapies will be summarized either by descriptive statistics or categorical tables for all enrolled subjects.

3.7 Interim Analyses

For Cohort A, there is one interim analysis planned in this study. There is no interim analysis planned for Cohort B. In each cohort separately, final analysis is to be performed 6 months after the last subject is enrolled. Subjects will continue to be followed after the final analysis until overall trial ends. The purpose of the interim analysis is efficacy analysis for primary endpoint ORR [REDACTED]

[REDACTED] Results will be reviewed by study team.

The O'Brien-Fleming alpha spending function will be used to control the Type-I error rate. [REDACTED]

[REDACTED]

[REDACTED]

3.8 Multiplicity

For Cohort A, the overall type I error is controlled at 2.5% (one-sided) by group sequential approach for interim analysis and final analysis. Refer to Section 3.7 for group sequential approach.

For Cohort B, no multiplicity adjustment will be applied.

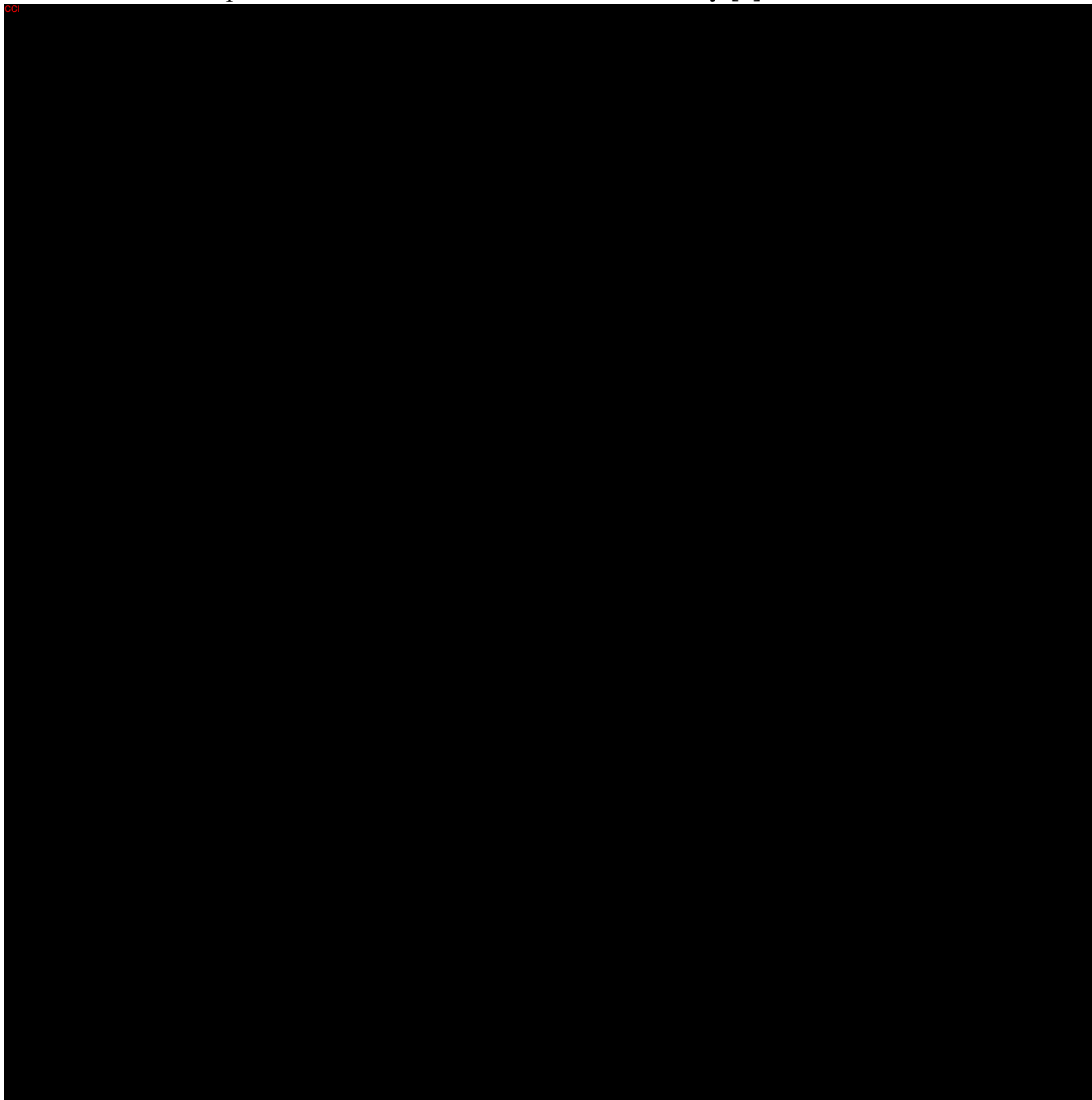
3.9 Sample Size and Power Calculations

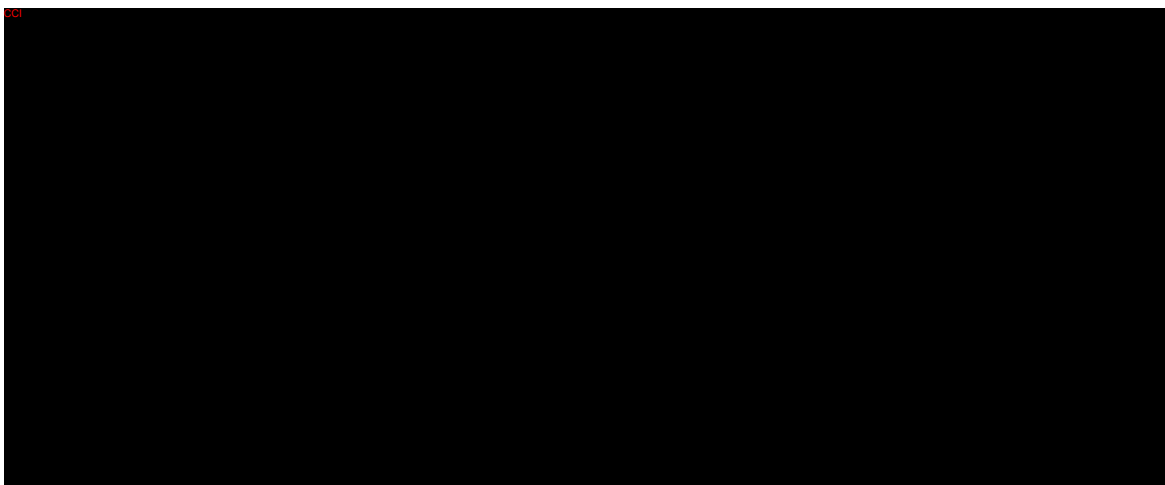
Efficacy and safety for each cohort will be analyzed separately.

In this study, approximately 60 subjects for each cohort will be enrolled.

Cohort A

With a sample size of 60, the study has 93% power to reject the null hypothesis of $ORR=15\%$ with a one-sided type I error rate of 2.5% if the true ORR is 35%. The historical response rate is less than 5% in CORRECT study [2].





3.10 Subgroup Analyses and Effect of Baseline Factors

The estimate of the treatment effect for the primary endpoint will be estimated and plotted within each category of the following classification variables:

- Age category (≤ 65 vs. > 65 years)
- Sex (Female vs. Male)
- Race (white vs. non-white)

The consistency of the treatment effect will be assessed descriptively via summary statistics by category for the classification variables listed above.

3.11 Compliance (Medication Adherence)

Drug accountability data for MK-3475 will be collected during the study. Any deviation from protocol-directed administration will be reported.

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.

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