Official Protocol Title:	A Phase 1 Trial of MK-4280 as Monotherapy and in Combination with Pembrolizumab with or without Chemotherapy or Lenvatinib (E7080/MK-7902) in Subjects with Advanced Solid Tumors
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TITLE:

A Phase 1 Trial of MK-4280 as Monotherapy and in Combination with Pembrolizumab with or without Chemotherapy or Lenvatinib (E7080/MK-7902) in Subjects with Advanced Solid Tumors

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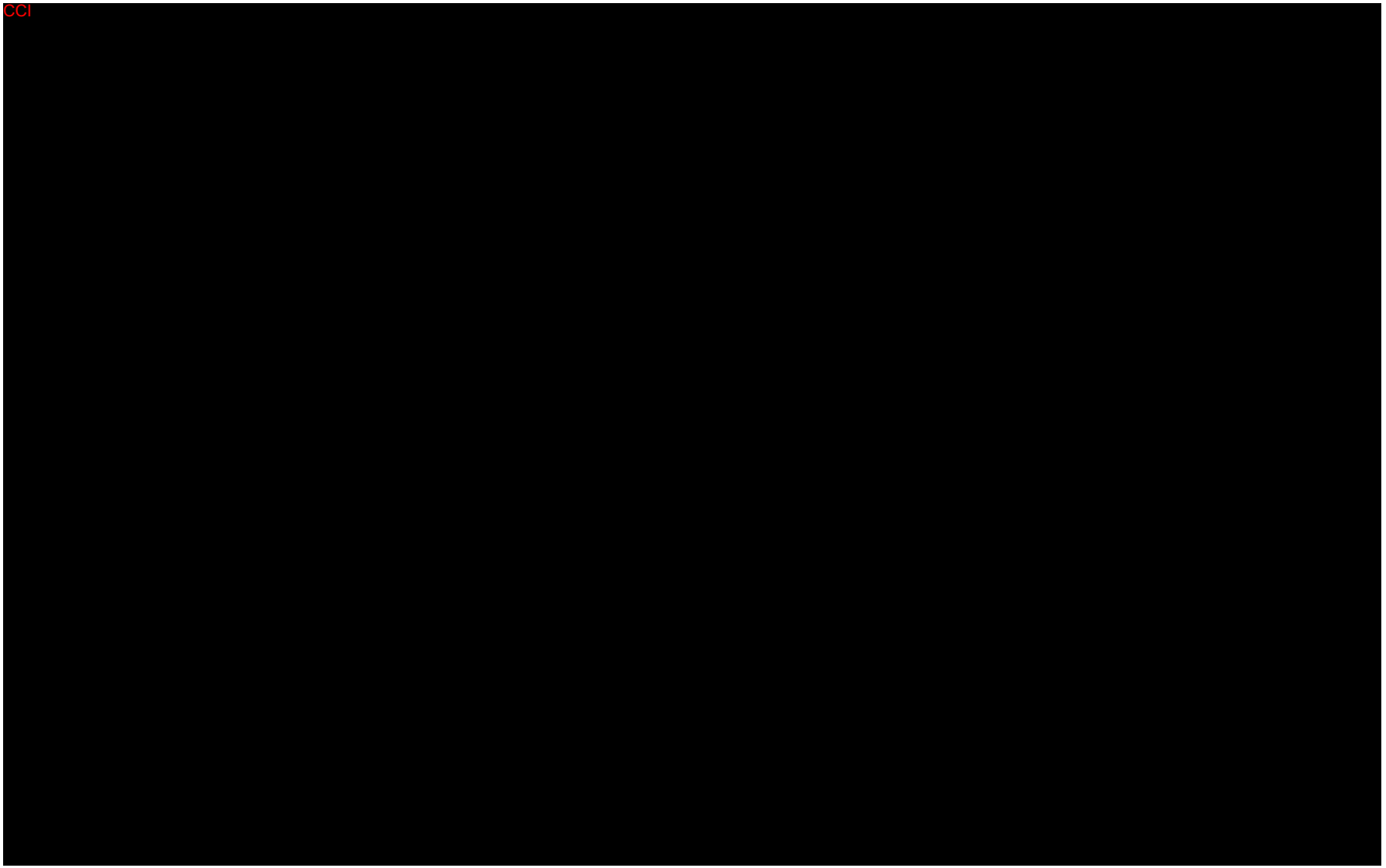

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SUMMARY OF CHANGES

PRIMARY REASON(S) FOR THIS AMENDMENT:

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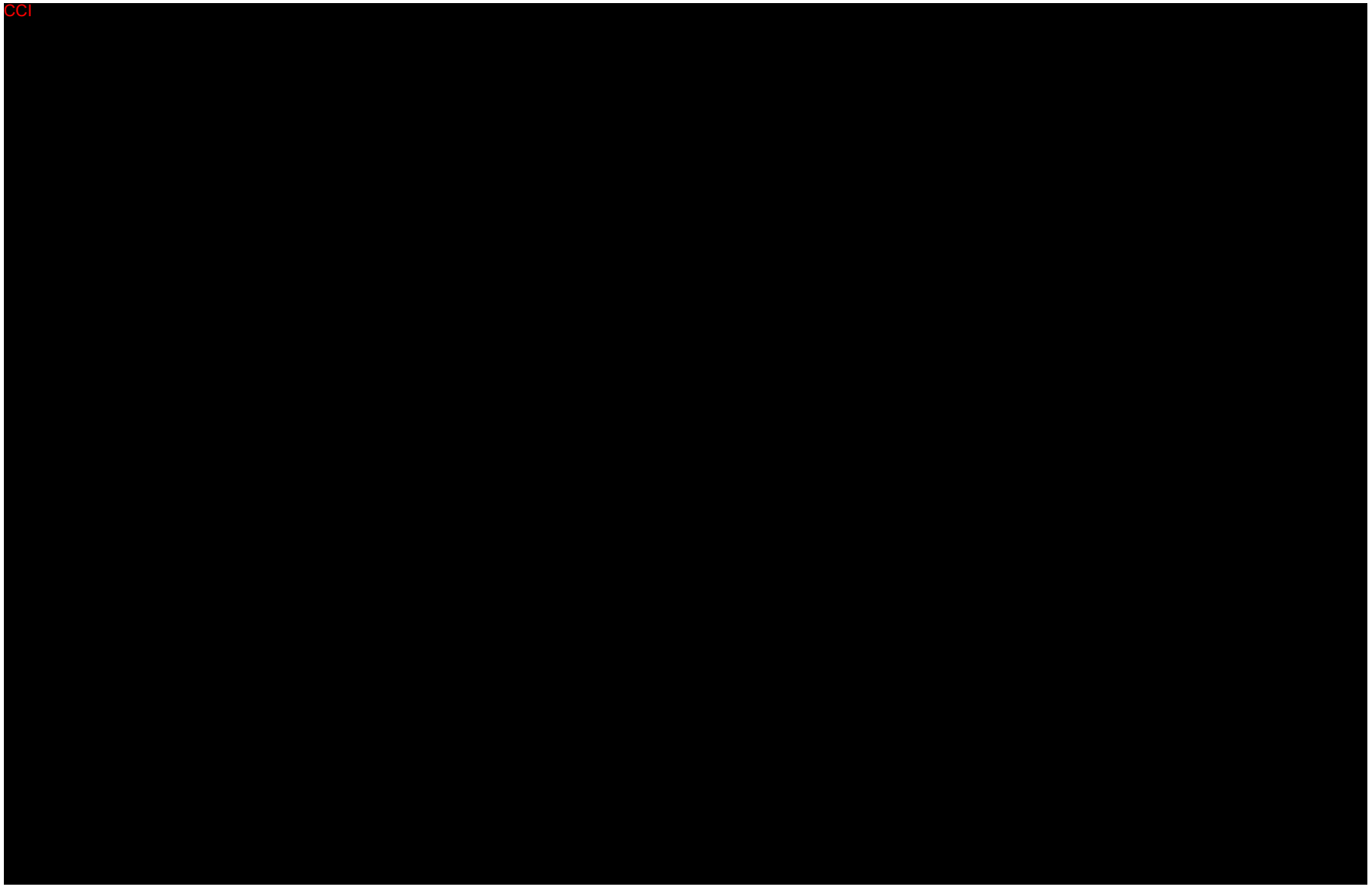

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1.0 TRIAL SUMMARY

Abbreviated Title	Phase 1 Trial of MK-4280 as Monotherapy and in Combination with Pembrolizumab with or without Chemotherapy or Lenvatinib (E7080/MK-7902) in Subjects with Advanced Solid Tumors
Sponsor Product Identifiers	MK-4280 Pembrolizumab MK-4280A Lenvatinib
Trial Phase	Phase 1b
Clinical Indication	Treatment of subjects with advanced solid tumors
Trial Type	Interventional
Type of control	None
Route of administration	Intravenous (MK-4280, pembrolizumab, and MK-4280A) Oral (lenvatinib)
Trial Blinding	Unblinded Open-label
Treatment Groups	During Part A of the study, subjects will be allocated by nonrandom assignment to 1 of 2 treatment arms: Arm 1: MK-4280 (escalating doses) as monotherapy Arm 2: MK-4280 (escalating doses) in combination with pembrolizumab (200 mg fixed dose every 3 weeks [Q3W]) Part B will be a dose confirmation of MK-4280 in combination with pembrolizumab. Additionally, expansion cohorts will assess the antitumor efficacy of MK-4280 as monotherapy and in combination with pembrolizumab with or without chemotherapy or lenvatinib. Part B will consist of 6 treatment arms and 7 cohorts: Arm 1: MK-4280 (800 mg Q3W) as monotherapy Arm 2A: MK-4280 (200 mg Q3W) in combination with pembrolizumab (200 mg Q3W) Arm 2B: MK-4280 (700 mg Q3W) in combination with pembrolizumab (200 mg Q3W) Arm 2C: MK-4280 (800 mg Q3W) in combination with pembrolizumab (200 mg Q3W) Arm 3: MK-4280 (800 mg Q3W) + pembrolizumab (200 mg Q3W) + mFOLFOX7 (oxaliplatin [85 mg/m^2], leucovorin [calcium folinate, 400 mg/m^2], fluorouracil [5-FU, 2400 mg/m^2 over 46 to 48 hours] every 2 weeks [Q2W]) Arm 4: MK-4280 (800 mg Q3W) + pembrolizumab (200 mg Q3W) + FOLFIRI (irinotecan [180 mg/m^2], leucovorin [calcium folinate, 400 mg/m^2], 5-FU [2400 mg/m^2 over 46 to 48 hours] Q2W) Arm 5: MK-4280A (800 mg MK-4280 + 200 mg pembrolizumab Q3W) Arm 6: MK-4280 (800 mg Q3W) + pembrolizumab (200 mg Q3W) + lenvatinib (20 mg QD)

	Cohort A: 3L+ CRC (PD-1-treatment naïve) Cohort B: 1L or 2L CRC (PD-1-treatment naïve) Cohort C: HNSCC (PD-1-treatment naïve) Cohort D: HNSCC (PD-1-treatment failure) Cohort E: Gastric Cancer (PD-1-treatment naïve) Cohort F: Chinese subjects from mainland China with advanced solid tumors Note: Chinese subjects from mainland China (Cohort F) will not enroll in Cohorts A through E or Cohort G. Cohort G: 3L CRC (PD-1-treatment naïve)
Number of trial subjects	Approximately 576 subjects will be enrolled.
Estimated duration of trial	The Sponsor estimates that the trial will require approximately 7 years from the time the first subject (or their legally acceptable representative) provides documented informed consent until the last subject's last study-related contact.
Duration of Participation	Each subject will participate in the study from the time the subject provides documented informed consent through the final contact. After a screening phase of up to 28 days, study treatment will begin on Day 1 of each 3-week cycle and will continue for up to 35 cycles. Treatment in all parts and arms of the study will continue until disease progression, unacceptable adverse event(s) (AEs), intercurrent illness that prevents further administration of treatment, the investigator's decision to withdraw treatment, subject withdrawal of consent, pregnancy of the subject, subject completion of 35 cycles of treatment, or administrative reasons requiring cessation of treatment. Subjects in Arm 1 of Part B may be allowed to crossover to Arm 2C following confirmed disease progression per irRECIST 1.1. Treatment with the combination therapy will then continue until further disease progression, unacceptable AEs, intercurrent illness that prevents further administration of treatment, the investigator's decision to withdraw treatment, subject withdrawal of consent, pregnancy of the subject, subject completion of 35 cycles of treatment, or administrative reasons requiring cessation of treatment. For subjects in Arm 6, pembrolizumab and MK-4280 treatment will be discontinued once the subject has received 35 cycles (approximately 2 years). Subjects experiencing clinical benefit, according to the PI, may continue treatment with lenvatinib beyond 2 years with Sponsor consultation and approval. After the end of treatment (EOT), subjects in Arm 1 of both parts will be followed for 30 days for recording of AEs and serious adverse events (SAEs). Subjects in Arms 2 (both parts), 3, 4, 5, or 6 will be followed for 30 days after the EOT for recording of AEs and 90 days for the recording of SAEs (or 30 days if the subject initiates new anticancer therapy). After documented disease progression, subjects will be contacted approximately every 12 weeks for survival until withdrawal of consent to participate in the trial, becoming lost to follow-up, death, or the end of the study, whichever occurs first.
Randomization Ratio	In Part A and all cohorts of Part B besides the gastric cancer cohort (Cohort E), subjects are allocated to their particular treatment arm without randomization. In Cohort E of Part B, subjects are randomized at a 1:1 ratio to 1 of 2 doses of MK-4280 (200 mg [Arm 2A] or 700 mg [Arm 2B]) in combination with a fixed dose of pembrolizumab. Allocation to Arm 3 or Arm 4 will be guided by a subject's eligibility for one arm or the other or, if eligible for both arms, will be determined by investigator choice. If Arms 1, 2C and 5 for 3L+ CRC subjects are enrolling at the same time, subjects will be assigned in an alternating fashion across the open arms at the study level through IVRS. Cohort F of Part B is only open to sites in China and these subjects will be assigned to Arm 5 only.

A list of abbreviations used in this document can be found in Appendix 12.6.

2.0 TRIAL DESIGN

2.1 Trial Design

This is a multisite, open-label, dose-escalation study of MK-4280 monotherapy (Part A, Arm 1) and MK-4280 in combination with pembrolizumab (Part A, Arm 2) followed by both nonrandomized and randomized dose confirmation of MK-4280 in combination with pembrolizumab along with efficacy evaluations of MK-4280 as monotherapy and in combination with pembrolizumab with or without chemotherapy or lenvatinib (also known as E7080 or MK-7902; hereafter referred to as lenvatinib) (Part B) in subjects with a histologically or cytologically confirmed diagnosis of advanced solid tumors.

This trial will use an adaptive design based on the pre-specified criteria of dose limiting toxicity (DLT). For dose escalation (Part A, Arm 1 and Arm 2), a 3+3 dose escalation design will be utilized (see Section 5.2 – Trial Treatments). For dose confirmation (Part B), the toxicity probability interval (TPI) design [1] will be utilized to refine the estimate of a preliminary RP2D from Part A, Arm 2. Additionally, Part B will compare the safety and antitumor efficacy of multiple doses of MK4280 in combination with pembrolizumab, the safety and efficacy of MK-4280 in combination with pembrolizumab and chemotherapy, and the safety and efficacy of MK-4280 in combination with pembrolizumab and lenvatinib.

2.1.1 Part A

In Part A, Arm 1 (MK-4280 monotherapy), the study will begin with a 3+3 design to identify a preliminary maximum tolerated dose (MTD) or maximum administered dose (MAD), as described in Section 5.2.1. During 3+3 dose escalation in both arms of Part A, an initial cohort of 3 subjects will be enrolled to a dose level. If none of the 3 subjects experiences a DLT during the first 21 day cycle, escalation to the next dose will occur. If 1 of the 3 subjects experiences a DLT, another 3 subjects will be enrolled at this dose level. If 1 DLT is observed among the 6 subjects, the dose escalation will continue. If more than 1 of 3 or more than 1 of 6 subjects at a dose level develop DLTs, dose escalation will be terminated, and the study will proceed at the previous dose level. At least 2 days of observation will occur between each of the first 3 subjects in the first 2 dose levels.

Treatment in Part A, Arm 2 (MK-4280 in combination with pembrolizumab) will begin with a 3+3 design to identify a preliminary RP2D for Part B. The starting dose of MK-4280 will be at least 1 dose level below that being tested in Part A, Arm 1. A fixed dose of 200 mg pembrolizumab will be used in Part A, Arm 2. During 3+3 dose escalation, at least 2 days of observation will occur between each of the first 3 subjects at the first 2 dose levels. Please note that intrasubject dose escalation is not allowed for any part of this study.

Enrollment to both arms of Part A will occur sequentially. The higher dose level cohort of Part A, Arm 1 must be fully enrolled and all subjects must begin dosing before Part A, Arm 2 is dosed. For example, the 70 mg MK-4280 monotherapy cohort must be fully enrolled and all subjects must have begun dosing before the 21 mg MK-4280 + 200 mg pembrolizumab cohort initiates recruitment and dosing. Doses of MK-4280 in combination with

pembrolizumab will be at least 1 dose level behind the monotherapy dose, and would not exceed the MTD or MAD of Part A, Arm 1. However, once the MTD or MAD for Part A, Arm 1 is established, the dose of MK-4280 in Part A, Arm 2 may continue escalation up to that dose. For enrollment to the last 2 dose levels of Arm 2, all 3 (or 6) subjects in the second highest dose level must complete 1 cycle of treatment and DLT evaluation before the highest dose level may begin enrollment.

2.1.2 Part B

In Part B, dose confirmation and preliminary antitumor efficacy will be assessed in subjects with colorectal cancer (CRC) that have progressed on all available standard-of-care therapies (Cohort A), that have received 1 or fewer lines of treatment (Cohort B), or that have received 2 lines of treatment (Cohort G), PD-1-treatment-naïve head and neck squamous cell cancer (HNSCC, Cohort C), PD-1-treatment-failure HNSCC (Cohort D), and gastric cancer (Cohort E). A TPI design will be used to refine the estimate of tolerability of the preliminary RP2D of MK-4280 administered in combination with pembrolizumab identified in Part A (Arm 2A, 200 mg), using the first 14 subjects enrolled in Arm 2A (Cohorts A, C or D). The safety, PK, and preliminary efficacy of MK-4280A, a co-formulated product of 800 mg MK-4280 and 200 mg pembrolizumab, will be assessed in subjects with CRC in the US (Cohort A) and Chinese subjects with advanced solid tumors in mainland China (Cohort F) enrolled in Arm 5. The combination of MK-4280, pembrolizumab, and lenvatinib will be evaluated in subjects with 3L CRC (Cohort G) in Arm 6.

Cohort A will enroll subjects with microsatellite stable (MSS) CRC that are naïve to prior PD-1/PD-L1 therapy and that have progressed on all available standard-of-care therapies. MK-4280 antitumor efficacy will be tested as monotherapy (Arm 1), in combination with pembrolizumab (Arm 2A and 2C), and as a coformulation (MK-4280A, Arm 5). Monotherapy MK-4280 (Arm 1) will be administered at a dose of 800 mg in up to 20 subjects. In Arm 2, up to 100 subjects may be treated with the combination of 200 mg MK-4280 plus pembrolizumab (Arm 2A), and approximately 40 subjects will be treated with the combination of 800 mg MK-4280 plus pembrolizumab (Arm 2C). Forty subjects in Cohort A will also be enrolled to assess the safety, PK, and preliminary efficacy of MK-4280A, a co-formulated product of 800 mg MK-4280 and pembrolizumab (Arm 5). The biocomparability of MK-4280A to the sequential administration of MK-4280 and pembrolizumab will also be assessed.

Cohort B will enroll subjects with MSS CRC naïve to prior PD-1/PD-L1 therapy that have progressed on ≤ 1 prior line of therapy. Cohort B will test the antitumor efficacy of MK-4280 (800 mg) administered in combination with pembrolizumab and mFOLFOX7 (up to 20 subjects, Arm 3) or FOLFIRI (up to 20 subjects, Arm 4). A TPI design will be used to assess the safety and tolerability of these triplet combinations in the first 14 subjects treated with each combination. If a de-escalation is called for by TPI, the dose of mFOLFOX7 or FOLFIRI will be reduced—the doses of MK-4280 and pembrolizumab will remain fixed.

Cohort C will enroll up to 40 subjects with HNSCC that are naïve to prior PD-1/PD-L1 therapy and have progressed after ≥1 prior line of chemotherapy. Subjects will receive 200 mg MK-4280 in combination with pembrolizumab (Arm 2A) to evaluate antitumor efficacy.

Cohort D will enroll up to 20 subjects with HNSCC that have progressed (defined in Section 5.1.2 – Subject Inclusion Criteria) following prior anti-PD-1/PD-L1 therapy. Subjects will receive 200 mg MK-4280 in combination with pembrolizumab (Arm 2A) to evaluate antitumor efficacy.

Cohort E will enroll up to 80 subjects with gastric adenocarcinoma that are naïve to prior PD-1/PD-L1 therapy and that have progressed on ≥1 prior line of chemotherapy. Cohort E will employ a randomized comparison of 2 doses of MK-4280 (200 mg [Arm 2A] and 700 mg [Arm 2B]) in combination with a fixed dose of pembrolizumab. This cohort will initiate enrollment only after the dose confirmation of the first 14 subjects in Cohorts A, C and D have completed. Additionally, if antitumor activity is observed in Arm 2 of Cohort E (≥8 of 40 subjects with an objective response, irrespective of dose) an additional 20 subjects with gastric cancer will be enrolled to receive MK-4280 (800 mg) monotherapy (Arm 1). If this predetermined ORR is not observed, the Sponsor will evaluate all available data before deciding whether to enroll these additional gastric cancer subjects in Arm 1 of Part B.

Cohort F will enroll up to 20 Chinese subjects from mainland China with advanced solid tumors for which there is no available therapy that may convey clinical benefit. Subjects will receive MK-4280A, a co-formulated product of 800 mg MK-4280 and 200 mg pembrolizumab, on Arm 5 to evaluate its safety and PK profile in Chinese subjects. Cohort F is only open to sites in China and these subjects will be assigned to Arm 5 only. Chinese subjects from mainland China will not enroll in Cohorts A through E or Cohort G.

Cohort G will enroll subjects with MSS CRC naïve to prior PD-1/PD-L1 therapy that have progressed on 2 prior lines of therapy. Cohort G will test the antitumor efficacy of MK-4280 (800 mg) administered in combination with pembrolizumab and lenvatinib (up to 40 subjects, Arm 6). A TPI design will be used to assess the safety and tolerability of this triplet combination in the first 14 subjects treated. If a de-escalation is called for by TPI, the dose of lenvatinib will be reduced; the doses of MK-4280 and pembrolizumab will remain fixed.

For Part B Cohorts A and C (MSS CRC and PD-1/PD-L1 naïve HNSCC), the antitumor efficacy of 200 mg MK-4280 in combination with pembrolizumab (Arm 2A) will be examined using an adaptive expansion design. If an individual cohort experiences an objective response rate (ORR) of at least 20% in the first 10 subjects enrolled in Arm 2A (ie, at least 2 of 10 subjects) as assessed by response evaluation criteria in solid tumors (RECIST) 1.1 criteria, these cohorts will be expanded to enroll additional subjects. Arm 2A of Cohort A (MSS CRC) cohort may enroll a maximum of 90 additional subjects, for a maximum total of 100 subjects. Arm 2A of Cohort C (PD-1 naïve HNSCC cohort) may enroll a maximum of 30 additional subjects, for a maximum total of 40 subjects.

Subjects with confirmed disease progression per irRECIST 1.1 in Arm 1 of Part B will be allowed to crossover to Arm 2C (Part B) and receive MK-4280 in combination with pembrolizumab. More details on crossover can be found in Section 5.2.7.

Specific details regarding the eligibility criteria for these tumor types can be found in Section 5.1 – Entry Criteria.

The final number of subjects enrolled in both parts of the study will depend on the DLT observations and, in particular, at what dose the 3+3 design is triggered and what dose is identified as the preliminary RP2D, and on which cohorts (if any) undergo expansion in Part B. For example, in Part A, the maximum sample size across Arm 1 and Arm 2 is 60 subjects (30 subjects each). In Part B, the sample size for the dose confirmation and expansion phase of the study will be a maximum of 516 subjects assuming both the PD-1-treatment-naïve HNSCC and CRC adaptive cohorts are expanded, the gastric cancer cohort (Cohort E) of Arm 1 is opened, and if a de-escalation is needed for the mFOLFOX7, FOLFIRI, and lenvatinib treatment arms. Therefore, the maximum total sample size across Part A and Part B is 576 subjects. See Section 8.9 – Sample Size and Power Calculations for alternate scenarios.

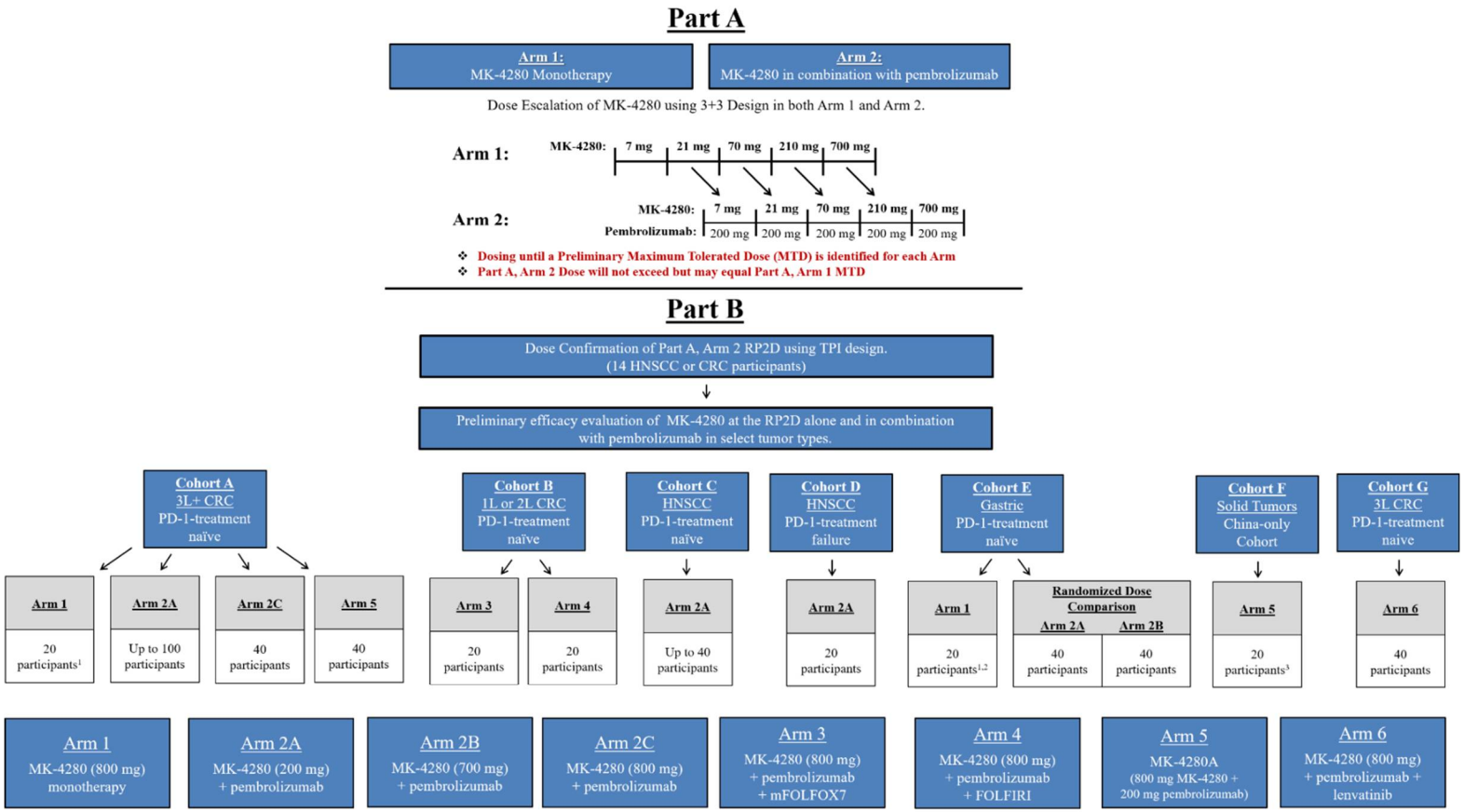
The trial will be conducted in conformance with Good Clinical Practices and the MSD Code of Conduct (Appendix 12.1). Adverse events will be evaluated according to criteria outlined in the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Experiences (CTCAE), Version 4 (Appendix 12.5).

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.

Figure 1 Study Design



1. Participants may be eligible for crossover to MK-4280 + pembrolizumab following irRECIST-confirmed disease progression
2. Cohort may only be opened if ORR ≥ 20% is observed in the Arm 2 cohort.
3. Cohort F will enroll Chinese subjects from mainland China. This cohort is only open to sites in China and these subjects will be assigned to Arm 5 only.

3.0 OBJECTIVE(S) & HYPOTHESIS(ES)

In male/female subjects of at least 18 years-of-age with:

Part A, Arm 1 and Arm 2 - histologically or cytologically confirmed metastatic solid tumor for which there is no available therapy that may convey clinical benefit, or

Part B – histologically or cytologically confirmed diagnosis of 1 of the tumor types described in Section 5.1 – Entry Criteria.

3.1 Primary Objective(s) & Hypothesis(es)

1) **Objective:** To determine the safety and tolerability of MK-4280 monotherapy (for subjects in Part A, Arm 1 and Part B, Arm 1) and to establish a maximum tolerated dose (MTD) or maximum administered dose (MAD)
2) **Objective:** To determine the safety and tolerability of MK-4280 in combination with pembrolizumab (for subjects in Part A, Arm 2 and Part B, Arm 2A, 2B and 2C) and to establish a preliminary recommended Phase 2 dose (RP2D) for combination therapy
3) **Objective:** To determine the safety and tolerability and to establish a preliminary RP2D of MK-4280 in combination with pembrolizumab and mFOLFOX7 (Arm 3) and of MK-4280 in combination with pembrolizumab and FOLFIRI (Arm 4) in subjects with MSS PD-1-treatment-naïve CRC that have received ≤1 line of prior therapy (Cohort B)
4) **Objective:** To determine the safety and tolerability of MK-4280 and pembrolizumab when administered as a co-formulated product (MK-4280A, Arm 5) and compare to the safety and tolerability of MK-4280 and pembrolizumab when administered sequentially (Part B subjects receiving MK-4280 800 mg plus pembrolizumab 200 mg Q3W, Arm 2C) (Cohort A)
5) **Objective:** To determine the safety and tolerability of MK-4280 and pembrolizumab when administered as a co-formulated product in subjects in China (MK-4280A, Arm 5, Cohort F)
6) **Objective:** To determine the safety and tolerability and to establish a preliminary RP2D of MK-4280 in combination with pembrolizumab and lenvatinib (Arm 6) in subjects with MSS PD-1-treatment-naïve CRC that have received 2 lines of prior therapy (Cohort G)

3.2 Secondary Objective(s) & Hypothesis(es)

1) **Objective**: To characterize the pharmacokinetic (PK) profile of MK-4280 in all subjects receiving MK-4280 alone, in combination with pembrolizumab, in combination with pembrolizumab and mFOLFOX7, in combination with pembrolizumab and FOLFIRI, and in combination with pembrolizumab and lenvatinib.

2) **Objective**: To characterize the PK profile of pembrolizumab in all subjects receiving pembrolizumab in combination with MK-4280 with or without mFOLFOX7, FOLFIRI, or lenvatinib

3) **Objective:** To characterize the PK profile of lenvatinib in subjects receiving lenvatinib in combination with MK-4280 and pembrolizumab

4) **Objective:** To evaluate the objective response rate (ORR) as determined by RECIST 1.1 as assessed by investigator review of MK-4280 alone and in combination with pembrolizumab for each tumor cohort in Part B separately

5) **Objective:** To evaluate the ORR as determined by RECIST 1.1 as assessed by investigator review of 2 doses of MK-4280 in combination with pembrolizumab for subjects with gastric cancer (Cohort E)

6) **Objective:** To evaluate the ORR as determined by RECIST 1.1 as assessed by investigator review of MK-4280 in combination with pembrolizumab and mFOLFOX7, and in combination with pembrolizumab and FOLFIRI in subjects with MSS PD-1-treatment-naïve CRC that have received ≤1 line of prior therapy (Cohort B)

7) **Objective:** To evaluate the ORR as determined by RECIST 1.1 as assessed by investigator review of MK-4280 in combination with pembrolizumab and lenvatinib in subjects with MSS PD-1-treatment-naïve CRC that have received 2 lines of prior therapy (Cohort G)

8) **Objective**: To compare the PK profile of MK-4280 when administered as a co-formulated product with pembrolizumab (MK-4280A, Arm 5, Cohort A) and that when administered sequentially with pembrolizumab (Part B subjects receiving MK-4280 800 mg plus pembrolizumab 200 mg Q3W, Arm 2C) (Cohort A)

9) **Objective**: To compare the PK profile of pembrolizumab when administered as a co-formulated product with MK-4280 (MK-4280A, Arm 5, Cohort A) and that when administered sequentially with MK-4280 (Part B subjects receiving MK-4280 800 mg plus pembrolizumab 200 mg Q3W, Arm 2C) (Cohort A)

10) **Objective**: To characterize the PK profile of MK-4280 when administered as a co-formulated product with pembrolizumab in subjects in China (MK-4280A, Arm 5, Cohort F)

11) **Objective**: To characterize the PK profile of pembrolizumab when administered as a co-formulated product with MK-4280 in subjects in China (MK-4280A, Arm 5, Cohort F)

3.3 Exploratory Objectives

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4.0 BACKGROUND & RATIONALE

4.1 Background

Detailed background information on MK-4280, MK-4280A, and pembrolizumab is available in the Investigator's Brochures (IBs) for MK-4280 and pembrolizumab.

Refer to the IB/approved labeling for detailed background information on lenvatinib.

4.1.1 Pharmaceutical and Therapeutic Background

4.1.1.1 MK-4280 Background

Lymphocyte-activation gene 3 (LAG-3) is an inhibitory immune modulatory receptor that regulates effector T-cell homeostasis, proliferation, and activation, and has a role in the suppressor activity of regulatory T cells (T_{regs}). MK-4280 is a humanized IgG4 monoclonal antibody that antagonizes LAG-3. LAG-3 is expressed on activated $CD8^+$ and $CD4^+$ T cells, T_{regs} and the T_r1 regulatory T-cell population, as well as on natural killer cells and a subset of tolerogenic plasmacytoid dendritic cells. Because of its proposed role on both effector T cells and T_{regs}, LAG-3 is one of several immune checkpoint molecules where simultaneous blockade of both cell populations has the potential to enhance antitumor immunity.

LAG-3 is structurally related to cluster of differentiation (CD) 4 and a member of the immunoglobulin (Ig) superfamily. Like CD4, its ligand is major histocompatibility complex (MHC) Class II molecules. Interaction with its ligand leads to dimerization and signal transduction resulting in altered T-cell activation. Following T-cell activation, LAG-3 is transiently expressed on the cell surface. A large proportion of LAG-3 molecules are found in intracellular stores and can be rapidly translocated to the cell membrane upon T-cell activation. LAG-3 expression is regulated at the cell surface by extracellular cleavage to yield a soluble form of LAG-3 (sLAG-3), which can be detected in serum. Expression of LAG-3 is tightly regulated and represents a self-limiting mechanism to counter uncontrolled T-cell activity.

LAG-3 is commonly co-expressed with PD-1 on anergic/exhausted T cells, and both in vitro and in vivo data indicate that dual blockade of LAG-3 and PD-1 can have a synergistic impact on reversing tumor-specific anergy. Indeed LAG-3 was selected as an initial target of interest based on published data indicating that the addition of an anti-LAG-3 antibody could enhance the activity of an anti-PD-1 antibody in rodent, preclinical tumor models. In addition to the data from preclinical models using anti-mouse antibodies, data from double knock-out mice ($LAG\text{-}3^{-/-}PD\text{-}1^{-/-}$) show the ability to resist growth of various tumor implants, indicating a clear synergy between these molecules.

4.1.1.2 Pembrolizumab (MK-3475) Background

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 CD28 and cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) and has been shown to negatively regulate antigen receptor signaling upon engagement of its ligands (PD-L1 and/or PD-L2) [2], [3].

The structure of murine PD-1 has been resolved [4]. PD-1 and family members are type I transmembrane glycoproteins containing an Ig-variable-type domain responsible for ligand binding and a cytoplasmic tail responsible for the binding of signaling molecules. The cytoplasmic tail of PD-1 contains 2 tyrosine-based signaling motifs, an immunoreceptor tyrosine-based inhibition motif (ITIM) and an immunoreceptor tyrosine-based switch motif (ITSM). Following T-cell stimulation, PD-1 recruits the tyrosine phosphatases SHP-1 and SHP-2 to the ITSM motif within its cytoplasmic tail, leading to the dephosphorylation of effector molecules such as CD3 zeta (CD3ζ), protein kinase C-theta (PKCθ) and zeta-chain-associated protein kinase (ZAP70), which are involved in the CD3 T-cell signaling cascade [2], [5], [6], [7]. 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 [8], [9]. As a consequence, the PD-1/PD-L1 pathway is an attractive target for therapeutic intervention.

4.1.1.3 Lenvatinib Background

Angiogenesis, the formation of new blood vessels from a pre-existing vascular network, is essential for tumor growth and metastasis. Vascular endothelial growth factor (VEGF) and its family of receptors (VEGF receptors [VEGFRs] 1-3) play a major role in tumor angiogenesis [10] [11] [12]. Accumulated evidence suggests that fibroblast growth factor (FGF) and its receptor tyrosine kinase, fibroblast growth factor receptor (FGFR) also play important roles for tumor angiogenesis [13] [14] [15].

Lenvatinib is a potent multiple receptor tyrosine kinase (RTK) inhibitor that selectively inhibits VEGF receptors, VEGFR1 (FLT1), VEGFR2 (KDR), and VEGFR3 (FLT4), FGFR1-4, PDGFRα, KIT, and RET. Among known kinase inhibitors in clinical use, lenvatinib is one of the only inhibitors currently labeled with a mechanism of action as an inhibitor of not only VEGFRs but also FGFRs, both of which are currently believed to be very important for tumor angiogenesis.

Lenvatinib inhibited cell free kinase activities for VEGFR1-3 and FGFR1-3 with Ki values around 1 nmol/L, and 8-22 nmol/L, respectively. In cell-based assays, lenvatinib inhibited VEGF-derived and FGF-derived tube formation of human umbilical vein endothelial cell (HUVEC) with IC50 values of 2.1 and 7.3 nmol/L, respectively. Analysis of the signal transduction molecules revealed that lenvatinib inhibited both the mitogen-activated protein kinase (MAPK) pathway and the mTOR-S6K-S6 pathway in HUVECs triggered by activated VEGFR and FGFR. Furthermore, lenvatinib (10, 30 mg/kg) significantly inhibited both VEGF- and FGF-driven angiogenesis in a murine in vivo model [16]. In vivo, lenvatinib exhibited antitumor activity against various human tumor xenografts in athymic mice including 5 types of thyroid carcinomas (differentiated [papillary and follicular], anaplastic, squamous, and medullary thyroid carcinomas), renal cell carcinoma (RCC), hepatocellular carcinoma (HCC), melanoma, gastric cancer, non-small cell lung cancer (NSCLC), ovarian

cancer, Ewing's sarcoma, and osteosarcoma. In addition, the antitumor activity of lenvatinib in combination with other anticancer agents in several xenograft models was greater than that of lenvatinib or the other agents alone.

In summary, lenvatinib inhibited VEGF-driven VEGFR2 phosphorylation and suppressed proliferation and tube formation in HUVEC models. Antitumor activity of lenvatinib in vivo has been shown in numerous xenograft animals. These results suggest that lenvatinib may be a novel anticancer therapy through inhibition of angiogenesis and may be useful as either monotherapy or in combination with other anticancer drugs.

4.1.1.4 Pembrolizumab Plus Lenvatinib Background

The importance of intact immune surveillance function in controlling outgrowth of neoplastic transformations has been known for decades [17]. Accumulating evidence shows a correlation between tumor-infiltrating lymphocytes in cancer tissue and favorable prognosis in various malignancies. In particular, the presence of CD8+ T-cells and the ratio of CD8+ effector T-cells/FoxP3+ regulatory T-cells (T-regs) correlates with improved prognosis and long-term survival in solid malignancies, such as ovarian, colorectal, and pancreatic cancer; HCC; malignant melanoma; and RCC. Tumor-infiltrating lymphocytes can be expanded ex vivo and reinfused, inducing durable objective tumor responses in cancers such as melanoma [18] [19].

In preclinical models, lenvatinib decreased the tumor-associated macrophage (TAM) population, which is known as an immune-regulator in the tumor microenvironment. The decrease in TAM population was accompanied by increases in activated cytotoxic T-cell populations through stimulation of interferon-gamma signaling, resulting in increased immune activation [20]. The immune-modulating effect of lenvatinib may result in a potent combination effect with PD-1/L1 signal inhibitors. The effect of combining lenvatinib with an anti-human PD-1 humanized mAb was investigated in 4 murine tumor isograft models, which showed significant tumor growth inhibition compared to control. In the RAG murine tumor isograft tumor model, survival in the group treated with the combination was significantly longer than that of the respective monotherapy groups. In the CT26 murine tumor isograft model, treatment with the combination significantly increased the population of activated cytotoxic T cells compared to that of the respective monotherapy groups [21]. All treatments were well tolerated and severe body weight loss was not observed.

An open-label, Phase 1b/2 study (KEYNOTE-146/Study E7080-A001-111) to assess the safety and preliminary antitumor activity of the combination of lenvatinib plus pembrolizumab in participants with selected solid tumors is currently ongoing. Phase 1b of this study determined the MTD and RP2D as 20 mg lenvatinib QD in combination with 200 mg of pembrolizumab Q3W. The safety and efficacy of the combination at the lenvatinib RP2D is being assessed in the Phase 2 portion of the study that includes 6 cohorts (ie, NSCLC, RCC, endometrial carcinoma, urothelial carcinoma, melanoma, and HNSCC). Based on results from the endometrial carcinoma cohort in KEYNOTE-146, pembrolizumab in combination with lenvatinib is indicated for the treatment of patients with advanced endometrial carcinoma that is not microsatellite instability-high (MSI-H) or mismatch repair deficient (dMMR), who have disease progression following prior systemic therapy and are

not candidates for curative surgery or radiation. This indication is approved under accelerated approval based on tumor response rate and durability of response [22].

4.2 Rationale

4.2.1 Rationale for the Trial and Selected Subject Population

MK-4280 is being developed for treatment of solid tumors. This trial is the first-in-human (FIH) trial designed to assess the safety, tolerability, antitumor efficacy, PK, and pharmacodynamics of escalating doses of MK-4280 alone and in combination with pembrolizumab with or without chemotherapy or lenvatinib in subjects with advanced solid tumors. The specific tumor types for Part B were selected based on the expression of LAG-3, the known response rates to anti-PD-1/PD-L1 monotherapy in these tumor types, unmet medical need, and preliminary efficacy data observed in Part A of the study.

HNSCC was chosen based on high expression of LAG-3, and known response to PD-1 therapy. Both PD-1/PD-L1 inhibitor treatment-refractory (Cohort D) and naïve (Cohort C) populations are being assessed. There is scientific evidence that the expression of alternate immune checkpoints including LAG-3 may increase after PD-1 blockade, promoting resistance to PD-1 therapy [23]. Co-blockade with LAG-3 and PD-1 may overcome resistance in some tumors. The intention of the PD-1 refractory cohort (Cohort D) is to determine if MK-4280 and pembrolizumab therapy can benefit patients that have progressed on prior PD-1 therapy. The intention of the PD-1 naïve HNSCC cohort (Cohort C) is to determine if MK-4280 and pembrolizumab therapy improves upon the response rates observed with pembrolizumab monotherapy in this population. Results from Keynote-055 demonstrated an objective response rate of 18% in PD-1 naïve HNSCC patients that had progressed on at least 2 prior lines of therapy [24].

MSS CRC was chosen based on high expression of LAG-3, little to no responsiveness to PD-1 monotherapy, and high unmet medical need [25]. Response rates for regorafenib and TAS-102, approved agents in 3L CRC, have an OS benefit of 2 months compared to best supportive care and ~1-2% ORR. Regorafenib improved median OS to 6.4 months from 5.0 months, and TAS-102 improved median OS to 7.1 months from 5.3 months [26] [27]. The intention of this cohort is to determine if MK-4280 plus pembrolizumab improves on the response rates observed for 3L standard of care therapies.

Gastric cancer was chosen based on LAG-3 expression and intermediate responsiveness to PD-1 blockade with an ORR 11.2% in PD-L1 positive gastric cancer patients that had received at least 2 prior lines of therapy.

Details regarding specific benefits and risks for subjects participating in this clinical trial may be found in the accompanying IB and ICF documents.

4.2.1.1 Rationale for Arm 3 and Arm 4 – Combining MK-4280 and Pembrolizumab With Either mFOLFOX7 or FOLFIRI

Rationale for FOLFOX in CRC

FOLFOX have been established as SOC first-line and second-line chemotherapy options for mCRC; however, FOLFOX is more frequently used in the first-line setting. Oxaliplatin combined with infusional 5-FU and leucovorin administered Q2W (FOLFOX) has been shown to be effective [28], and the mFOLFOX7 regimen is considered one of the SOC regimens for first-line line treatment of mCRC [29]. The most common AE overall was peripheral sensory neuropathy (PSN) (76.0%), followed by fatigue (70.9%), nausea (63.7%), diarrhea (53.6%), constipation (39.7%), and vomiting (31.3%); other AEs occurred in <30% of subjects. The most common SAE was neutropenia (16.7%), PSN (11.1%), diarrhea (8.3%), lymphopenia (2.8%), hypertension (2.8%), vomiting (2.8%), and fatigue (2.8%) [30]. Neutropenia/neutropenic fever is a known toxicity associated with mFOLFOX6 chemotherapy and may be related to the 5-FU bolus for this regimen, which is known to be associated with myelosuppression. Hochster et al. reported 18.2% Grade 3/4 neutropenia with mFOLFOX7 (without 5-FU bolus), while FOLFOX regimens that contain 5-FU bolus reported significantly higher frequency of approximately 44% to 47% [30] [31] [32]. For this reason in KN651 and MK-4280-001, the Sponsor elected to use the mFOLFOX7 regimen, which lacks a 5-FU bolus and is associated with less neutropenia than mFOLFOX6.

Rationale for FOLFIRI in CRC

FOLFIRI have been established as SOC first-line and second-line chemotherapy options for mCRC. However, FOLFIRI is more frequently used in the second-line setting after oxaliplatin-based first-line therapies. Irinotecan combined with infusional 5-FU and leucovorin administered Q2W (FOLFIRI) has been shown to be more effective than when irinotecan is combined with bolus 5FU [33]. The regimen is considered one of the SOC regimens in second-line mCRC [29] and has also been shown to be effective in previously untreated patients [34]. For example, in the randomized Phase II/III FIRIS study comparing FOLFIRI vs irinotecan/S-1 (IRIS) in second-line treatment of mCRC, FOLFIRI was associated with ORR of 16.7% and median PFS of 5.1 months. The incidence of Grade 3 or 4 neutropenia was 52.1%. The most common non-hematological toxicities were diarrhea (4.7%), anorexia (5.2%), nausea (4.3%), fatigue (3.3%), and febrile neutropenia (0.9%), all at Grade 3. One treatment-related death from hypotension due to shock was reported in the FOLFIRI group within 28 days after the end of treatment [35].

Rationale for MK-4280 Plus Pembrolizumab Plus FOLFOX/FOLFIRI in CRC

There is accumulating evidence demonstrating that chemotherapy agents including 5-FU and oxaliplatin that are commonly used to treat CRC may modulate the intrinsic immunogenicity of tumor and sensitize tumors to immunotherapy agents [36] [37]. Preclinical and clinical evidence suggest that conventional chemotherapies reactivate antitumor immune responses by increasing immunogenic cell death and antigen release, and/or by inhibiting immunosuppressive factors in the tumor microenvironment [38] [39] [40]. Further, chemotherapies can enhance tumor antigen presentation by upregulating the expression of tumor T-cell receptor (TCR) themselves, or of the MHC1 molecules to which the TCRs bind [38]. A substantial body of scientific evidence has emerged to suggest that the efficacy of

immunotherapy can be enhanced by chemotherapy such as fluorouracil (5-FU) and oxaliplatin. Therefore, Arm 3 will combine MK-4280 and pembrolizumab with mFOLFOX7, a commonly-used treatment regimen for advanced CRC. Although evidence of similar immune-modulating effect and synergy from clinical studies is scant for irinotecan, FOLFIRI may potentially sensitize tumors to checkpoint inhibitors similarly to mFOLFOX7 and therefore Arm 4 will combine MK-4280 and pembrolizumab with FOLFIRI, another commonly used chemotherapy for the treatment of advanced CRC. Given the preliminary clinical efficacy observed with the combination of MK-4280 plus pembrolizumab in MSS CRC, the Sponsor seeks to test whether the combination of MK-4280 plus pembrolizumab plus chemotherapy (mFOLFOX7 or FOLFIRI) could augment antitumor activity compared to chemotherapy alone.

There is preliminary clinical safety and efficacy data for the combination of pembrolizumab plus mFOLFOX6 in CRC. Modified FOLFOX6 + pembrolizumab has been previously tested in an investigator-initiated study in unresectable CRC (NCT02375672). The study employed a 3+3 design for dose confirmation. In the initial 6 patients tested with the combination of mFOLFOX6 ([OX 85 mg/m^2, leucovorin 400 mg/m^2, 5FU 400 mg/m^2, 5FU infusion 2400 mg/m^2 over 46 hours] and pembrolizumab 200 mg Q3W), 3 DLTs were observed, 2 patients with G3 neutropenia, and 1 patient with G4 neutropenia. As a result, mFOLFOX6 was dose reduced to oxaliplatin 68 mg/m^2, leucovorin 400 mg/m^2, 5-FU of 320 mg/m^2, 5-FU infusion of 1920 mg/m^{2}over 46 hours. Pembrolizumab remained at 200 mg IV Q3W. This dose was used for the remaining 24 subjects on the study. Rate of G3/4 toxicity associated with FOLFOX + pembrolizumab and pembrolizumab alone was 36.7% and 13.2%, respectively. No Grade 5 toxicity was seen on study. Best response was recorded as: 1 complete response, 15 partial response (CR + PR = 53%), and 14 stable disease, with 100% DCR at 8 weeks. By comparison, FOLFOX and FOLFIRI have both demonstrated an ORR of ~55% in 1L metastatic CRC, with PFS ~8 months.

The Sponsor is also currently conducting a study to determine the safety and efficacy of pembrolizumab + mFOLFOX7 or FOLFIRI in subjects with advanced CRC (KEYNOTE-651, NCT03374254). Notably, this study utilizes mFOLFOX7, which in comparison to mFOLFOX6, lacks a 5-FU bolus, resulting in a lower incidence of neutropenia. The study design employs a mTPI dose confirmation phase followed by expansion phase at the RP2D. As of 05-NOV-2018, 15 subjects have completed the DLT period in the mFOLFOX7 + pembrolizumab arm, and 0 subjects experienced a DLT. Sixteen subjects have completed the DLT period in the FOLFIRI + pembrolizumab arm, and 1 subject experienced a DLT (small bowel obstruction). The dose finding portion of the study has completed. The starting dose of 200 mg pembrolizumab with full dose mFOLFOX7 and 200 mg pembrolizumab with full dose FOLFIRI will be used to treat patients in the expansion phase of the study. For more information on the safety and tolerability of pembrolizumab when administered in combination with chemotherapy, refer to the pembrolizumab IB.

In summary, available clinical data suggests that immuno-oncology therapies given with FOLFOX and FOLFIRI may be well tolerated. Preliminary data suggest that the combination of MK-4280 plus pembrolizumab is well tolerated with a side effect profile similar to pembrolizumab monotherapy. There is no clinical safety data for the combination of MK-4280, pembrolizumab, and chemotherapy to date. This study will test the safety and

tolerability of MK-4280 plus pembrolizumab in combination with mFOLFOX7 or FOLFIRI in CRC subjects. The safety and tolerability of 1. MK-4280 plus pembrolizumab plus standard dose mFOLFOX7 and 2. MK-4280 plus pembrolizumab plus standard dose FOLFIRI will be tested using a TPI design. In the event of unacceptable toxicity, dose reduction of chemotherapy will be performed, consistent with the standard dose modification guidelines for these regimens. Chemotherapy rather than MK-4280 or pembrolizumab dose modification will be implemented. The rationale for this strategy is that chemotherapy regimens are defined by MTD, with dose limited by rate of DLTs. Biologics often do not reach MTD, since off-target toxicity rates are usually low. This was true in the case of pembrolizumab and MK-4280. On this study, no DLTs were observed during dose escalation at any dose of MK-4280, either alone or in combination with pembrolizumab. Therefore, chemotherapy is the most likely agent to cause DLT on this study, and therefore dose reduction of chemotherapy is planned in the event of toxicity.

4.2.1.2 Rationale for MK-4280A – Co-formulated MK-4280 and Pembrolizumab

MK-4280A is a single drug product containing a fixed dose combination of 800 mg MK-4280 and 200 mg pembrolizumab antibodies. The single formulation vial could provide significant benefit to subjects and providers, including simplified preparation and reduced infusion times compared to separate formulations. Data from Cohort A subjects enrolled in Part B, Arm 5 will be used to compare PK and safety parameters between sequentially administered (Part B, Arm 2C) and co-formulated (Part B, Arm 5) MK-4280 and pembrolizumab.

Rationale for MK-4280A in Chinese Subjects

MK-4280A will also be evaluated in Chinese subjects from mainland China with advanced solid tumors (Arm 5, Cohort F). The purpose of this cohort is to characterize the PK and safety profile of MK-4280A in subjects in China. Data from this evaluation will be used to demonstrate acceptable safety and PK of MK-4280A in Chinese subjects and will be leveraged to support use of MK-4280A in China in future studies.

4.2.1.3 Rationale for Arm 6 – Combining MK-4280 and Pembrolizumab With Lenvatinib in CRC

While PD-1/PD-L1 blocking antibodies have not demonstrated clear monotherapy activity in MSS CRC, combinations of anti-PD-1 antibodies with either an anti-LAG3 blocking antibody or a TKI have demonstrated promising clinical activity in this patient population. Modest but reproducible activity has been observed in 3L+ MSS CRC subjects treated with MK-4280 in combination with pembrolizumab in study MK-4280-001. Further, the combination of an anti-PD-1 antibody and a TKI has demonstrated improved efficacy over TKI alone. In CRC patients treated with both regorafenib plus nivolumab, objective tumor response was observed in 9 out of 25 patients (36%) and the median PFS was 7.9 months (95% CI, 2.9 months to not reached) [41]. In CRC patients treated with regorafenib monotherapy, by comparison, 5 out of 505 patients (1%) experienced an objective response and the median PFS was 1.9 months (IQR 1.6-3.9) [26].

CCI

[redacted]

CCI

Based on these data, the triplet combination of MK-4280, pembrolizumab, and lenvatinib may further improve the activity seen in the doublet combinations in CRC patients. Available clinical data also suggest that this combination will be well tolerated. The AE profile of MK-4280 plus pembrolizumab is similar to pembrolizumab monotherapy. Given the distinct mechanism of action and safety profile of lenvatinib, as well as the tolerable safety profile seen with the combination of lenvatinib and pembrolizumab, no safety issues are anticipated with this triplet combination.

4.2.2 Rationale for Dose Selection/Regimen/Modification

The FIH dose selection for MK-4280 will be guided by PK, pharmacodynamics, and safety studies in cynomolgus monkeys.

4.2.2.1 Starting Dose for This Trial

4.2.2.1.1 Rationale for MK-4280 Dose

CCI

CCI

[redacted]

CCI

[redacted]

4.2.2.1.2 Rationale for Preliminary RP2D (200 mg) and Additional MK-4280 Dose (800 mg)

CCI

[redacted]

4.2.2.1.3 Rationale for Pembrolizumab Dose

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

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

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

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

No dose reduction is allowed for pembrolizumab in this study.

4.2.2.1.4 Rationale for MK-4280A Dose and Biocomparability Study

The dose of MK-4280A will be comprised of 800 mg of MK-4280 and 200 mg of pembrolizumab. This dosing will allow for comparisons of Cohort A subjects in Arm 5 against subjects in Arm 2C of Part B receiving the sequential administration of 800 mg of MK-4280 and 200 mg of pembrolizumab.

Data collected from Cohort A subjects receiving sequentially administered MK-4280 + pembrolizumab (Arm 2C) will serve as a comparator to subjects from Cohort A receiving MK-4280A (Arm 5). Since 800 mg is a new dose of MK-4280 and no subjects on study that have yet received this dose, additional subjects in Cohort A to receive 800 mg MK-4280 and pembrolizumab (Arm 2C) were added to enable comparison.

The dose of MK-4280A will also allow for comparisons within Arm 5 of subjects in China (Cohort F) against subjects in the US (Cohort A).

4.2.2.1.5 Rationale for mFOLFOX7 and FOLFIRI Doses

mFOLFOX7 Starting Dose

The starting dose of mFOLFOX7 is oxaliplatin 85 mg/m^2 IV infusion, leucovorin 400 mg/m^2 IV infusion, 5-FU 2400 mg/m^2 IV infusion over 46 to 48-hour infusion Q2W, which is considered a globally accepted SOC.

FOLFIRI Starting Dose

The starting dose of FOLFIRI is irinotecan 180 mg/m^2 IV over 30-90 minutes, leucovorin 400 mg/m^2 IV infusion, 5-FU 2400 mg/m^2 IV over 46 to 48-hour infusion) Q2W, which is considered a globally accepted SOC.

If the TPI design calls for a de-escalation, the doses of mFOLFOX7 and/or FOLFIRI may be reduced as follows:

- mFOLFOX7: Oxaliplatin (65 mg/m^2), leucovorin (calcium folinate, 400 mg/m^2), and 5-FU (2000 mg/m^2) Q2W
- FOLFIRI: Irinotecan (150 mg/m^2), leucovorin (calcium folinate, 400 mg/m^2), and 5-FU (2000 mg/m^2) Q2W

The dose levels of mFOLFOX7 and/or FOLFIRI will not be reduced below these. If the TPI design calls for an additional de-escalation, enrollment into that particular arm will be closed.

4.2.2.1.6 Rationale for Lenvatinib Dose

The dosing regimen of lenvatinib was selected based on the results of the Phase 1b portion of KEYNOTE-146, which determined the MTD and RP2D as lenvatinib 20 mg QD when administered in combination with pembrolizumab 200 mg Q3W [43].

If the TPI design calls for a de-escalation, reduced doses of lenvatinib (14 mg and 10 mg) will be used. If the TPI design calls for additional de-escalation, enrollment into Arm 6 will be closed.

4.2.2.2 DLTs and AEs for Part A

As of 09-JUN-2017, Part A dose escalation has been fully enrolled and all subjects have completed the DLT period. No DLTs were observed in any subjects. After the DLT period, one subject in the 21 mg cohort of MK-4280 monotherapy experienced Grade 3 pneumonitis. For this reason, this cohort was expanded to enroll an additional 3 subjects. No DLTs were observed in these additional 3 subjects.

A total of 61.1% of subjects (11/18) receiving MK-4280 monotherapy and 53.3% (8/15) of subjects receiving MK-4280 in combination with pembrolizumab experienced one or more drug-related AEs. There have been no observed ECIs. There did not appear to be any dose-dependency on the frequency or severity of AEs in Part A. For more information on expected AEs refer to the IBs for MK 4280 and pembrolizumab.

4.2.2.3 DLTs for the Combination of Pembrolizumab With mFOLFOX7 or FOLFIRI

Given the Sponsor's observation in this study that pembrolizumab + MK-4280 is well tolerated (with no DLTs up to the 700 mg dose level) as well as the observation in KEYNOTE-651 that pembrolizumab + mFOLFOX7 and pembrolizumab + FOLFIRI were also well tolerated (with no DLTs at the same proposed starting doses in this study, see Section 4.2.1.1), the Sponsor considers it acceptably safe to begin the dose confirmation of the 2 triplet combination arms at the proposed starting doses.

4.2.2.4 Maximum Dose/Exposure for This Trial

Although dose escalation will depend on AEs observed, a potential dose up to 800 mg of MK-4280 is planned. Because current target engagement predictions are based on normal cynomolgus monkeys, doses higher than 7 mg are expected to account for LAG-3 target engagement in humans with tumors. Although the maximum clinical dose to be evaluated in this trial is 800 mg, studies in cynomolgus monkeys showed no AEs at doses at which the C_{max} and $AUC_{0\text{-}tau}$ values were 22-fold and 14-fold higher respectively relative to the predicted human exposure at this maximum dose. Pembrolizumab will be administered at the approved fixed dose of 200 mg. mFOLFOX7 and FOLFIRI will be administered at their approved doses. Lenvatinib will be administered at the RP2D for combination therapy with pembrolizumab.

4.2.3 Rationale for Endpoints

4.2.3.1 Efficacy Endpoints

Secondary and exploratory objectives for this trial are to evaluate the antitumor activity of MK-4280 alone and in combination with pembrolizumab with or without chemotherapy or lenvatinib in subjects with several types of advanced solid malignancies, as detailed in Section 5.1 – Entry Criteria. Additionally, the antitumor activity of 2 different doses of MK-4280 in combination with a fixed dose of pembrolizumab will be evaluated as a secondary trial objective in subjects with gastric cancer. Tumor response will be assessed using both RECIST 1.1 and irRECIST 1.1 by investigator review. Antitumor activity will be measured through such endpoints as the ORR, DCR, DOR, BOR, Best Target Lesion

Response, and the Time to Confirmed Response, which are further described in Section 8.0 – Statistical Analysis Plan.

irRECIST 1.1 is an exploratory assessment criteria, based on RECIST 1.1, and accounts for the unique tumor response characteristics seen following treatment with immunotherapeutic agents as described in [44]. With other immunotherapeutic agents, up to 7% of evaluable subjects experienced delayed or early tumor pseudoprogression. Of note, subjects who had progressive disease (PD) by RECIST 1.1 but not by irRECIST 1.1 had longer overall survival than subjects with PD by both criteria. These findings support the need to apply a modification to RECIST 1.1 that takes into account the unique patterns of atypical response in immunotherapy and enable treatment beyond initial radiographic progression.

The assessment of unidimensional target lesions and response categories per irRECIST 1.1 are identical to RECIST 1.1. However, MSD has implemented an adaptation related to new lesions, non-target lesions, and tumor burden assessment to confirm radiographic progression. irRECIST 1.1 will be used by local site investigators to assess tumor response and progression, and make treatment decisions. RECIST 1.1 will be used for the formal statistical analysis of the secondary trial objective.

Therefore, irRECIST 1.1 consists of RECIST 1.1 with the following adaptations:

Subjects who have initial evidence of radiological PD by RECIST 1.1 after starting study treatment should, at the discretion of the investigator, continue on study treatment per the conditions outlined in Section 7.1.2.6 until repeat imaging is obtained ≥4 weeks later to confirm PD.

Disease progression will be considered to be "confirmed" at repeat imaging if ANY of the following occur (as assessed by irRECIST 1.1):

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

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

Disease progression will be considered to be "not confirmed" at repeat imaging if ALL of the following occur (as assessed by irRECIST 1.1):

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

If repeat imaging does not confirm PD by irRECIST 1.1 and the subject continues to be clinically stable, treatment may continue and follow the regular imaging schedule.

This allowance to continue treatment despite initial radiologic PD takes into account the observation that some subjects can have a transient tumor flare in the first few months after the start of immunotherapy, and then experience subsequent disease response. Subjects that are deemed clinically unstable are not required to have repeat tumor imaging for confirmation of PD. Tumor flare includes any of the following scenarios:

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

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

4.2.3.2 Safety Endpoints

The primary objective of this trial is to characterize the safety and tolerability of MK-4280 monotherapy and in combination with pembrolizumab (either administered sequentially or as a co-formulated product), in combination with pembrolizumab and chemotherapy, and in combination with pembrolizumab and lenvatinib in subjects with advanced solid tumors. The primary safety analysis will be based on subjects who experience toxicities as defined by CTCAE criteria. Safety will be assessed by quantifying the toxicities and grades of toxicities experienced by subjects who have received MK-4280, including SAEs and events of clinical interest (ECIs).

Safety will be assessed by reported AEs using CTCAE, Version 4.0. The attribution to drug, time-of-onset, duration of the event, its resolution, and any concomitant medications administered will be recorded. Adverse events will be analyzed including, but not limited to, all AEs, SAEs, fatal AEs, and laboratory changes.

4.2.3.3 Pharmacokinetic Endpoints

A secondary objective of this trial is to characterize the PK profile of MK-4280 following administration as a single agent, and the profiles of both MK-4280 and pembrolizumab following administration of MK-4280 in combination with pembrolizumab (or administration of MK-4280A), the profiles of both MK-4280 and pembrolizumab when administered in combination with mFOLFOX7 or FOLFIRI, as well as the profiles of MK-4280, pembrolizumab, and lenvatinib when administered together. The serum concentrations of each antibody will serve as the primary readout for the PK, and these data will be used to assess PK profiles of the agents alone and in combination. Furthermore, the results of these analyses will be used in conjunction with the pharmacodynamics, safety and antidrug antibody endpoints to help assess future dosing strategies for MK-4280.

4.2.3.3.1 Biocomparability Endpoints

An additional objective of the study is to demonstrate the biocomparability of MK-4280A, a co-formulated product of MK-4280 and pembrolizumab, to that of the sequential administration of MK-4280 and pembrolizumab. Endpoints such as the $AUC_{0\text{-}21days}$ and C_{max} will be used to demonstrate the biocomparability of MK-4280A. More details regarding the biocomparability analyses can be found in Section 8.6.4.

4.2.3.4 Pharmacodynamic Endpoints

4.2.3.4.1 Target Engagement: Receptor Availability of Cell Surface LAG-3

The active form of LAG-3 that mediates regulation of activated T cells is the cell-bound form, which forms a dimer and is the only form of LAG-3 that has high affinity for its ligand MHC Class II [45], [46]. The expression of cell surface LAG-3 is tightly regulated, with a majority found stored in intracellular vesicles, which undergo rapid translocation to the membrane upon lymphocyte activation, and finally, regulation by cleavage with metalloproteases to release sLAG-3 as a waste product [47], [48]. This process allows for a tightly controlled modulation of the immune response. Both cell surface expression of LAG-3 and subsequent cleavage to form sLAG-3 increase upon immune activation. The actual level of cell surface LAG-3 expression has been found to be negligible by flow cytometric staining of both human, nonhuman primate (NHP), and mouse cell populations from peripheral blood, precluding the use of receptor binding or receptor availability assays for measuring target engagement. The levels of sLAG-3 are easily detectable, and represent an alternative method to assess target engagement of MK-4280. An immunoassay has been developed up to assess levels of total sLAG-3, both free and bound to MK-4280. Administration of MK-4280 showed dose-dependent increases of total sLAG-3 following multiple-dose administration of MK-4280 in a cynomolgus monkey safety study.

4.2.3.4.2 Antidrug Antibodies

Formation of antidrug antibodies (ADAs) can potentially confound drug exposures at therapeutic doses, and prime for subsequent infusion-related toxicities. The presence of ADAs will be determined at the beginning of each cycle to understand drug metabolism, exposure and safety. Incidence of ADAs and neutralizing ADAs will be evaluated and summarized over time by dose. Correlations between the presence/absence in subjects of ADAs with PK and pharmacodynamic markers, activity, and safety of MK-4280 will be explored.

4.2.3.5 Serum Cytokines

Because treatment with anti-LAG-3 and/or anti-PD-1 can result in immune stimulation and resulting potential for cytokine release, serum cytokines will be monitored to provide supplementary information to assist in the evaluation of any response outcomes (for example tumor necrosis factor-alpha [TNF-α], interleukin [IL]-2, and IL-6).

4.2.3.6 Planned Exploratory Biomarker Research

Mechanistic markers of anti-LAG-3/anti-PD-1 combination activity have been observed after administration of the surrogate monoclonal antibody (mAb) 28G10 in mouse syngeneic tumor models, including induction of gene expression changes of various immune mediators (eg, interferon gamma [IFN-γ], perforin, and granzymes). These changes in candidate pathway biomarkers are predominantly seen within the tumor, though some transient changes in gene expression in peripheral blood were observed. Immunophenotyping by immunohistochemistry (IHC) and gene expression profiling of tumor biopsies, and by whole blood flow cytometry will be performed to explore changes in lymphocyte populations. These include the expression of LAG-3, MHC Class II, and PD-L1 by IHC as well as levels of IFN-γ-pathway genes, effector T-cell response genes, T-cell immunomodulatory receptors (IMRs), and other related markers of immune response. Additional candidate biomarkers including positivity for human papillomavirus (HPV), Epstein-Barr virus (EBV), human epidermal growth factor receptor 2 (HER2/neu), and microsatellite instability (MSI) will also be assessed by appropriate tests.

Subjects will be required to provide an archival tumor tissue sample and/or a fresh biopsy of tumor before treatment for these biomarker analyses. Subjects will also be asked to agree to a biopsy of tumor after initiation of study treatment and to provide the acquired tissue for these biomarker analyses.

Immune modulatory agents may alter populations of circulating immune cells in blood. To assess the effect of MK-4280 on these cell populations, peripheral blood samples will be obtained at designated times before and after study treatment. Changes in immune cell populations will be evaluated by comparing changes in T-cell repertoire and expression of immune function genes or proteins from baseline to after treatment.

The mechanism of action of many new therapeutics is not completely understood and much remains to be learned regarding how best to leverage new drugs in treating participants. Thus, to aid future participants, it is important to investigate the determinants of response or resistance to the treatments administered, as well as determinants of AEs during our clinical studies. These efforts may identify novel predictive/pharmacodynamic biomarkers and generate information that may better guide single-agent and combination therapies. To identify novel biomarkers, biospecimens (eg, blood components, tissue material) will be collected to support analyses of cellular components (eg, protein, DNA, RNA, metabolites) and other circulating molecules. Investigations may include but are not limited to:

Germline (Blood) Genetic Analyses

This research may evaluate whether genetic variation within a clinical trial population correlates with response to the treatment(s) under evaluation. Genome and exome wide approaches may be used for this effort. In addition, epigenetic characterization techniques (ie, DNA methylation status, histone profiling) may be explored. If genetic and/or epigenetic 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 deoxyribonucleic acid (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, and 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 Ribonucleic Acid (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 IFN-γ 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.

Blood/Tissue Protein biomarker Analyses

Tissue and/or blood samples from this study may undergo protein-based biomarker analyses using a variety of platforms that could include, but are not limited to; immunoassays (e.g., ELISA) liquid chromatography/mass spectrometry, cytometry, and immunohistochemistry. These approaches may be used to quantify soluble, cell- and/or tissue-based analytes to further elucidate therapy mechanism of action and/or assess disease-related parameters. For immunohistochemical analyses information on spatial context and cellular distribution may also be included. Correlation of protein expression to response to therapy may be performed to identify novel predictive biomarkers that could aid in participant selection for therapy. This research would serve to develop such assays for future clinical use.

Biomarker research using the human microbiome

The human microbiome plays a critical role in maintaining tissue homeostasis. Abnormal composition of the microbiome has been observed in several disease states. Furthermore, the composition of different bacterial signatures may be predictive of the efficacy of treatment and participant response. The microbiome may thus serve as a valuable diagnostic tool for properly assessing and managing disease states.

4.2.3.7 Planned Genetic Analysis

Genetic variation may impact a subject's response to therapy, susceptibility to, and severity and progression of disease. Variable response to therapy may be due to genetic determinants that impact drug absorption, distribution, metabolism, and excretion; mechanism of action of the drug; disease etiology; and/or molecular subtype of the disease being treated. Therefore,

where local regulations and institutional review board (IRB)/ independent ethics committee (IEC) allow, a sample will be collected for DNA analysis from consenting subjects.

DNA samples will be used for research related to the study treatment(s), the disease under study and related diseases. They may also be used to develop tests/assays including diagnostic tests related to the disease under study, related diseases and study drug(s). Genetic research may consist of the analysis of one or more candidate genes or the analysis of genetic markers throughout the genome.

DNA samples will be analyzed for variation across the entire genome. Analyses may be conducted if it is hypothesized that this may help further understand the clinical data.

The samples may be analyzed as part of a multi-study assessment of genetic factors involved in the response to understand study disease or related conditions.

4.2.3.8 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 Future Biomedical Research 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 IB and ICF documents.

5.0 METHODOLOGY

5.1 Entry Criteria

5.1.1 Diagnosis/Condition for Entry into the Trial

Male/Female subjects of at least 18 years-of-age with advanced solid tumors will be enrolled in this trial.

As stated in the Code of Conduct for Clinical Trials (Appendix 12.1) this study includes participants of varying age (as applicable), race, ethnicity, and sex (as applicable). The collection and use of these demographic data will follow all local laws and participant confidentiality guidelines while supporting the study of the disease, its related factors, and the IMP under investigation.

5.1.2 Subject Inclusion Criteria

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

1. Part A - Have a histologically or cytologically confirmed metastatic solid tumor for which there is no available therapy that may convey clinical benefit.

   Part B – Have 1 of the following histologically or cytologically confirmed tumor types:

   a. **Cohort A - CRC for Arm 1, Arm 2A, Arm 2C, and Arm 5:** CRC originating in either the colon or rectum that is locally advanced unresectable or metastatic (ie, Stage IV) and that has received, and progressed on, all available standard-of-care therapies including fluoropyrimidine, oxaliplatin, and irinotecan but has not been treated with prior anti-PD-1/PD-L1 therapy.

      Note: Only subjects at sites in the US may be enrolled to Cohort A, Arm 5.

   b. **Cohort B - CRC for Arm 3 and Arm 4 :** CRC originating in either the colon or rectum that is locally advanced unresectable or metastatic (ie, Stage IV) and has been treated with ≤1 line of systemic therapy but has not been treated with prior anti-PD-1/PD-L1 therapy. Subjects eligible to receive EGFR-targeted therapy must have previously received this treatment in order to be eligible for the study.

   c. **Cohort G - CRC for Arm 6**: CRC originating in either the colon or rectum that is locally advanced unresectable or metastatic (ie, Stage IV) and has been treated with 2 prior lines of therapy but has not been treated with prior anti-PD-1/PD-L1 therapy. Study medication will treat 3L CRC.

      Note: Subjects must have received oxaliplatin and irinotecan in separate lines of therapy, these are usually provided with fluoropyrimidine (eg, FOLFOX and FOLFIRI).

      Note: Capecitabine is acceptable as equivalent to fluoropyrimidine in prior therapy (XOLFOX, XOLFIRI)

      Note: Subjects who have previously received fluoropyrimidine, oxaliplatin, and irinotecan as part of the same and only chemotherapy regimen, eg, FOLFOXIRI or FOLFIRINOX, will be considered 2L patients, and do not qualify for the study.

      Note: Adjuvant chemotherapy counts as a first line of prior systemic therapy if there is documented disease progression within 6 months of chemotherapy completion.

Note: All systemic cytotoxic chemotherapy, including antibody–drug conjugates with a cytotoxic warhead, are considered prior lines of therapy.

Note: Definitive surgery with curative intent and radiation therapy or systemically administered radiopharmaceutical therapy are NOT considered prior lines of therapy.

Note: If a treatment regimen is discontinued for any reason and a different regimen is started, it should be considered a new line of therapy. Switching (eg, cisplatin to carboplatin) will NOT be considered a line of therapy change (unless a delay in treatment is required for ≥2 months). Switching for toxicity will be considered a line of therapy change if there is a change in mechanism of action between the therapies. Interruptions will NOT be considered a line of therapy change (unless the interruption is ≥2 months).

Note: Maintenance regimens administered with the purpose of maintaining response following treatment will not be considered lines of therapy.

Note: Hyperthermic intraperitoneal chemotherapy (HIPEC) or other locoregional therapies are allowed, but will not be counted as prior lines of therapies.

d. **Cohort C and Cohort D-** HNSCC that is considered incurable by local therapies. Subjects should have progressed after receiving platinum-containing systemic therapy. Systemic therapy given as part of multimodal treatment for locally advanced disease is allowed. The eligible primary tumor locations are oropharynx, oral cavity, hypopharynx, and larynx. Subjects may not have a primary tumor site of nasopharynx (any histology). Subjects enrolled in the PD-1-treatment-naïve HNSCC cohort (Cohort C) may not have been treated with prior anti-PD-1/PD-L1 therapy.

   Subjects enrolled in the PD-1-treatment-failure HNSCC cohort (Cohort D) must be refractory to an FDA approved anti-PD-1/PD-L1 monoclonal antibody (mAb) as either monotherapy or in combination with other approved checkpoint inhibitors or other therapies according to their label, defined as (subjects must meet all of the following criteria):

   i. Have received at least 2 doses of anti-PD-1/PD-L1 mAb.

   ii. Have progressive disease after anti-PD-1/PD-L1 mAb defined according to RECIST 1.1. The initial evidence of PD is to be confirmed by a second assessment, no less than 4 weeks from the date of the first documented PD, in the absence of rapid clinical progression. (Note, this determination is made by investigator. If PD is confirmed, the initial date of PD documentation will be considered the date of disease progression.)

   iii. Have documented PD within 24 weeks of the last dose of anti-PD-1/PD-L1 mAb. Patients who were re-treated with anti-PD-1/PD-L1 mAb and patients who were on maintenance with anti-PD-1/PD-L1 mAb will be allowed to enter the trial as long as

there is documented PD within 24 weeks of the last treatment date (with anti-PD-1/PD-L1 mAb).

e. **Cohort E** - Adenocarcinoma of the stomach and/or gastric-esophageal junction (GEJ) that is considered inoperable and that has received, and progressed on, at least 1 prior chemotherapy regimen or HER2/neu-targeted approved therapy (if HER2/neu-positive). In both cases, subjects must not have been treated with prior anti-PD-1/PD-L1 therapy.

Note – Subjects with known MSI high or MMR deficient gastric cancer or CRC (as determined by either PCR or IHC) are excluded from participating in this study. MSI high is defined as at least 2 allelic shifts occurring among the 5 analyzed microsatellite markers as detected by PCR. MMR deficient is defined as loss of expression of at least 1 of 4 proteins (MLH1, MSH2, MSH6, and/or PMS2) by IHC. If a subject's MSI/MMR status is unknown, testing is not required to determine eligibility.

Note – Subjects with CRC enrolled into Arm 3 or Arm 4 are not eligible to be re-enrolled in the study on Arm 1 or Arm 2 following discontinuation.

Note – 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.

f. **Cohort F –** Have a histologically or cytologically confirmed metastatic solid tumor for which no more than 2 prior lines of therapy were administered and there is no available therapy that may convey clinical benefit.

AND

Be a Chinese subject from mainland China.

Note – Chinese subjects from mainland China are not eligible for Cohorts A through E or Cohort G.

2. Have measurable disease by irRECIST 1.1 criteria.
3. Be ≥18 years of age on the day of signing informed consent.
4. Have a performance status of 0 or 1 on the Eastern Cooperative Oncology Group (ECOG) Performance Scale (Appendix 12.4).
5. Demonstrate adequate organ function as defined in Table 2 (labs to be obtained within 7 days of initiation of treatment).

Table 2 Adequate Organ Function Laboratory Values

System	Laboratory Value
Hematological	
Absolute neutrophil count (ANC)	≥1500/mcL without growth factor dependency (including erythropoietin (EPO), granulocyte-colony stimulating factor (G-CSF), or platelet derived growth factor (PDGF) stimulating agents) within 7 days of assessment
Platelets	≥100,000/mcL
Hemoglobin	≥9 g/dL or ≥5.6 mmol/L without transfusion or EPO dependency (within 7 days of assessment)
Renal	
Creatinine **OR** Measured or calculated creatinine clearance (glomerular filtration rate [GFR] can also be used in place of creatinine or creatinine clearance [CrCl])	≤1.5 X upper limit of normal (ULN) **OR** ≥60 mL/min for subject with creatinine levels >1.5 X institutional ULN *Note: Creatinine clearance should be calculated per institutional standard*
Hepatic	
Total Bilirubin	≤1.5 X ULN **OR** Direct bilirubin ≤ULN for subjects with total bilirubin levels >1.5 ULN
Aspartate aminotransferase (AST) (serum glutamic oxaloacetic transaminase [SGOT]) and Alanine aminotransferase (ALT) (serum glutamic-pyruvic transaminase [SGPT])	≤2.5 X ULN **OR** ≤5 X ULN for subjects with liver metastases
Coagulation	
International Normalized Ratio (INR) or Prothrombin Time (PT)	≤1.5 X ULN unless the subject is receiving anticoagulant therapy
Activated Partial Thromboplastin Time (aPTT) or Partial Thromboplastin Time (PTT)	≤1.5 X ULN unless the subject is receiving anticoagulant therapy

6. A female subject is eligible to participate if she is not pregnant or breastfeeding, and at least one of the following conditions applies:

   - Is not a WOCBP

   OR

   - Is a WOCBP and using a contraceptive method that is highly effective (with a failure rate of <1% per year), with low user dependency, or be abstinent from heterosexual intercourse as their preferred and usual lifestyle (abstinent on a long term and persistent basis), as described in Section 12.8 during the intervention period and for at least 180 days after the last dose of chemotherapy, 120 days after the last dose of pembrolizumab or MK-4280, or 30 days after the last dose of lenvatinib, whichever occurs last. The investigator should evaluate the potential

for contraceptive method failure (ie, noncompliance, recently initiated) in relationship to the first dose of study intervention.

- **Arm 3 and Arm 4 only:** WOCBP must also agree not to donate eggs (ova, oocytes) to others or freeze/store for her own use for the purpose of reproduction during and for at least 180 days after the last dose of chemotherapy.
- A WOCBP must have a negative highly sensitive pregnancy test (urine or serum as required by local regulations) within 72 hours before the first dose of study intervention.

  Arm 6 only: A WOCBP must have a negative highly sensitive pregnancy test (urine or serum as required by local regulations) within 24 hours before the first dose of study intervention.
- If a urine test cannot be confirmed as negative (eg, an ambiguous result), a serum pregnancy test is required. In such cases, the participant must be excluded from participation if the serum pregnancy result is positive.
- Abstain from breastfeeding during the study intervention period and for at least 180 days after the last dose of chemotherapy, 120 days after the last dose of pembrolizumab or MK-4280, or 30 days after the last dose of lenvatinib, whichever occurs last.
- Additional requirements for pregnancy testing during and after study intervention are located in Section 7.1.2.7.
- The investigator is responsible for review of medical history, menstrual history, and recent sexual activity to decrease the risk for inclusion of a woman with an early undetected pregnancy.
- Contraceptive use by women should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies.
- If the contraception requirements in the local label for any of the study drugs is more stringent than the requirements above, the local label requirements should be followed.

7. Male subjects are eligible to participate if they agree to the following during the intervention period and for at least 95 days after the last dose of chemotherapy or 7 days after the last dose of lenvatinib, whichever occurs last:
   - Be abstinent from heterosexual intercourse as their preferred and usual lifestyle (abstinent on a long term and persistent basis) and agree to remain abstinent

     OR
   - Must agree to use contraception unless confirmed to be azoospermic (vasectomized or secondary to medical cause Section 12.8) as detailed below:
     - Agree to use a male condom plus partner use of an additional contraceptive method when having penile-vaginal intercourse with a WOCBP who is not currently pregnant. Note: Men with a pregnant or breastfeeding partner must agree to remain abstinent from penile-vaginal

intercourse or use a male condom during each episode of penile-vaginal penetration.

- **Arm 3 and Arm 4 only:** Male subjects must also refrain from donating sperm for at least 95 days after the last dose of chemotherapy.
- Contraceptive use by men should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies.
- If the contraception requirements in the local label for any of the study drugs is more stringent than the requirements above, the local label requirements should be followed.
- Note: For male participants who only receive pembrolizumab or MK-4280, or a combination of the aforementioned drugs, no contraception measures are needed.

8. Voluntarily agree to participate by the subject (or their legally acceptable representative) providing documented informed consent/assent for the trial. The subject (or their legally acceptable representative) may also provide consent/assent for Future Biomedical Research. However, the subject may participate in the main trial without participating in Future Biomedical Research.

The following criterion applies to all subjects except those being considered for enrollment into Cohort F:

9. Submit an evaluable baseline tumor sample for PD-L1 analysis (either a newly obtained or archival tumor sample) as specified in the Procedures Manual.

The following criterion applies only to subjects being considered for treatment on Arm 6:

10. Have adequately controlled BP with or without antihypertensive medications, defined as BP ≤150/90 mm Hg with no change in antihypertensive medications within 1 week prior to randomization.

5.1.3 Subject Exclusion Criteria

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

1. Has had chemotherapy, radiation, or biological cancer therapy within 4 weeks prior to the first dose of study therapy, or who has not recovered to CTCAE Grade 0 or 1 from the AEs due to cancer therapeutics administered more than 4 weeks earlier (this includes subjects who received previous immunomodulatory therapy with residual immune-related adverse events [irAEs]). Subjects receiving ongoing replacement hormone therapy for endocrine irAEs will not be excluded from participation in this study.

   Note: Subjects with Grade 2 neuropathy are excluded from Arm 3 of Part B but may be eligible for all other arms of Part B.

2. Is currently participating and receiving study therapy, or has participated in a study of an investigational agent and received study therapy, or used an investigational device within 4 weeks of the first dose of study treatment.
3. Has received previous treatment with another agent targeting the LAG-3 receptor.

4. Has received previous treatment with an immunomodulatory therapy (eg, anti-PD-1/PD-L1 or CTLA-4 agent) and was discontinued from that therapy due to a Grade 3 or higher irAE.
5. Is expected to require any other form of antineoplastic therapy while on study.
6. Has a diagnosis of immunodeficiency or is receiving chronic systemic steroid therapy in excess of replacement doses, or on any other form of immunosuppressive medication. Subjects (ie, with asthma) that require intermittent use of bronchodilators, inhaled steroids, or local steroid injections would not be excluded from the study.
7. Has a history of a previous, additional malignancy, unless potentially curative treatment has been completed, with no evidence of malignancy for 5 years.
    a. Note: The time requirement for no evidence of disease for 5 years does not apply to the tumor for which a subject is enrolled in the study. The time requirement does not apply to subjects who underwent successful definitive resection of basal cell carcinoma of the skin, superficial bladder cancer or in situ cervical cancer, or other in situ cancers.
8. Has known active central nervous system (CNS) metastases and/or carcinomatous meningitis. Subjects with previously treated brain metastases may participate provided they are radiologically stable, ie, without evidence of progression for at least 4 weeks by repeat imaging (note that the repeat imaging should be performed during study screening), clinically stable and without requirement of steroid treatment for at least 14 days prior to first dose of trial treatment.
9. Has had a severe hypersensitivity reaction to treatment with another monoclonal antibody.
10. Has an active autoimmune disease or a documented history of autoimmune disease, except vitiligo or resolved childhood asthma/atopy. Replacement therapy (eg, thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency, etc.) is not considered a form of systemic treatment.
11. Has an active infection requiring therapy.
12. Has a history of (non-infectious) pneumonitis that required steroids or has current pneumonitis.
13. Has had a prior stem cell or bone marrow transplant.
14. Has a known history of or screens positive for Human Immunodeficiency Virus (HIV) (HIV 1/2 antibodies), or an active chronic or acute Hepatitis B (eg, hepatitis B surface antigen [HBsAg] reactive) or Hepatitis C infection (eg, hepatitis C virus [HCV] RNA [qualitative] is detected).
15. Has a history or current evidence of any condition, therapy, or laboratory abnormality that might confound the results of the study, interfere with the subject's participation for the full duration of the study, or is not in the best interest of the subject to participate, in the opinion of the treating investigator.

16. Has known psychiatric or substance abuse disorders that would interfere with cooperation with the requirements of the trial.
17. Is a regular user as determined by investigator judgement (including "recreational use") of any illicit drugs or has a recent history (within the last year) of substance abuse (including alcohol), at the time of signing informed consent.
18. Has symptomatic ascites or pleural effusion. A subject who is clinically stable following treatment for these conditions (including therapeutic thoraco- or paracentesis) is eligible.
19. Has clinically significant heart disease that affects normal activities.
20. Has had major surgery in the past 4 weeks.
21. Has received a live or live-attenuated vaccine within 30 days before the first dose of study intervention. Seasonal flu vaccines that do not contain live virus are permitted. Refer to Section 5.5.2 for information on COVID-19 vaccines.

Subjects being considered for enrollment into Arm 4 with CRC in Part B are also excluded if any of the following additional criteria (22 through 24) apply:

22. Has plans to use, or is using, any herbal medications/supplements or any medications or foods that are strong inhibitors or inducers of cytochrome P450 3A 4/5 ≤1 week prior to the start of study treatment.
23. Has received previous treatment with irinotecan.
24. Has a known diagnosis of Gilbert's Syndrome.

Subjects being considered for enrollment into Arm 6 in Part B are also excluded if any of the following additional criteria (25 through 36) apply:

25. Has received previous treatment with lenvatinib.

    Note: Prior therapy with other kinase inhibitors that target VEGF are not exclusionary.
26. Has had major surgery within 3 weeks prior to first dose of study interventions. Note: Adequate wound healing after major surgery must be assessed clinically, independent of time elapsed for eligibility.
27. Has preexisting ≥Grade 3 gastrointestinal or non-gastrointestinal fistula.
28. Has urine protein ≥1 g/24 hours.

    Note: Subjects with proteinuria >1+ on urine dipstick testing/urinalysis will undergo 24-hour urine collection for quantitative assessment of proteinuria.
29. Has a left ventricular ejection fraction (LVEF) below the institutional (or local laboratory) normal range, as determined by multigated acquisition (MUGA) or echocardiogram (ECHO).

30. Has radiographic evidence of encasement or invasion of a major blood vessel, or of intratumoral cavitation.

    NOTE: The degree of proximity to major blood vessels should be considered because of the potential risk of severe hemorrhage associated with tumor shrinkage/necrosis following lenvatinib therapy.

31. Prolongation of QTcF interval to >480 ms.
32. Has clinically significant cardiovascular disease within 12 months from first dose of study intervention, including New York Heart Association Class III or IV congestive heart failure, unstable angina, myocardial infarction, cerebral vascular accident, or cardiac arrhythmia associated with hemodynamic instability. Note: Medically controlled arrhythmia would be permitted.
33. Has present or progressive accumulation of pleural, ascitic, or pericardial fluid requiring drainage or diuretic drugs within 2 weeks prior to enrollment. The subject can receive diuretic drugs as needed per the treating physician, outside of the above mentioned conditions. Consult with the Sponsor if the subject has more than trivial/trace fluid accumulation.
34. Serious nonhealing wound, ulcer or bone fracture.
35. Has presence of gastrointestinal condition including malabsorption that might affect the absorption of lenvatinib.
36. Has clinically significant hemoptysis or tumor bleeding within 2 weeks prior to the first dose of study drug.

5.2 Trial Treatment(s)

The treatment(s) to be used in this trial are outlined below in Table 3.

Country-specific differences are noted in Appendix 12.7.

Table 3 Trial Treatments

Drug	Dose/ Potency	Dose Frequency	Route of Administration	Regimen/ Treatment Period	Use
Part A, Arm 1					
MK-4280	7 mg 21 mg 70 mg 210 mg 700 mg	Q3W	Intravenous (IV) Infusion	Day 1 of each 21-day cycle	Test Product
Part A, Arm 2					
MK-4280	7 mg 21 mg 70 mg 210 mg 700 mg	Q3W	Intravenous (IV) Infusion	Day 1 of each 21-day cycle	Test Product
Pembrolizumab	200 mg	Q3W	IV Infusion	Day 1 of each 21-day cycle	Test Product
Part B, Arm 1					
MK-4280	800 mg[a]	Q3W	IV infusion	Day 1 of each 21-day cycle	Test Product
Part B, Arm 2A					
MK-4280	200 mg[a]	Q3W	IV infusion	Day 1 of each 21-day cycle	Test Product
Pembrolizumab	200 mg	Q3W	IV Infusion	Day 1 of each 21-day cycle	Test Product
Part B, Arm 2B					
MK-4280	700 mg	Q3W	IV infusion	Day 1 of each 21-day cycle	Test Product
Pembrolizumab	200 mg	Q3W	IV Infusion	Day 1 of each 21-day cycle	Test Product
Part B, Arm 2C					
MK-4280	800 mg	Q3W	IV infusion	Day 1 of each 21-day cycle	Test Product
Pembrolizumab	200 mg	Q3W	IV Infusion	Day 1 of each 21-day cycle	Test Product

Drug		Dose/ Potency	Dose Frequency	Route of Administration	Regimen/ Treatment Period	Use
Part B, Arm 3						
MK-4280		800 mg	Q3W	IV infusion	Day 1 of each 21-day cycle	Test Product
Pembrolizumab		200 mg	Q3W	IV Infusion	Day 1 of each 21-day cycle	Test Product
mFOLFOX7	Oxaliplatin	85 mg/m^2 65 mg/m^2 [b]	Q2W	IV infusion	Odd Number Cycles: Day 1, Day 15 Even Number Cycles: Day 8	Background Therapy[d]
	Leucovorin[c] (Calcium Folinate)	400 mg/m^2		IV infusion		
	5-FU	2400 mg/m^2 2000 mg/m^2 [b]		IV infusion		
Part B, Arm 4						
MK-4280		800 mg	Q3W	IV infusion	Day 1 of each 21-day cycle	Test Product
Pembrolizumab		200 mg	Q3W	IV Infusion	Day 1 of each 21-day cycle	Test Product
FOLFIRI	Irinotecan	180 mg/m^2 150 mg/m^2 [b]	Q2W	IV infusion	Odd Number Cycles: Day 1, Day 15 Even Number Cycles: Day 8	Background Therapy[d]
	Leucovorin[c] (Calcium Folinate)	400 mg/m^2		IV infusion		
	5-FU	2400 mg/m^2 2000 mg/m^2 [b]		IV infusion		
Part B, Arm 5						
MK-4280A		800 mg MK-4280 + 200 mg pembrolizumab	Q3W	IV infusion	Day 1 of each 21-day cycle	Test Product

Drug	Dose/ Potency	Dose Frequency	Route of Administration	Regimen/ Treatment Period	Use
Part B, Arm 6					
MK-4280	800 mg	Q3W	IV infusion	Day 1 of each 21-day cycle	Test Product
Pembrolizumab	200 mg	Q3W	IV Infusion	Day 1 of each 21-day cycle	Test Product
Lenvatinib	20 mg 14 mg 10 mg 8 mg	QD	Oral	QD of each 21-day cycle	Test Product

a. From a preliminary analysis of MK-4280 PK and pharmacodynamic biomarker data collected during Part A, the preliminary RP2D for MK-4280 to carry forward into Part B of the study was determined to be 200 mg. Following the accumulation of more data, the Sponsor has elected to test the higher 800 mg dose of MK-4280 in Part B as well.
b. Reduced doses for components of mFOLFOX7 and/or FOLFIRI will only be used if the TPI calls for a de-escalation.
c. Depending on local practice guidelines, levofolinate calcium (200 mg/m^2 Q2W) may be substituted for leucovorin.
d. Every attempt should be made to source these supplies from a single lot/batch number. The trial site is responsible for recording the lot number, manufacturer, and expiry date for any locally purchased product as per local guidelines unless otherwise instructed by the Sponsor.

5.2.1 Part A – Dose Escalation of Arm 1 (MK-4280 Monotherapy) and Arm 2 (MK-4280 + Pembrolizumab)

In Part A, Arm 1 dose escalation will follow a 3+3 design and will begin with 7 mg of MK-4280 in cohorts of 3 to 6 subjects each (expansion to 6 subjects based on the occurrence of a DLT in the first 3 subjects), and may proceed based on safety events up to a dose of 700 mg until an MTD or MAD is identified.

Enrollment to Part A, Arm 2, (MK-4280 in combination with pembrolizumab) will begin once all subjects complete 1 cycle of MK-4280 monotherapy at both the 7 mg and 21 mg dose levels in Arm 1, and will follow a 3+3 design to identify a preliminary RP2D for MK-4280. The higher dose level cohort of Arm 1 must be fully enrolled and all subjects must begin dosing before the next lower dose level of Arm 2 begins enrollment. However, once an MTD or MAD is identified in Arm 1, the dose of MK-4280 in Arm 2 may continue escalation up to that dose. For enrollment to the last 2 dose levels of Arm 2, all 3 (or 6) subjects in the second highest dose level must complete 1 cycle of treatment and DLT evaluation before the highest dose level may begin enrollment.

The starting dose of MK-4280 for both arms will be 7 mg and will be escalated as described in Table 3. The dose of pembrolizumab will be fixed at 200 mg. During the 3+3 dose escalation, at least 2 days of observation will occur between each of the first 3 subjects at each dose level.

Enrollment to both arms will occur in parallel with treatment allocation accomplished by nonrandom assignment to Arm 1 or Arm 2 of Part A using an interactive voice response system/integrated web response system (IVRS/IWRS).

In Arm 2, pembrolizumab will be administered first and then, after a 30 minute observation period, MK-4280 will be administered.

5.2.2 Part B – Dose Confirmation and Efficacy Expansion Cohorts

5.2.2.1 Arm 1 MK-4280 Monotherapy

The 2 Arm 1 monotherapy cohorts of Part B (Cohort A in 3L+ CRC and Cohort E in PD-1 treatment naïve gastric cancer) will each enroll 20 subjects at the 800 mg MK-4280 dose to assess the antitumor activity of MK-4280 monotherapy. Monotherapy subjects with confirmed disease progression per irRECIST 1.1 will be allowed to crossover to Arm 2C and receive 800 mg MK-4280 in combination with pembrolizumab (see Section 5.2.7).

The gastric monotherapy cohort (Cohort E Arm 1) will be opened only if preliminary antitumor activity is observed (≥8 of 40 subjects with an objective response, irrespective of dose, Section 5.2.2.2.4) in the gastric cancer combination cohort (Cohort E Arm 2). Enrollment will not be paused in the Arm 2 gastric cancer cohort to make this determination.

DLTs will also be evaluated in subjects enrolling at the 800 mg dose level after at least 10 subjects have completed the DLT evaluation period. Enrollment will not be paused while this evaluation is performed.

5.2.2.2 Arm 2 – MK-4280 + Pembrolizumab

5.2.2.2.1 Dose Confirmation Using TPI in Subjects With HNSCC or CRC (Arm 2A)

Part B dose confirmation will refine the estimate of tolerability of the preliminary RP2D of MK-4280 in combination with 200 mg pembrolizumab identified in Part A, Arm 2 using a TPI design [1] for the first 14 subjects enrolled in Cohort A, Cohort C, and Cohort D. Enrollment of subjects into Cohort E should not begin until the TPI portion of this part has been completed.

5.2.2.2.2 Adaptive Efficacy Expansion Cohorts (Arm 2A)

The CRC and PD-1-treatment-naïve HNSCC cohorts (Cohort A and Cohort C) in Arm 2A are designed to allow for expanded subject enrollment if a predefined ORR is observed in these cohorts. Specifically, these cohorts (see Section 5.1 – Entry Criteria) will each initially enroll 10 subjects. If, within an individual cohort, an ORR of 20% or greater is observed (ie, 2 or more of 10 subjects experience an objective response), that specific cohort will be expanded to enroll additional subjects. The CRC cohort (Cohort A) may enroll a maximum of 90 additional subjects, for a maximum enrollment of 100 subjects. The HNSCC cohort (Cohort C) may enroll a maximum of 30 additional subjects, for a maximum enrollment of 40 subjects. Enrollment will not be paused in the time period between when 10 subjects have been enrolled and when the interim analysis is completed. If a cohort does not reach this efficacy threshold, the Sponsor will evaluate all available data to determine whether or not to expand enrollment. For more details on how these adaptive cohorts will affect the total

number of trial subjects, see Section 8.9 - Sample Size and Power Calculations. Subject enrollment and the decision to expand these cohorts in Part B will be controlled using an IVRS/IWRS along with regular communication from the Sponsor.

5.2.2.2.3 PD-1/PD-L1-treatment-failure HNSCC Cohort (Arm 2A)

A cohort of 20 subjects with HNSCC that have progressed following anti-PD-1/PD-L1 therapy (as defined in Section 5.1.2 – Subject Inclusion Criteria, Cohort D) will be enrolled in a nonadaptive fashion controlled using an IVRS/IWRS.

5.2.2.2.4 Dose Finding in Subjects With Gastric Cancer (Arm 2A and 2B)

Subjects with gastric cancer (Cohort E) of Part B will be randomized 1:1 via an IVRS/IWRS to either the preliminary RP2D from Part A (200 mg, Arm 2A) or 700 mg (Arm 2B) dose level of MK-4280 in combination with a fixed dose of pembrolizumab to more thoroughly assess differences in activity and safety/tolerability of these doses. However, if the TPI portion of Part B calls for a de-escalation of the RP2D, these doses will be modified accordingly, and the decision to modify these doses will be communicated to sites via an administrative letter before enrollment into this cohort begins.

5.2.2.2.5 Additional MK-4280 Dose in Part B (Arm 2C)

Based on accumulating data from the study, the Sponsor has elected to test an 800 mg dose of MK-4280 in Part B (see Section 4.2.2.1.2 for rationale). An additional 40 subjects with CRC will be enrolled and receive 800 mg MK-4280 in combination with pembrolizumab (Arm 2C).

DLTs will be evaluated in the subjects enrolling at the 800 mg dose level in combination with pembrolizumab after at least 10 subjects have completed the DLT evaluation period. Enrollment will not be paused while this evaluation is performed.

5.2.2.3 Arm 3 and Arm 4 – MK-4280 + Pembrolizumab + mFOLFOX7/FOLFIRI

Subjects with CRC that have received ≤1 line of prior systemic therapy in Part B (Cohort B) will be assigned to receive MK-4280 (800 mg) in combination with pembrolizumab (200 mg) and either mFOLFOX7 (Arm 3) or FOLFIRI (Arm 4). Arm 3 and 4 will not begin enrollment until 10 subjects have completed the DLT period in Arm 2C. A TPI design will be used to assess the safety and tolerability of Arms 3 and 4 in the first 14 subjects enrolled into each arm, independently. If the TPI calls for a de-escalation, the reduced doses of FOLFOX and/or FOLFIRI designated in Table 3 will be used. The doses of MK-4280 and pembrolizumab will not be adjusted.

5.2.2.4 Arm 5 – MK-4280A

Forty subjects with CRC from Cohort A and all subjects from Cohort F (up to 20 Chinese subjects with solid tumors) will be enrolled to receive MK-4280A, a co-formulated product of MK-4280 and pembrolizumab. Subjects will receive a dose of MK-4280A consisting of 800 mg of MK-4280 and 200 mg pembrolizumab. The dose of MK-4280A will not be adjusted. Arm 5 will not begin enrollment until 10 subjects have completed the DLT period in Arm 2C.

In Arm 5, Cohort A, the Sponsor will evaluate DLTs when at least 10 subjects have completed the DLT period to confirm the safety of Arm 5. Only subjects at sites in the US may be enrolled to Arm 5, Cohort A. Only subjects at sites in China may be enrolled to Arm 5, Cohort F.

5.2.2.5 Arm 6 – MK-4280 + Pembrolizumab + Lenvatinib

Subjects with CRC that have received 2 lines of prior systemic therapy in Part B (Cohort G) will be assigned to receive MK-4280 800 mg Q3W in combination with pembrolizumab 200 mg Q3W and lenvatinib 20 mg QD. A TPI design will be used to assess the safety and tolerability of Arm 6 in the first 14 subjects enrolled. If the TPI calls for a de-escalation, reduced doses of lenvatinib (14 mg and 10 mg) will be used. The doses of MK-4280 and pembrolizumab will not be adjusted.

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

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.

5.2.3 Dose Selection/Escalation

5.2.3.1 Dose Selection (Preparation)

The rationale for selection of doses to be used in this trial is provided in Section 4.0 – Background & Rationale.

Details on preparation of administration of MK-4280, pembrolizumab, mFOLFOX7, and FOLFIRI are provided in the Procedure Manual.

5.2.3.2 3+3 Dose Escalation Design

In Part A, Arm 1 (MK-4280 monotherapy), a 3+3 dose escalation design will be used to identify a preliminary MTD or MAD for MK-4280. Part A, Arm 2 (MK-4280 in combination with pembrolizumab) will also use a 3+3 dose escalation design to identify a preliminary RP2D for MK-4280 when given in combination with pembrolizumab. The starting dose of MK-4280 for both arms will be 7 mg and will be escalated as described in Table 3. The dose of pembrolizumab will be fixed at 200 mg Q3W.

During Part A, Arm 1, the study will enroll 3 subjects at each dose level, with at least 2 days of observation occurring between each of the first 3 subjects at each of the first 2 dose levels. The rules for the preliminary MK-4280 dose escalation using the 3+3 design are as follows (all dose adjustments are made only to MK-4280):

An initial cohort of 3 subjects is enrolled:

- If 0 of 3 subjects develops a DLT, escalation to the next dose of MK-4280 will occur.
- If 1 of 3 subjects develops a DLT, another 3 subjects will be enrolled at this dose level.
    - If 0 of the 3 new subjects develops a DLT (for a total of 1 of 6 subjects with a DLT at this dose level), escalation to the next dose level will occur.
    - If 1 or more of the 3 new subjects develop a DLT (for a total of at least 2 of 6 subjects with a DLT at this dose level), the dose escalation stage of the trial will be terminated. If the dose level directly below the current dose level had been studied in at least 3 subjects, the dose level directly below the current dose level will be considered the preliminary RP2D, and the study will proceed to the confirmation stage. If the dose level directly below the current dose level had been studied in less than 3 subjects, more subjects to a total of 3 will be enrolled at the dose level directly below the current dose level before proceeding to the confirmation stage.
- If at least 2 of 3 subjects develop a DLT, the dose escalation stage of the trial will be terminated. If the dose level directly below the current dose level had been studied in at least 3 subjects, the dose level directly below the current dose level will be considered the preliminary RP2D, and the study will proceed to the confirmation stage. If the dose level directly below the current dose level had been studied in less than 3 subjects, more subjects to a total of 3 will be enrolled at the dose level directly below the current dose level before proceeding to the confirmation stage.

It is conceptually acceptable to de-escalate to an intermediate, not predefined and not previously-studied dose of MK-4280, if evaluation of toxicity at such a dose level is desired in lieu of proceeding directly to the dose confirmation stage of the study. If this approach is taken, 3 new subjects should be enrolled at the new intermediate dose level, and the aforementioned rules should be used to determine further enrollment at this dose level. This would be communicated to sites via an administrative letter.

If the highest candidate dose of MK-4280 is studied during dose escalation of Part A, Arm 2, and 0 of 3, or less than 2 of 6, subjects develop a DLT at that dose, then dose escalation will terminate with this finding and this dose level may be taken to the confirmation stage (Part B).

5.2.3.3 Dose Confirmation – Arm 2A

The objective of dose confirmation in Part B is to refine the estimate of tolerability of the MK-4280 preliminary RP2D (when delivered in combination with pembrolizumab) based on a TPI design [1] with a target toxicity rate less than or equal to 30%, utilizing the first 14 subjects enrolled in this part in Cohort A, Cohort C, and Cohort D. Dose confirmation involves the expansion of at least 1 dose level studied in the dose-escalation stage of the study. After dosing of the first 14 subjects in Part B, dosing will continue as planned.

The 200 mg dose of pembrolizumab will not be adjusted.

Table 4 Dose Confirmation Rules

	Number of Subjects Treated at Current Dose										
Number of Toxicities	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**
0	S	E	E	E	E	E	E	E	E	E	E
1	S	S	S	S	S	S	E	E	E	E	E
2	D	S	S	S	S	S	S	S	S	S	S
3	DU	D	D	S	S	S	S	S	S	S	S
4	DU	DU	DU	D	D	D	S	S	S	S	S
5		DU	DU	DU	DU	DU	D	D	S	S	S
6			DU	DU	DU	DU	DU	DU	D	D	D
7				DU	DU	DU	DU	DU	DU	DU	D
8					DU	DU	DU	DU	DU	DU	DU
9						DU	DU	DU	DU	DU	DU
10							DU	DU	DU	DU	DU
11								DU	DU	DU	DU
12									DU	DU	DU
13										DU	DU
14											DU
E = Escalate to the next higher dose. S = Stay at the current dose. D = De-escalate to the next lower dose. DU = The current dose is unacceptably toxic. Target toxicity rate = 30%. Noninformative prior is used: a=1; b=1; k1=1; k2=1.5; pow=1 per [1].											

Subjects may be enrolled continuously (ie, without waiting for Cycle 1 completion of subjects who have received the first dose) unless a DLT is observed at the particular dose. Once a DLT is observed, the number of subjects who are enrolled at that dose but are not yet fully evaluable for DLT assessment may not exceed the number of remaining subjects who are at risk of developing a DLT before the dose would be considered unacceptably toxic (denoted as DU in Table 4). For example, if 3 of 7 subjects have experienced a DLT at a given dose level, no more than an additional 2 subjects should be enrolled at this dose level until additional DLT data are available. This is because this dose level would be considered unacceptably toxic if all 2 of the additional subjects experience a DLT (ie, 5 of 9 subjects with DLT in Table 4). To find out how many more subjects can be enrolled, one can count

steps in diagonal direction (down and to the right) from the cell (7 subjects, 3 toxicities) to the first cell marked DU.

If enrollment expands to 14 subjects for a dose level, and less than or equal to 5 of 14 subjects develop a DLT, then the dose confirmation will stop. If enrollment expands to 14 subjects for a dose level and greater than 5 of 14 subjects develop a DLT, then the next lower dose may be expanded to further explore the dose-response relationship. Even if less than or equal to 5 of 14 subjects develop a DLT for a dose level, the next lower dose level may be expanded if there is a potential safety concern. Note that although 30% has been the target toxicity rate used to generate the guidelines in Table 4, the observed rate of subjects with DLT at the MTD may be slightly above or below 30%.

5.2.3.4 Dose Confirmation – Arm 3 and Arm 4

A TPI design will be used to assess the safety and tolerability of MK-4280 and pembrolizumab when administered in combination with either mFOLFOX7 or FOLFIRI and to determine RP2Ds of the triplet combinations, with a target toxicity rate less than or equal to 30%, utilizing the first 14 subjects enrolled in each arm. At the start of each new dose, 3 subjects will be enrolled (with at least 24 hours between each of these 3 subjects) and must complete their DLT evaluation period before additional subjects can be enrolled. Assuming no DLTs in the first 3 subjects have completed their DLT evaluation period, up to 6 subjects at a time can be enrolled and evaluated for DLTs following TPI rules, until 14 subjects are enrolled. If 1 or more DLTs are observed in the first 3 subjects on either cohort, 3 subjects at a time may enroll simultaneously for DLT assessment, until 14 subjects are treated. All other rules regarding the enrollment of subjects and de-escalation of doses are the same as in Section 5.2.3.3 and in Table 4. If the TPI calls for an initial de-escalation, the doses of mFOLFOX7 and/or FOLFIRI will be adjusted as described in Table 3. If this lower dose is still determined to be unacceptably toxic, enrollment into that Arm will be closed. If, after 14 subjects are treated at a particular dose level, the TPI calls for “Stay” (or “Escalate” at the highest dose level), this dose will be considered the RP2D and an additional 6 subjects will be enrolled. Note that the TPI will operate independently for Arm 3 and Arm 4.

5.2.3.5 Dose Confirmation – Arm 6

A TPI design will be used to assess the safety and tolerability of MK-4280 and pembrolizumab when administered in combination with lenvatinib and to determine the RP2D of this triplet combination, with a target toxicity rate less than or equal to 30%, utilizing the first 14 subjects enrolled in this arm. At the start of each new dose, 3 subjects will be enrolled (with at least 24 hours between each of these 3 subjects) and must complete their DLT evaluation period before additional subjects can be enrolled. Assuming no DLTs in the first 3 subjects after completing their DLT evaluation period, up to 6 subjects at a time can be enrolled and evaluated for DLTs following TPI rules, until 14 subjects are enrolled. If 1 or more DLTs are observed in the first 3 subjects, 3 subjects at a time may enroll simultaneously for DLT assessment, until 14 subjects are treated. All other rules regarding the enrollment of subjects and de-escalation of doses are the same as in Section 5.2.3.3 and in Table 4. If the TPI calls for de-escalation, the reduced doses of lenvatinib (14 mg and 10 mg) will be used. If TPI calls for de-escalation to the lowest dose of lenvatinib, and this lower dose is still determined to be unacceptably toxic, enrollment into this Arm will be closed. If,

after 14 subjects are treated at a particular dose level, the TPI calls for "Stay" (or "Escalate"), this dose will be considered the RP2D and the remainder of the cohort will be enrolled.

5.2.4 Definition of Dose Limiting Toxicity

Dose limiting toxicities will be defined from toxicities observed during the first cycle of treatment (21 days) for each dose level. See Section 5.9 for rules on replacement of subjects in the DLT period.

The occurrence of any of the following toxicities during Cycle 1, if assessed by the investigator to be unrelated to the underlying disease, will be considered a DLT:

- Grade 4 non-hematologic toxicity (not laboratory)
- Grade 4 hematologic toxicity lasting at least 7 days, except thrombocytopenia
    a. Grade 4 thrombocytopenia of any duration
    b. Grade 3 thrombocytopenia if associated with bleeding
- Grade 3 nonhematologic toxicity (not laboratory) lasting more than 3 days despite optimal supportive care. Grade 3 nausea, vomiting, or diarrhea will be considered a DLT if lasting more than 3 days despite optimal supportive care.

  Arm 6 only: Excluding Grade 3 hypertension able to be controlled by medication.
- Any Grade 3 or Grade 4 nonhematologic laboratory abnormality, if
    - medical intervention is required, or
    - the abnormality leads to hospitalization, or
    - the abnormality persists for more than 1 week.
- Febrile neutropenia Grade 3 or Grade 4:
    - Grade 3 is defined as absolute neutrophil count (ANC) <1000/mm^3 with a single temperature of >38.3°C (101°F) or a sustained temperature of ≥38°C (100.4°F) for more than 1 hour.
    - Grade 4 is defined as ANC <1000/mm^3 with a single temperature of >38.3 degrees C (101 degrees F) or a sustained temperature of ≥38 degrees C (100.4 degrees F) for more than 1 hour, with life-threatening consequences and urgent intervention indicated.
- Any drug-related AE that caused the subject to discontinue treatment during Cycle 1
- Grade 5 toxicity
- Any treatment-related toxicity that causes a greater than 2-week delay in initiation of Cycle 2

5.2.5 Timing of Dose Administration

Trial treatment may be administered up to 3 days before or 5 days after the scheduled Day 1 of each cycle, beginning in Cycle 3. Cycle 2 Day 1 may be administered up to 5 days after the scheduled Day 1. For Arm 6 only, trial treatment may be administered up to 3 days before or 3 days after the scheduled Day 1 of each cycle, beginning in Cycle 3. Cycle 2 Day 1 may be administered up to 3 days after the scheduled Day 1. In addition, dosing interruptions are permitted in the case of medical / surgical events or logistical reasons not related to study therapy (eg, elective surgery, unrelated medical events, subject vacation, and/or holidays). Subjects should be placed back on study therapy within 2 weeks of the scheduled interruption, unless otherwise discussed with the Sponsor. The reason for interruption should be documented in the subject's study record.

In Arm 2 of Part A and Part B, pembrolizumab will be administered first on Day 1 of each cycle, with administration of MK-4280 occurring approximately 30 minutes after completion of the pembrolizumab administration.

In Arm 3 and Arm 4 of Part B, pembrolizumab will be administered first, with administration of MK-4280 occurring approximately 30 minutes after completion of the pembrolizumab administration. On visits where MK-4280, pembrolizumab, and chemotherapy are to be administered, chemotherapy should be given according to local practice guidelines 30 minutes after completion of the MK-4280 administration.

In Arm 6 of Part B, pembrolizumab will be administered first and then, following a 30-minute interval, MK-4280 will be administered. Lenvatinib will be taken orally with water (with or without food) at approximately the same time each day in 21-day cycles. However, on visit days when pembrolizumab and MK-4280 are also administered, lenvatinib will be administered 0 to 4 hours after the MK-4280 infusion is complete.

5.2.6 Dose Modification (Escalation/Titration/Other)

CTCAE Version 4.0 must be used to grade the severity of adverse events. If appropriate, the investigator may attribute each toxicity event to MK-4280, pembrolizumab, mFOLFOX7, FOLFIRI, or lenvatinib alone, or to any combination of these agents, and follow the dose modification guidelines accordingly in Table 5, Section 5.2.6.2, and Table 7. If a dose modification for toxicity occurs with any agent, the dose may not be re-escalated in that subject. Dose modifications are always based on the previous cycle.

For Part A, subjects may have 1 dose modification to MK-4280 throughout the course of the study. If further toxicity occurs or the criteria for resuming treatment are not met, the subject must be discontinued from the agent. If a subject experiences several toxicities and there are conflicting recommendations, following the most conservative dose adjustment is recommended (dose reduction appropriate to the most severe toxicity). For Part B, no dose reductions of MK-4280, pembrolizumab, or MK-4280A are permitted.

Reduction or holding of 1 agent and not the other agents is appropriate if, in the opinion of the investigator, the toxicity is clearly related to 1 of the study drugs. However for subject convenience in Arm 2, Arm 3, and Arm 4 (and crossover treatment), if 1 drug is delayed then the other drug(s) can be delayed until they can be administered. If, in the opinion of the

investigator, the toxicity is related to a combination of agents, both drugs should be held according to recommended dose modifications.

For Arm 6, subjects who interrupt or discontinue one or more drug(s) in the lenvatinib plus pembrolizumab plus MK-4280 combination due to toxicity can continue with the other drug(s) in the combination until criteria for treatment discontinuation are met (eg, unacceptable toxicity, disease progression).

Refer to Section 5.2.6.4 for dose modification guidance for overlapping toxicity for the lenvatinib plus pembrolizumab plus MK-4280 combination.

Exceptional circumstances to following the dose modification tables below may be considered after consultation with the Sponsor.

5.2.6.1 Immune-Related Events and Dose Modification (Withhold, Treat, Discontinue)

Dose Modification and Toxicity Management for Immune-related AEs Associated with Pembrolizumab Monotherapy, Coformulations or IO Combinations

AEs associated with pembrolizumab monotherapy, coformulation, or IO combination exposure may represent an immune-related response. These irAEs may occur shortly after the first dose or several months after the last dose of pembrolizumab monotherapy, coformulation, or IO combination treatment and may affect more than one body system simultaneously. Therefore, early recognition and initiation of treatment is critical to reduce complications. Based on existing clinical study data, most irAEs were reversible and could be managed with interruptions of pembrolizumab monotherapy, coformulation, or IO combination 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.

Attribution of Toxicity:

When study interventions are administered in combination, attribution of an adverse event to a single component is likely to be difficult. Therefore, while the investigator may attribute a toxicity event to pembrolizumab monotherapy, coformulations, or IO combinations, pembrolizumab monotherapy, coformulations, or IO combinations must be held according to the criteria in the Dose Modification and Toxicity Management Guidelines for Immune-Related Adverse Events.

In these cases where the toxicity is attributed to pembrolizumab coformulations or IO combinations, re-initiation of pembrolizumab as a monotherapy may be considered after communication with and agreement by the Sponsor.

Holding Study Interventions:

When study interventions are administered in combination and if the AE is considered immune-related, pembrolizumab monotherapy, coformulations, or IO combinations should be held according to recommended Dose Modification criteria.

If the toxicity does not resolve or the criteria for resuming treatment are not met, the participant must be discontinued from pembrolizumab monotherapy, coformulations, or IO combinations.

Restarting Study Interventions:

Participants may restart pembrolizumab monotherapy, coformulations, or IO combinations as described below:

If the toxicities do resolve and conditions are aligned with what is defined in the Dose Modification and Toxicity Management Guidelines for irAEs, pembrolizumab monotherapy, coformulations, or IO combinations may be restarted at the discretion of the investigator.

Dose Modification and Toxicity Management Guidelines for irAEs associated with pembrolizumab monotherapy, coformulations, or IO combinations are provided in Table 5.

Table 5 Dose Modification and Toxicity Management Guidelines for Immune-related Adverse Events Associated with Pembrolizumab Monotherapy, Coformulations or IO Combinations

General instructions:
1. Severe and life-threatening irAEs should be treated with IV corticosteroids followed by oral steroids. Other immunosuppressive treatment should begin if the irAEs are not controlled by corticosteroids.
2. Pembrolizumab monotherapy, coformulations or IO combinations must be permanently discontinued if the irAE does not resolve or the corticosteroid dose is not ≤10 mg/day within 12 weeks of the last treatment.
3. The corticosteroid taper should begin when the irAE is ≤ Grade 1 and continue at least 4 weeks.
4. If pembrolizumab monotherapy, coformulations or IO combinations have been withheld, treatment may resume after the irAE decreased to ≤ Grade 1 after corticosteroid taper.

irAEs	Toxicity Grade (CTCAEv4.0)	Action With Pembrolizumab Monotherapy, Coformulations or IO Combinations	Corticosteroid and/or Other Therapies	Monitoring and Follow-up
Pneumonitis	Grade 2	Withhold	• Administer corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper	• Monitor participants for signs and symptoms of pneumonitis • Evaluate participants with suspected pneumonitis with radiographic imaging and initiate corticosteroid treatment • Add prophylactic antibiotics for opportunistic infections
	Recurrent Grade 2 or Grade 3 or 4	Permanently discontinue		
Diarrhea / Colitis	Grade 2 or 3	Withhold	• Administer corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper	• Monitor participants 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) • Participants with ≥Grade 2 diarrhea suspecting colitis should consider GI consultation and performing endoscopy to rule out colitis • Participants 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.
	Recurrent Grade 3 or Grade 4	Permanently discontinue		

irAEs	Toxicity Grade (CTCAEv4.0)	Action With Pembrolizumab Monotherapy, Coformulations or IO Combinations	Corticosteroid and/or Other Therapies	Monitoring and Follow-up
AST / ALT Elevation or Increased Bilirubin	Grade 2	Withhold	• Administer corticosteroids (initial dose of 0.5-1 mg/kg prednisone or equivalent) followed by taper	• Monitor with liver function tests (consider weekly or more frequently until liver enzyme value returned to baseline or is stable)
	Grade 3 or 4	Permanently discontinue	• Administer corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper	
T1DM or Hyperglycemia	New onset T1DM or Grade 3 or 4 hyperglycemia associated with evidence of β-cell failure	Withhold [a]	• Initiate insulin replacement therapy for participants with T1DM • Administer anti-hyperglycemic in participants with hyperglycemia	• Monitor participants for hyperglycemia or other signs and symptoms of diabetes
Hypophysitis	Grade 2	Withhold	• Administer corticosteroids and initiate hormonal replacements as clinically indicated	• Monitor for signs and symptoms of hypophysitis (including hypopituitarism and adrenal insufficiency)
	Grade 3 or 4	Withhold or permanently discontinue [a]		
Hyperthyroidism	Grade 2	Continue	• Treat with non-selective beta-blockers (eg, propranolol) or thionamides as appropriate	· Monitor for signs and symptoms of thyroid disorders
	Grade 3 or 4	Withhold or Permanently discontinue [a]		

irAEs	Toxicity Grade (CTCAEv4.0)	Action With Pembrolizumab Monotherapy, Coformulations or IO Combinations	Corticosteroid and/or Other Therapies	Monitoring and Follow-up
Hypothyroidism	Grade 2-4	Continue	• Initiate thyroid replacement hormones (eg, levothyroxine or liothyronine) per standard of care	• Monitor for signs and symptoms of thyroid disorders
Nephritis and renal dysfunction	Grade 2	Withhold	• Administer corticosteroids (prednisone 1-2 mg/kg or equivalent) followed by taper	• Monitor changes of renal function
	Grade 3 or 4	Permanently discontinue		
Myocarditis	Grade 1	Withhold	• Based on severity of AE administer corticosteroids	• Ensure adequate evaluation to confirm etiology and/or exclude other causes
	Grade 2, 3 or 4	Permanently discontinue		
All Other irAEs	Persistent Grade 2	Withhold	• Based on severity of AE administer corticosteroids	• Ensure adequate evaluation to confirm etiology or exclude other causes
	Grade 3	Withhold or discontinue [b]		
	Recurrent Grade 3 or Grade 4	Permanently discontinue		

AE(s)=adverse event(s); ALT= alanine aminotransferase; AST=aspartate aminotransferase; CTCAE=Common Terminology Criteria for Adverse Events; DRESS=Drug Rash with Eosinophilia and Systemic Symptom; GI=gastrointestinal; IO=immuno-oncology; ir=immune related; IV=intravenous; SJS=Stevens-Johnson Syndrome; T1DM=type 1 diabetes mellitus; TEN=Toxic Epidermal Necrolysis; ULN=upper limit of normal.

Note: Non-irAE will be managed as appropriate, following clinical practice recommendations.

[a] The decision to withhold or permanently discontinue pembrolizumab monotherapy, coformulations or IO combinations is at the discretion of the investigator or treating physician. If control achieved or ≤ Grade 2, pembrolizumab monotherapy, coformulations or IO combinations may be resumed.

[b] Events that require discontinuation include, but are not limited to: Guillain-Barre Syndrome, encephalitis, myelitis, DRESS, SJS, TEN and other clinically important irAEs (eg, vasculitis and sclerosing cholangitis).

Dose modification and toxicity management of infusion-reactions related to MK-4280 and pembrolizumab (or MK-4280A)

Pembrolizumab and MK-4280 (or MK-4280A) 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 study drug-related infusion reaction are provided in Table 6.

Table 6 Pembrolizumab and MK-4280 (or MK-4280A) Infusion Reaction Dose Modification and Treatment Guidelines

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

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

5.2.6.2 Dose Modification and Toxicity Management of AEs Related to mFOLFOX7 or FOLFIRI

mFOLFOX7

Dose delays and treatment restarts will be made at the discretion of the site investigator according to institutional guidelines or local standard practice. The recommended dose reduction is stepwise by 20%. Discontinuation of treatment should be considered if dose reduction below the following dosage is required: Oxaliplatin 50 mg/m^2 and 5-FU infusion 1600 mg/m^2 46 to 48 hours.

FOLFIRI

Dose delays and treatment restarts will be made at the discretion of the site investigator according to institutional guidelines or local standard practice. The recommended dose reduction is stepwise by 20%. Discontinuation of treatment should be considered if dose reduction below the following dosage is required: Irinotecan 120 mg/m^2 and 5-FU infusion 1600 mg/m^2 46 to 48 hours.

5.2.6.3 Dose Modification with Lenvatinib

Lenvatinib dose reduction and interruption for subjects who experience lenvatinib plus pembrolizumab plus MK-4280 combination therapy-related toxicity will be in accordance with the dose modification guidelines described in Table 7. An interruption of study treatment for more than 28 days will require Sponsor approval before treatment can be resumed.

The starting dose of lenvatinib is 20 mg/day. Dose reductions of lenvatinib occur in succession based on the previous dose level (14, 10, 8 mg/day). Any dose reduction below 8 mg mg/day must be discussed with the Sponsor. Once the lenvatinib dose has been reduced, it may not be increased at a later date, unless the dose has been mistakenly decreased; in this situation, the Sponsor's approval is required to increase the dose.

Refer to the subsections below for management of hypertension (Section 5.2.6.3.1), proteinuria (Section 5.2.6.3.2), diarrhea (Section 5.2.6.3.3), hepatotoxicity (Section 5.2.6.3.4), thromboembolic events (Section 5.2.6.3.5), posterior reversible encephalopathy syndrome/ reversible posterior leukoencephalopathy syndrome (PRES/RPLS; Section 5.2.6.3.6), hypocalcemia (Section 5.2.6.3.7), hemorrhage (Section 5.2.6.3.8), gastrointestinal perforation or fistula formation (Section 5.2.6.3.9), QT prolongation (Section 5.2.6.3.10), and osteonecrosis of the jaw (Section 5.2.6.3.11) as appropriate, before consulting the dose modification table (Table 7). For overlapping toxicities of pembrolizumab, MK-4280, and lenvatinib, please refer to Section 5.2.6.4.

Table 7 Dose Modification Guidelines for Lenvatinib-Related Adverse Events

Treatment-Related Toxicity[a,b]	**Management**	**Dose Adjustment**
Grade 1 or Tolerable Grade 2		
	Continue treatment	No change
Intolerable Grade 2[c, d] **or Grade 3**[e, f]		
First occurrence	Interrupt lenvatinib until resolved to Grade 0-1, or tolerable Grade 2	Reduce lenvatinib dose to 14 mg once a day (1-level reduction)
Second occurrence (same toxicity or new toxicity)	Interrupt lenvatinib until resolved to Grade 0-1, or tolerable Grade 2	Reduce lenvatinib dose to 10 mg once a day (1-level reduction)
Third occurrence (same toxicity or new toxicity)	Interrupt lenvatinib until resolved to Grade 0-1, or tolerable Grade 2	Reduce lenvatinib dose to 8 mg orally once a day (1-level reduction)
Fourth occurrence (same toxicity or new toxicity)	Interrupt lenvatinib	Discuss with Sponsor
Grade 4[g]**:** Discontinue Study Treatment		

Treatment-Related Toxicity[a,b]	Management	Dose Adjustment
Abbreviations: AE = adverse event; BMI = body mass index; CTCAE = Common Terminology Criteria for Adverse Events. Note: For grading see CTCAE version 4.0. Collect all AE grades (ie, decreasing and increasing CTCAE grade). a. An interruption of study treatment for more than 28 days will require Sponsor approval before treatment can be resumed. b. Initiate optimal medical management for nausea, vomiting, hypertension, hypothyroidism and/or diarrhea prior to any lenvatinib interruption or dose reduction. c. Applicable only to Grade 2 toxicities judged by the subject and/or physician to be intolerable. d. Obese subjects (BMI ≥30) with weight loss do not need to return to their baseline weight or within 10% of their baseline weight (ie, Grade 1 weight loss). These subjects may restart study intervention at a lower dose once their weight remains stable for at least 1 week and they have a minimum BMI of 25. The new stable weight should be used as the new baseline for further dose reductions. e. For asymptomatic laboratory abnormalities, such as Grade ≥3 elevations of amylase and lipase that are not considered clinically relevant by the investigator, continuation of treatment should be discussed with Sponsor. f. For Grade 3 thromboembolic event, permanently discontinue lenvatinib. See Section 5.2.6.3.5. g. Excluding laboratory abnormalities judged to be non-life-threatening, in which case manage as Grade 3.		

5.2.6.3.1 Management of Hypertension

Hypertension is a recognized side effect of treatment with drugs inhibiting VEGF signaling. Investigators should therefore ensure that subjects enrolled to receive treatment with lenvatinib have BP of ≤150/90 mm Hg at the time of study entry and, if known to be hypertensive, have been on a stable dose of antihypertensive therapy for at least 1 week before C1D1. Early detection and effective management of hypertension are important to minimize the need for lenvatinib dose interruptions and reductions.

Regular assessment of BP should be as detailed in the SoA (Section 6.3). Hypertension will be graded using NCI CTCAE v4.0, based on BP measurements only (and not on the number of antihypertensive medications).

If the subject's first BP measurement of the current assessment is elevated (ie, systolic BP ≥140 mm Hg or diastolic BP ≥90 mm Hg), the BP measurement should be repeated at least 5 minutes later. One BP assessment is defined as the mean value of 2 measurements at least 5 minutes apart. If the BP assessment (ie, the mean of the 2 BP measurements obtained at least 5 minutes apart) is elevated (systolic BP ≥140 mm Hg or diastolic BP ≥90 mm Hg), a confirmatory assessment should be obtained at least 30 minutes later by performing 2 measurements (at least 5 minutes apart) to yield a mean value.

Antihypertensive agents should be started as soon as elevated BP (systolic BP ≥140 mm Hg or diastolic BP ≥90 mm Hg) is confirmed on 2 assessments at least 30 minutes apart. The choice of antihypertensive treatment should be individualized to the subject's clinical

circumstances and follow standard medical practice. For previously normotensive subjects, appropriate antihypertensive therapy should be started when systolic BP ≥140 mm Hg or diastolic BP ≥90 mm Hg is first observed on 2 assessments at least 30 minutes apart. For those subjects already on antihypertensive medication, treatment modification may be necessary if hypertension persists.

Lenvatinib should be withheld in any instance where a subject is at imminent risk to develop a hypertensive crisis or has uncontrolled hypertension (eg, BP ≥160/100 mm Hg) with significant risk factors for severe complications, significant risk factors for cardiac disease, intracerebral hemorrhage, or other significant co-morbidities. Once the subject has been on the same antihypertensive medications for at least 48 hours and the BP is controlled, lenvatinib should be resumed as described below.

Subjects who have had systolic BP ≥160 mm Hg or diastolic BP ≥100 mm Hg must have their BP monitored on Day 15 (or more frequently as clinically indicated) until systolic BP has been ≤150 mm Hg and diastolic BP has been ≤95 mm Hg for 2 consecutive treatment cycles. If a repeat event of systolic BP ≥160 mm Hg or diastolic BP ≥100 mm Hg occurs, the subject must resume the Day 15 evaluation until systolic BP has been ≤150 mm Hg and diastolic BP has been ≤95 mm Hg for 2 consecutive treatment cycles. A diary will be provided to the subject to capture the blood pressure evaluations between study visits.

The following guidelines should be followed for the management of systolic BP ≥160 mm Hg or diastolic BP ≥100 mm Hg confirmed on 2 BP assessments at least 30 minutes:

1. Continue study drug and institute antihypertensive therapy for subjects not already receiving this.
2. For those subjects already on antihypertensive medication, the dose of the current agent may be increased, if appropriate, or 1 or more agents of a different class of antihypertensive should be added. Study treatment can be continued without dose modification.
3. If systolic BP ≥160 mm Hg or diastolic BP ≥100 mm Hg persists despite maximal antihypertensive therapy, then lenvatinib administration should be interrupted and restarted at 1 dose level reduction only when systolic BP ≤150 mm Hg and diastolic BP ≤95 mm Hg and the subject has been on a stable dose of antihypertensive medication for at least 48 hours.
    - If systolic BP ≥160 mm Hg or diastolic BP ≥100 mm Hg recurs on the first dose reduction despite optimal management of hypertension with antihypertensive medications (either by dose increase or the addition of a different class of antihypertensive), then lenvatinib administration should be interrupted and restarted at an additional dose reduction only when systolic BP ≤150 mm Hg and diastolic BP ≤95 mm Hg and the subject has been on a stable dose of antihypertensive medication for at least 48 hours.
    - If systolic BP ≥160 mm Hg or diastolic BP ≥100 mm Hg recurs on the second dose reduction despite optimal management of hypertension with antihypertensive medications (either by dose increase or the addition of a different class of antihypertensive), then lenvatinib administration should be

interrupted and restarted at a third dose reduction only when systolic BP ≤150 mm Hg and diastolic BP ≤95 mm Hg and the subject has been on a stable dose of antihypertensive medication for at least 48 hours.

- Additional dose reduction should be discussed with the Sponsor.

The following guidelines should be followed for the management of Grade 4 hypertension (life threatening consequences):

1. Institute appropriate medical management
2. Discontinue study drug

5.2.6.3.2 Management of Proteinuria

Regular assessment of proteinuria should be conducted as detailed in the SoA (Section 6.3). Guidelines for assessment and management of proteinuria are as follows:

Detection and Confirmation

1. Perform urine dipstick testing or urinalysis per the SoA (Section 6.3). Urine dipstick testing is the preferred method for testing for urinary protein, however, urinalysis may be used if the use of urine dipsticks is not feasible.
2. A 24-hour urine collection initiated as soon as possible and at least within 72 hours (or an immediate spot urine protein-to-creatinine ratio [UPCR] test) is required in the following situations:
   - The first (initial) occurrence of ≥2+ (≥100 mg/dL) proteinuria on urine dipstick (or urinalysis) while the subject is receiving lenvatinib.
   - A subsequent increase in severity of urine dipstick or urinalysis proteinuria occurring on the same lenvatinib dose level.
   - When there has been a lenvatinib dose reduction and at the new dose level the urine protein dipstick result is ≥2+ (≥100 mg/dL).
3. A 24-hour urine collection (initiated as soon as possible and at least within 72 hours) to verify the grade of proteinuria is required when UPCR is ≥2.4.

Grading of Proteinuria

- Grading according to NCI CTCAE v4.0 will be based on the 24-hour urinary protein result if one has been obtained. If the participant has 4+ proteinuria by dipstick (≥1000 mg/dL by urinalysis), a 24-hour urinary protein result is required to confirm Grade 3 proteinuria. Management of lenvatinib administration will be based on the grade of proteinuria according to Table 7.

Monitoring

- Urine dipstick or urinalysis testing for subjects with proteinuria ≥2+ (≥100 mg/dL) should be performed on Day 15 (or more frequently as clinically indicated) until the results have been 1+ (30 mg/dL) or negative for 2 consecutive treatment cycles.

- Proteinuria monitoring can be performed at the local laboratory or investigator site, but must be managed by the site physician.
- In the event of nephrotic syndrome, lenvatinib must be discontinued.

5.2.6.3.3 Management of Diarrhea

An anti-diarrheal agent should be recommended to the subject at the start of study treatment, and subjects should be instructed and educated to initiate anti-diarrheal treatment at the first onset of soft bowel movements. The choice of anti-diarrheal agent should be individualized to the subject's clinical circumstances and follow standard medical practice. If signs/symptoms of diarrhea persist despite optimal medical management, instructions contained in Table 7 should be followed.

5.2.6.3.4 Management of Hepatotoxicity

Liver function tests (alanine transaminase [ALT], aspartate transaminase [AST], bilirubin levels) should be conducted as detailed in the SoA (Section 6.3) and as clinically indicated. If signs/symptoms indicating liver injury occur, instructions contained in Table 7 should be followed. Appropriate supportive care should be provided together with close monitoring. If hepatic failure (any grade per CTCAE v4.0) occurs, the study drug must be discontinued.

5.2.6.3.5 Management of Thromboembolic Events

Subjects should be advised to pay attention to symptoms suggestive of venous thromboembolic events which include acute onset of shortness of breath, dyspnea, chest pain, cough, hemoptysis, tachypnea, tachycardia, cyanosis, DVT signs including lower-extremity swelling, and warmth to touch or tenderness. In case any of these symptoms appear, subjects should be instructed to report such symptoms promptly to the treating physician. If a thromboembolic event is confirmed, instructions contained in Table 7 should be followed. Appropriate supportive care should be provided together with close monitoring. If a subject experiences a Grade 3 or a life threatening (Grade 4) thromboembolic reaction, including pulmonary embolism, lenvatinib must be discontinued.

Arterial thromboembolic events (eg, new onset, worsening, or unstable angina, myocardial infarction, transient ischemic attack, and cerebrovascular accident) of any grade require study treatment discontinuation.

5.2.6.3.6 Management of Posterior Reversible Encephalopathy Syndrome/Reversible Encephalopathy Syndrome/ Reversible Posterior Leukoencephalopathy Syndrome

Posterior Reversible Encephalopathy Syndrome/Reversible Encephalopathy Syndrome/ Reversible Posterior Leukoencephalopathy Syndrome (PRES/RPLS) is a neurological disorder that can present with headache, seizure, lethargy, confusion, altered mental function, blindness, and other visual or neurological disturbances. Mild to severe hypertension may be present. MRI is necessary to confirm the diagnosis of PRES/RPLS. Appropriate measures should be taken to control BP. In subjects with signs or symptoms of PRES/RPLS, instructions in Table 7 should be followed.

5.2.6.3.7 Management of Hypocalcemia

Serum calcium should be monitored per the SoA (Section 6.3). Corrected serum calcium should be used to assess the grade of hypocalcemia per CTCAE v4.0, using the following formula:

Corrected calcium = ([4 – serum albumin in g/dL] × 0.8 + serum calcium)

The formula is not applicable when serum albumin concentration is normal (>4 g/dL); in such situations, the total (uncorrected) serum calcium should be used instead.

Hypocalcemia should be treated per institutional guidelines (eg, using appropriate calcium, magnesium, and Vitamin D supplementation) until resolution.

5.2.6.3.8 Management of Hemorrhage

Instructions in Table 7 should be followed for the management of hemorrhage. Either resume at a reduced dose or discontinue lenvatinib depending on the severity and persistence of hemorrhage.

5.2.6.3.9 Management of Gastrointestinal Perforation or Fistula Formation

Lenvatinib should be discontinued in any subjects who develop gastrointestinal perforation of any grade or Grade 4 fistula.

5.2.6.3.10 Management of QT Prolongation

Lenvatinib should be withheld in the event of development of QT interval prolongation greater than 500 msec. Lenvatinib should be resumed at a reduced dose when QTc prolongation is resolved to <480 msec or baseline. Monitor potassium, calcium and magnesium, and replenish as appropriate.

5.2.6.3.11 Management of Osteonecrosis of the Jaw

Perform an oral examination prior to treatment with lenvatinib and periodically during lenvatinib treatment. Advise participants regarding good oral hygiene practices. Avoid invasive dental procedures, if possible, while on lenvatinib treatment, particularly in participants at higher risk. For participants requiring invasive dental procedures, discontinuation of bisphosphonate treatment may reduce the risk of ONJ. Withhold lenvatinib if ONJ develops and restart based on clinical judgement of adequate resolution (See Section 5.2.6.5).

All study-related medical or dental decisions must be made by an investigator who is a qualified physician.

5.2.6.4 Dose Modifications for Overlapping Toxicities

Based on the known toxicity profiles of pembrolizumab, MK-4280, and lenvatinib, certain treatment-related AEs are uniquely associated with one drug versus the other. For example, hypertension, arterial thrombotic events, proteinuria, and hemorrhagic events are known risks for lenvatinib treatment, while immune-related AEs are risks for pembrolizumab and MK-

4280 treatment. However, certain AEs, such as such as diarrhea, hypothyroidism, and liver enzyme elevation, may be initially considered attributable to any study drug. Therefore, evaluation of attribution is important for determining the study drug most likely related to the AE, or an alternative etiology, and subsequently proper clinical management. The following aspects should be considered:

1. Timing of AE onset

   Since lenvatinib is dosed daily and continuously due to a relatively short half-life (28 hours), and pembrolizumab is dosed Q3W due to a long half-life, lenvatinib can be interrupted to assess whether an AE improves/resolves with dechallenge (ie, interruption of treatment) based on the following two scenarios:

   - If an AE is identified during a treatment cycle (ie, between 2 pembrolizumab doses), only lenvatinib dose interruption is needed.
   - If an AE is identified at the beginning of a treatment cycle, lenvatinib can be interrupted and dosing of pembrolizumab should be held.

   If the subject recovers from an AE in response to lenvatinib interruption (ie, positive dechallenge), the event is more likely to be related to lenvatinib. Otherwise, after excluding other alternative explanations, an immune-related AE should be considered.

2. Severity of AE

   If an AE is suspected to be treatment related and is severe/life threatening at the time of onset or is rapidly worsened, action including interrupting all drugs and initiating treatment with a corticosteroid (with exception of hypothyroidism, TIDM) and other supportive care should be taken promptly.

3. Subjects receiving the combination therapy (pembrolizumab + MK-4280 + lenvatinib) must discontinue study therapy if any of the following occur:

   - ALT or AST >5 X ULN for more than 2 weeks.

     Pembrolizumab and MK-4280 will have already been permanently discontinued per Table 5, but lenvatinib may be administered at a reduced dose by the time this criterion is met and must be permanently discontinued immediately.

   - ALT or AST >3 X ULN and (TBL >2 X ULN or INR >1.5).

     Although Table 5 advises pembrolizumab and MK-4280 to be withheld (interrupted), and Table 7 advises lenvatinib to have no dose modification or a reduction, if this criterion is met, all drugs must be permanently discontinued immediately.

5.2.6.5 Other Allowed Dose Interruptions

If the subject is receiving treatment with lenvatinib and requires surgery during the study, the stop time and restart time of lenvatinib should be as follows:

- For minor procedures: stop lenvatinib at least 2 days before the procedure and restart it at least 2 days after, once there is evidence of adequate healing and no risk of bleeding.
- For major procedures: stop lenvatinib at least 1 week (5 half-lives) prior to surgery and then restart it at least 2 weeks after, once there is evidence of adequate healing and no risk of bleeding.
- For scheduled dental surgery or invasive dental procedures, stop lenvatinib for at least 1 week before the procedure, then restart lenvatinib when deemed clinically appropriate.

5.2.7 Crossover Criteria

After Sponsor consultation, subjects in Arm 1 of Part B may be allowed to crossover to Arm 2C and receive MK-4280 in combination with pembrolizumab. In order to be eligible for crossover, the subject must have radiographically documented and confirmed disease progression per irRECIST 1.1 while in Arm 1. Subjects who discontinue treatment in Arm 1 for any reason other than disease progression are not eligible for crossover.

If crossover is being considered, the risks and benefits of continuing treatment after disease progression should be reviewed prior to performing any crossover-related procedures. Subjects will continue receiving MK-4280 at the dose-level they were assigned (ie, 800 mg), and pembrolizumab will be administered at the fixed 200 mg Q3W dose. Crossover will not be permitted until six subjects have completed the DLT period on Arm 2C. The subject may receive up to a total of 35 cycles of combination treatment (irrespective of how many cycles of monotherapy treatment they received).

Specific procedures to be performed for crossover subjects can be found in Section 6.3 – Crossover Flow Chart. Special considerations regarding imaging and disease assessment for crossover subjects can be found in Section 7.1.2.6 – Disease Assessments.

5.2.8 Second Course of Study Treatment

All participants who have completed the first course may be eligible for up to an additional 17 cycles of study treatment if there is investigator-determined progressive disease after initial treatment has been completed. This retreatment is the Second Course of this study.

Note: Sponsor consultation is required prior to starting participants on Second Course.

Participants may enter the Second Course if all of the following criteria are met:

1. No new anticancer treatment was administered after the last dose of study intervention
2. The participant meets all of the inclusion criteria and none of the exclusion criteria
3. The study is ongoing

For participants in Arm 3, Arm 4 and Arm 6, continuation or resumption of the same concomitant therapy received during the initial treatment phase (ie, chemotherapy or lenvatinib) may be administered with Second Course MK-4280 and Pembrolizumab at the discretion of the Investigator. Note that chemotherapy or agent other than lenvatinib that is different from that received in the initial treatment phase is not permitted

5.2.9 Trial Blinding

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

5.3 Randomization or Treatment Allocation

Treatment allocation by nonrandom, sequential assignment to Part A, Arm 1 or Arm 2 will occur centrally using an IVRS/IWRS. Randomization for Cohort E in Part B will be performed at a 1:1 ratio by an IVRS/IWRS. An IVRS/IWRS will be used to control the sequential enrollment of Part B. Enrollment to Arm 3 or Arm 4 will be guided by a subject's eligibility for one arm or the other or, if eligible for both arms, will be determined by investigator choice. If Arms 1, 2C and 5 for 3L+ CRC subjects are enrolling at the same time, subjects will be assigned in an alternating fashion across the open arms at the study level through IVRS. Cohort F of Part B is only open to sites in China and these subjects will be assigned to Arm 5 only.

5.4 Stratification

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

5.5 Concomitant Medications/Vaccinations (Acceptable & 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/Procedures

Listed below are some specific restrictions for concomitant therapy use during the course of the trial. 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 electronic case report form (eCRF) 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 will also be included on the eCRF.

Palliative and supportive care is permitted during the course of the trial for underlying medical conditions and management of symptoms. Surgery or radiotherapy for tumor control

is not permitted during the study; however, radiotherapy or procedures for symptom management are allowed.

All concomitant medications received within 30 days before the first dose of study treatment through the Safety Follow-up Visit should be recorded. After the Safety Follow-up Visit, all medications taken for SAEs as defined in Section 7.2 should be recorded.

In cases of melanoma, local surgical excision may be allowed after discussion with the Sponsor.

5.5.2 Prohibited Concomitant Medications/Procedures

Subjects are prohibited from receiving the following therapies/vaccinations during the Screening and Treatment Phases of this trial:

- Immunotherapy not specified in this protocol
- Antineoplastic systemic chemotherapy or biological therapy not specified in this protocol
- Investigational agents not specified in this protocol
- Radiation therapy; radiotherapy for symptom management is allowed
- 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, *Bacillus* Calmette-Guérin (BCG), and typhoid vaccine. Seasonal influenza vaccines for injection are generally killed virus vaccines and are allowed. However, intranasal influenza vaccines (eg, FluMist®) are live-attenuated vaccines, and are not allowed.

  Note: Any licensed COVID-19 vaccine (including for Emergency use) in a particular country is allowed in the study as long as they are mRNA vaccines, replication incompetent adenoviral vaccines, or inactivated vaccines. These vaccines will be treated just as any other concomitant therapy.

  Investigational vaccines (i.e., those not licensed or approved for Emergency Use) are not allowed
- Systemic glucocorticoids except when used for the following purposes:
  - To modulate symptoms of an AE that is suspected to have an immunologic etiology
  - For the prevention of emesis
  - To premedicate for IV contrast allergies
  - To treat asthma or COPD exacerbations (only short-term oral or IV use in doses >10 mg/day prednisone equivalent)
  - For chronic systemic replacement not to exceed 10 mg/day prednisone equivalent

- Other glucocorticoid use except when used for the following purposes:
  - For topical use or ocular use
  - Intraarticular joint use
  - For inhalation in the management of asthma or COPD
  - Note: Use of prophylactic corticosteroids as a part of anti-emetic therapy for chemotherapy is permitted.

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

Section 5.1.3 – Exclusion Criteria describes other medications that are prohibited in this trial.

There are no prohibited therapies during the follow-up visits.

5.5.3 Lenvatinib Drug Interactions

There are no drug-drug interaction (DDI)-related concomitant medication prohibitions or restrictions.

Lenvatinib is not expected to clinically meaningfully alter exposure to CYP3A4/ P-glycoprotein (Pgp) substrates based on results from a lenvatinib DDI study with midazolam (a sensitive CYP3A and Pgp substrate).

Clinical studies also showed that co-administration of lenvatinib with either inducers or inhibitors of CYP3A4/Pgp are not of clinical concern.

No drug interaction is expected between pembrolizumab, MK-4280, and lenvatinib because of their divergent metabolic pathways. Pembrolizumab and MK-4280 are monoclonal antibodies and are primarily catabolized like other proteins, while lenvatinib is metabolized by enzymatic (CYP3A and aldehyde oxidase) and non-enzymatic processes (lenvatinib IB).

Concomitant medications with potential for overlapping toxicity with study medications should be given judiciously and with close monitoring. QTc prolongation has been seen in some lenvatinib studies. Drugs known to prolong QTc interval (including Class Ia and III antiarrhythmics) must be used cautiously. Please refer to the lenvatinib IB.

5.6 Rescue Medications & Supportive Care

No rescue or supportive medications are specified to be used in this trial.

5.6.1 Supportive Care Guidelines

Subjects should receive appropriate supportive care measures as deemed necessary by the treating investigator. Suggested supportive care measures for the management of AEs with potential immunologic etiology are outlined in Table 5. For participants receiving pembrolizumab + MK-4280 + lenvatinib, suggested supportive care measures for the management of AEs with potential immunologic etiology are outlined in Table 5 in Section 5.2.6.1 along with the dose modification guidelines in Table 7 in Section 5.2.6.3. Where

appropriate, these guidelines include the use of oral or IV treatment with corticosteroids as well as additional anti-inflammatory agents if symptoms do not improve with administration of corticosteroids. Note that several courses of steroid tapering may be necessary as symptoms may worsen when the steroid dose is decreased. For each disorder, attempts should be made to rule out other causes such as metastatic disease or bacterial or viral infection, which might require additional supportive care. The treatment guidelines are intended to be applied when the investigator determines the events to be related to pembrolizumab, MK-4280, MK-4280A, or lenvatinib.

Note: If after the evaluation of the event, it is determined not to be related to pembrolizumab, MK-4280, MK-4280A, or lenvatinib the investigator does not need to follow the treatment guidance. Refer to Section 5.2.6 for dose modification.

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

5.7 Diet/Activity/Other Considerations

5.7.1 Diet

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

5.7.2 Lifestyle Restrictions

Subjects receiving 5-FU (mFOLFOX7 or FOLFIRI) should avoid exposure to sunlight due to potential drug-induced photosensitivity.

5.7.3 Contraception

MK-4280, pembrolizumab, MK-4280A, and lenvatinib may have adverse effects on a fetus in utero. Refer to Section 12.8 for approved methods of contraception.

5.7.4 Use in Pregnant Women

If a subject inadvertently becomes pregnant while on study treatment, 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 within 24 hours if the outcome is a serious adverse experience (eg, death, abortion, congenital anomaly, or other disabling or life-threatening complication to the mother or newborn). The study investigator will make every effort to obtain permission to follow the outcome of the pregnancy and report the condition of the fetus or newborn to the Sponsor. If a male subject impregnates his female partner the study personnel at the site must be informed immediately and the pregnancy reported to the Sponsor and followed as described above and in Section 7.2.2.

5.7.5 Use in Nursing Women

It is unknown whether MK-4280 or pembrolizumab (or MK-4280A) is excreted in human milk. Because many drugs are excreted in human milk, and because of the potential for

serious adverse reactions in the nursing infant, subjects who are breastfeeding are not eligible for enrollment.

5.8 Subject Withdrawal/Discontinuation Criteria

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

In this trial, a subject may discontinue from treatment but continue to participate in the regularly scheduled activities, as long as the subject does not withdraw consent. Discontinuation from treatment is permanent. Once a subject has discontinued treatment, even though they continue to be monitored in the trial, they shall not be allowed to begin treatment again. The only exception to this, as described in Section 5.2.6, is for subjects who discontinued treatment of MK-4280 after 8 cycles in accordance with the original protocol.

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 may continue to be monitored in the trial) for any of the following reasons:

- Confirmed disease progression per response assessment criteria (Section 7.1.2.6)
- Investigator's decision to withdraw the subject
- Clinical progression
- Subject has a confirmed pregnancy test
- Unacceptable AEs
- Intercurrent illness that prevents further administration of treatment
- Administrative reasons
- The subject completes 35 cycles of MK-4280 monotherapy (Arm 1) or MK-4280 in combination with pembrolizumab (Arm 2 and crossover).

  Note: For subjects in Arm 6, pembrolizumab and MK-4280 treatment will be discontinued once the subject has received 35 cycles (approximately 2 years). Subjects experiencing clinical benefit, according to the PI, may continue treatment with lenvatinib beyond 2 years with Sponsor consultation and approval.

- Subjects receiving MK-4280 in combination with pembrolizumab and lenvatinib (Arm 6) must discontinue study therapy if any of the following occur:

  ALT or AST elevation meeting the following criteria:

  - ALT or AST >5 × ULN for more than 2 weeks

  Pembrolizumab and MK-4280 will have already been permanently discontinued per Table 5, but lenvatinib may be administered at a reduced dose by the time this criterion is met and must be permanently discontinued immediately.

  - ALT or AST >3 × ULN and (TBL >2X ULN or INR > 1.5)

  Although Table 5 advises pembrolizumab and MK-4280 to be withheld (interrupted), and Table 7 advises lenvatinib to have no dose modification or a reduction, if this criterion is met, all drugs must be permanently discontinued immediately

Note: Subjects who discontinue treatment 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.

5.9 Subject Replacement Strategy

To determine safety, all subjects selected must meet the criteria for evaluability for Cycle 1. Subjects are considered nonevaluable and will be replaced if:

- They are enrolled but not treated
- They discontinue from the trial prior to completing all the safety evaluations for reasons other than treatment-related AEs
- They receive less than 90% of the total MK-4280, pembrolizumab, MK-4280A or mFOLFOX7/FOLFIRI infusion in Cycle 1 (eg, because the infusion had to be discontinued due to an infusion reaction) and did not experience a DLT

Nonevaluable subjects will not be counted toward the cohort total for DLT evaluation.

If a subject experiences a DLT in Cycle 1, trial treatment may be discontinued following discussion between the Sponsor and investigator. However, if the subject is deriving clinical benefit from the trial treatment, the subject may be allowed to continue after discussion between the Sponsor and the investigator.

5.10 Beginning and End of the Trial

The overall trial begins when the first subject (or their legally acceptable representative) provides documented informed consent. The overall trial ends when the last subject completes the last study-related contact, discontinues from the trial or is lost to follow-up (i.e. the subject is unable to be contacted by the investigator).

For purposes of analysis and reporting, the overall study ends when the Sponsor receives the last laboratory test result or at the time of final contact with the last subject, whichever comes last.

If the study includes countries in the European Economic Area (EEA), the local start of the study in the EEA is defined as First Site Ready (FSR) in any Member State.

5.11 Clinical Criteria for Early Trial Termination

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

- Incidence or severity of adverse drug reactions in this or other trials suggest a potential health hazard to subjects
- Plans to modify or discontinue the development of the trial drug
- Poor adherence to protocol and regulatory requirements
- Quality or quantity of data recording is inaccurate or incomplete

Ample notification will be provided in the event of Sponsor decision to no longer supply MK-4280, MK-4280A, pembrolizumab, or lenvatinib.

6.0 TRIAL FLOW CHART

6.1 Part A - Arm 1 and Arm 2; Part B - Arm 1, Arm 2A, Arm 2B, Arm 2C, and Arm 5 Flow Chart

	Screening Phase	Treatment Phase Cycle = 21 days										End of Treatment	Post Treatment Phase	
Treatment Cycle/Title	Screening (Visit 1)	Cycle 1				Cycles 2-4[1]				Cycles 5-8[1]	Cycle 9 and Beyond[1]	Discon.	Safety Follow-up Visit	Survival Follow-up[27]
Cycle Day		1	2	8	15	1	8	15	9 weeks after 1st dose	1	1		30 days after last dose	Every 12 weeks
Scheduling Window (Days)	-28 to -1			±3	±3		±3	±3	±7				±7	±7
Administrative Procedures														
Informed Consent[2]	X													
Informed Consent for Future Biomedical Research[3]	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	X	
Prior Oncology Treatment History	X													
MK-4280 Drug Administration (Arm 1 and Arm 2 only)		X				X				X	X			
Pembrolizumab Drug Administration[4] (Arm 2 only)		X				X				X	X			
MK-4280A Drug Administration (Arm 5 only)		X				X				X	X			

	Screening Phase	Treatment Phase Cycle = 21 days										End of Treatment	Post Treatment Phase	
Treatment Cycle/Title	Screening (Visit 1)	Cycle 1				Cycles 2-4[1]				Cycles 5-8[1]	Cycle 9 and Beyond[1]	Discon.	Safety Follow-up Visit	Survival Follow-up[27]
Cycle Day		1	2	8	15	1	8	15	9 weeks after 1st dose	1	1		30 days after last dose	Every 12 weeks
Scheduling Window (Days)	-28 to -1			±3	±3		±3	±3	±7				±7	±7
Clinical Procedures/Assessments														
Adverse Events Monitoring	X	X	X	X	X	X	X	X		X	X	X	X	
Full Physical Examination	X	X[5]				X[5]				X[5]	X[5]	X	X	
Height	X													
Weight	X	X				X				X	X	X	X	
Vital Signs (respiratory rate, blood pressure, pulse, temperature)[6]	X	X	X	X	X	X	X	X		X	X	X	X	
12-Lead Electrocardiogram[7]	X	X[5]				X[5]							X	
ECOG Performance Status	X	X[5]				X[5]				X[5]	X[5]	X	X	
Survival Status[27]		←											→	X
Efficacy Procedures/Assessments														
Tumor Imaging and irRECIST Response Assessment[8]	X								X[8]	X[8]	X[8]			
Laboratory Procedures/Assessments –Analysis by Local Lab														
Complete blood count (CBC) with differential	X[9]	X[5,10]		X		X[5,10]	X			X[5,10]	X[5,10]	X	X	
PT/INR and aPTT	X[9]													

	Screening Phase	Treatment Phase Cycle = 21 days										End of Treatment	Post Treatment Phase	
Treatment Cycle/Title	Screening (Visit 1)	Cycle 1				Cycles 2-4[1]				Cycles 5-8[1]	Cycle 9 and Beyond[1]	Discon.	Safety Follow-up Visit	Survival Follow-up[27]
Cycle Day		1	2	8	15	1	8	15	9 weeks after 1st dose	1	1		30 days after last dose	Every 12 weeks
Scheduling Window (Days)	-28 to -1			±3	±3		±3	±3	±7				±7	±7
Chemistry Panel	X[9]	X[5,10]		X		X[5,10]	X			X[5,10]	X[5,10]	X	X	
CEA Testing (subjects in Part B with CRC only)[28]	X[9]	X[5]				X[28]				X[28]	X[28]			
Lactate dehydrogenase (LDH), gamma-glutamyl transferase (GGT)	X[9]	X[5]				X[5]				X[5]				
Pregnancy Test – Urine Serum β-human chorionic gonadotropin (β-hCG), if applicable[11]	X	X												
Urinalysis	X[9]													
Thyroid Function (thyroxine [T4], triiodothyronine [T3], thyroid stimulating hormone [TSH])[12]		X[5]				X[5]				X[5]	X		X	
BRAF Status[29]	X													
HIV, Hepatitis B and C[13]	X													
Laboratory Procedures/Assessments-Analysis to be Performed by Central Lab														
Cytokine Panel[14]		X[5]	X			X				X[14]				
Anti-MK-4280 Antibodies[15]		X				X				X	X		X	

	Screening Phase	Treatment Phase Cycle = 21 days										End of Treatment	Post Treatment Phase	
Treatment Cycle/Title	Screening (Visit 1)	Cycle 1				Cycles 2-4[1]				Cycles 5-8[1]	Cycle 9 and Beyond[1]	Discon.	Safety Follow-up Visit	Survival Follow-up[27]
Cycle Day		1	2	8	15	1	8	15	9 weeks after 1st dose	1	1		30 days after last dose	Every 12 weeks
Scheduling Window (Days)	-28 to -1			±3	±3		±3	±3	±7				±7	±7
PK for MK-4280 [15, 16] (Arm 1 only)		X	X	X	X	X	X	X		X	X	X	X	
Anti-Pembrolizumab Antibodies[17] (Arm 2 and Arm 5 only)		X				X				X	X		X	
PK for Pembrolizumab and MK-4280 [17, 18] (Arm 2 and Arm 5 only)		X	X	X	X	X	X	X		X	X	X	X	
Blood for DNA Correlative Studies[19, 30]		X				X						X		
Blood for RNA Correlative Studies[19, 30]		X				X						X		
Blood for Genetic Analysis[20, 30]		X												
Blood for Exploratory Protein Analysis (serum)[19, 30]		X				X						X		
Pharmacodynamic receptor availability[23, 24, 30]	X	X	X	X[24]	X	X	X[24]	X		X	X	X		
Lipase and Amylase[25, 30]	X	X				X				X	X	X	X	
T-cell flow cytometry analysis[26, 30]		X		X	X	X		X						

	Screening Phase	Treatment Phase Cycle = 21 days										End of Treatment	Post Treatment Phase	
Treatment Cycle/Title	Screening (Visit 1)	Cycle 1				Cycles 2-4[1]				Cycles 5-8[1]	Cycle 9 and Beyond[1]	Discon.	Safety Follow-up Visit	Survival Follow-up[27]
Cycle Day		1	2	8	15	1	8	15	9 weeks after 1st dose	1	1		30 days after last dose	Every 12 weeks
Scheduling Window (Days)	-28 to -1			±3	±3		±3	±3	±7				±7	±7
Tumor Tissue Collection														
Archival or New Obtained Tumor Tissue[21, 30]	X													
Post Treatment Tumor Biopsy[22, 30]				X										

1. Trial treatment may be administered up to 3 days before or 5 days after the scheduled Day 1 of each cycle, beginning in Cycle 3. Cycle 2 Day 1 may be administered up to 5 days after the scheduled Day 1.
2. Documented informed consent must be obtained prior to performing any protocol-specific procedure. Tests 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.
3. Providing documented informed consent for Future Biomedical Research (FBR) is optional, and may be provided at any time during the subject's participation in the trial. Detailed instructions for the collection and management of FBR specimens are provided in the Procedure Manual. FBR is not applicable to subjects in Cohort F.
4. In Arm 2 of Part A and Part B, pembrolizumab is administered first and then, following a 30-minute interval, MK-4280 will be administered.
5. These samples and procedures required predose on Day 1 may be performed up to 72 hours prior to dosing. If Screening was performed ≤72 hours prior to dosing in Cycle 1, the results obtained at Screening can also be used for the Cycle 1, Day 1 predose values.
6. Vital signs (VS) to include temperature, pulse, respiratory rate, and blood pressure for all subjects. On Day 1 of Cycles 1-4, collect prior to dosing and at 2 hrs, 4 hrs, and 6 hrs (±10 mins for each) after start of the MK-4280 or MK-4280A infusion. Beginning with Cycle 5, collect VS predose on Day 1 of each cycle for all subjects.
7. Twelve-lead electrocardiogram (ECG) should be performed at screening for all subjects and repeated only for subjects in Arm 1 of Part A and Arm 5 of Part B prior to and within 30 minutes after the end of the MK-4280 or MK-4280A infusion in Cycles 1-4, and at the Safety Follow-up Visit.
8. Tumor imaging (computerized tomography [CT] scan or magnetic resonance imaging [MRI]) should be performed within 28 days of enrollment. Tumor imaging and response assessment are to be performed 9 weeks after first dose, then every 9 weeks until disease progression. Imaging assessments should be repeated every 9 weeks and follow calendar days and should not be adjusted for delays in cycle starts. If institutional standard of care for imaging frequency differ from these guidelines, follow the institutional standard of care after confirming with the Sponsor. The same imaging technique should be used on a subject throughout the trial. Information for disease assessments may be requested and submitted for central review.
9. Laboratory tests at Screening are to be performed within 7 days prior to the first dose of study treatment.
10. On Day 1 in Cycles 1-4, CBC with differential and the Chemistry Panel should be drawn prior to dosing.
11. For women of reproductive potential, a urine pregnancy test will be performed at Screening and within 72 hours of receiving the first dose of study medication. If urine pregnancy test cannot be confirmed as negative, a serum pregnancy test is required.
12. Thyroid function testing is to be performed starting in Cycle 1 and then every other cycle and at the post treatment Safety Follow-up Visit.
13. Include HCV RNA (qualitative) or Hepatitis C antibody, HBsAg, and HIV type 1 and type 2 (eg, HIV-1/-2 antibody screening test and evaluation of HIV viral load as needed).
14. Collect cytokine panel on Day 1 predose and 1 hr and 4 hrs after the start of the first infusion and on Day 2 of Cycle 1 for all subjects in Part A. Also collect cytokine panel on Day 1 predose of Cycles 2-4 for subjects in Part A, Arm 1 and Cycles 2-6 in Part A, Arm 2. Cytokine panel will not be collected for subjects in Part B.

15. MK-4280 PK (predose; Arm 1 – Part A and Part B) and ADA samples (predose; all subjects) will be drawn within 24 hours prior to start of infusion on Day 1 of Cycles 1-4, 6, and 8, and every 4 cycles thereafter. For Cohort F only: Additional MK-4280 ADA samples (predose) will be drawn within 24 hours prior to start of infusion on Day 1 of Cycle 5 and Cycle 9.
16. Postdose PK in Arm 1 – (Part A and Part B): Postdose MK-4280 PK samples will be drawn on Day 1 of Cycles 1-4, 6, and 8 at the end of MK-4280 infusion (+10 minutes) and 2 hrs after the start of the MK-4280 infusion (±10 minutes). Additional postdose MK-4280 PK samples in Cycles 1-4 will be collected on Day 2 (Cycle 1 only), Day 8, and Day 15. PK samples will also be drawn at Discontinuation, and at the Safety Follow-up Visit.
17. Pembrolizumab and MK-4280 PK samples (predose) and pembrolizumab ADA samples (predose) will be drawn from subjects in Arm 2A, Arm 2B, Arm 2C and Arm 5 within 24 hours prior to start of infusion on Day 1 of Cycles 1-4, 6, 8 and every 4 cycles thereafter. For Cohort F only: Additional pembrolizumab and MK-4280 PK samples (predose) and pembrolizumab ADA samples (predose) will be drawn from subjects within 24 hours prior to start of infusion on Day 1 of Cycle 5 and Cycle 9.
18. Postdose PK in Arm 2A, Arm 2B, Arm 2C, and Arm 5: Postdose pembrolizumab and MK-4280 PK samples will be drawn on Day 1 of Cycles 1, 2, 4, 6, and 8 at the end of the pembrolizumab infusion (+10 minutes; Arm 2 only; pembrolizumab PK assessed alone), at the end of MK-4280 (or MK-4280A) infusion (+10 minutes), and 2 hrs after the start of the MK-4280 (or MK-4280A) infusion (±10 minutes). Additional postdose pembrolizumab and MK-4280 PK samples in Cycles 1, 2, and 4 will be collected on Day 2 (Cycle 1 only), Day 8, and Day 15. PK samples will also be drawn at Discontinuation and at the Safety Follow-up Visit. For Cohort F only: Additional postdose pembrolizumab and MK-4280 PK samples will also be drawn in Cycle 4 on Day 2 and in Cycle 8 on Day 2, Day 8, and Day 15.
19. Blood for correlative studies (RNA and DNA samples) and serum for exploratory protein analysis will be drawn prior to dosing on Day 1 of Cycle 1, on Day 1 of Cycle 2 (or Day 22 of Cycle 1 for subjects who do not receive a second dose of MK-4280 or MK-4280A), and at discontinuation. Detailed instructions for the collection and management of these samples are provided in the Procedure Manual.
20. This sample should be drawn for planned analysis of the association between genetic variants in DNA and drug response. If there is either a documented law or regulation prohibiting collection, or if the IRB/IEC does not approve the collection of the sample for these purposes, then this sample will not be collected at that site. If the sample is collected, leftover extracted DNA will be stored for FBR if the subject (or their legally acceptable representative) provides documented informed consent for FBR. 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.
21. Tumor tissue (archival or newly obtained biopsy) will be required at Screening for all subjects. For all subjects in Part B (except subjects in Cohort F), PD-L1 testing will be performed but does not need to be completed during Screening. For subjects in Part B (except subjects in Cohort F) with HNSCC (of oropharyngeal origin, only), prior HPV testing is required. For subjects with gastric cancer (except subjects in Cohort F), prior HER2/neu and EBV testing are required. For subjects with CRC and gastric cancer (except subjects in Cohort F), prior MSI testing is required. If subjects with HNSCC, gastric cancer, or CRC have not had these tests previously performed, they should be performed by the local laboratory at Screening. Leftover tissue may also be saved for Future Biomedical Research if the subject provides documented informed consent for FBR.
22. Post treatment tumor biopsy is optional, but strongly encouraged, for all subjects (except subjects in Cohort F) in Cycle 1 between Day 8 and Day 15. Leftover tissue may also be saved for FBR if the subject provides documented informed consent for FBR.
23. Pharmacodynamic receptor availability samples (predose) for all subjects (except subjects in Cohort F) will be drawn within 24 hours prior to start of infusion on Day 1 of Cycles 1-4, 6, 8, and every 4 cycles thereafter
24. Postdose pharmacodynamic receptor availability samples will be drawn on Day 1 of Cycles 1, 2, 4, 6, and 8 at the end of the pembrolizumab infusion (for subjects receiving pembrolizumab; +10 minutes), at the end of the MK-4280 (or MK-4280A) infusion (+10 minutes), and 2 hrs after the start of the MK-4280 (or MK-4280A) infusion (±10 minutes). Additional postdose pharmacodynamic receptor availability samples in Cycles 1, 2, and 4 will be collected on Day 2 (Cycle 1 only), Day 8, and Day 15. Pharmacodynamic receptor availability samples will also be drawn at Discontinuation.
25. On Day 1 in Cycles 1-4, amylase and lipase samples should both be drawn predose and repeated 4 hours (±10 mins) after the start of the first infusion. Beginning with Cycle 5, amylase and lipase should be drawn predose on Day 1 for all subjects (except subjects in Cohort F).
26. Predose T-cell flow cytometry analysis samples will be drawn from subjects in Part B within 24 hours prior to start of infusion on Day 1 of Cycles 1-4. Postdose samples will be drawn from subjects in Part B on Day 8 of Cycle 1 only and on Day 15 of Cycles 1-4. The Sponsor may direct certain sites to not perform this assessment if it is determined to be infeasible for logistical or administrative reasons.
27. After confirmed disease progression, or the start of new anticancer treatment; contacts are approximately every 12 weeks. 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).
28. For subjects in Part B with CRC, CEA will be assessed during screening and predose at every other cycle beginning with Cycle 1 (C1, C3, C5, etc.).
29. For subjects with CRC only. If BRAF status is unknown at the time of screening, the site should submit sample for local testing. If local testing is not available and a subject's BRAF status is unknown, this procedure does not need to be performed.
30. Not applicable to subjects in Cohort F.

6.2 Part B - Arm 3 and Arm 4 Flow Chart

	Screening Phase	Treatment Phase Cycle = 21 days																	End of Treatment	Post treatment Phase	
Treatment Cycle/Title	Screening	Cycle 1				Cycle 2[1]			Cycle 3[1]			Cycle 4[1]			Odd Number Cycles[1] (Cycle 5, 7, 9 etc.)		Even Number Cycles[1] (Cycle 6, 8, 10 etc.)		Discon	Safety Follow-up Visit	Survival Follow-up[23]
Cycle Day		1	2	8	15	1	8	15	1	8	15	1	8	15	1	15	1	8		30 days after last dose	Every 12 weeks
Scheduling Window (Days)	-28 to -1			±3	±3		±3	±3		±3	±3		±3	±3		±3		±3			
Administrative Procedures																					
Informed Consent[2]	X																				
Informed Consent for Future Biomedical Research[3]	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	X	X	X	X	X	X	X	X	X	
Prior Oncology Treatment History	X																				
MK-4280 Administration		X				X			X			X			X		X				

	Screening Phase	Treatment Phase Cycle = 21 days																		End of Treatment	Post treatment Phase	
Treatment Cycle/Title	Screening	Cycle 1				Cycle 2[1]			Cycle 3[1]			Cycle 4[1]			Odd Number Cycles[1] (Cycle 5, 7, 9 etc.)		Even Number Cycles[1] (Cycle 6, 8, 10 etc.)		Discon	Safety Follow-up Visit	Survival Follow-up[23]
Cycle Day		1	2	8	15	1	8	15	1	8	15	1	8	15	1	15	1	8		30 days after last dose	Every 12 weeks
Scheduling Window (Days)	-28 to -1			±3	±3		±3	±3		±3	±3		±3	±3		±3		±3			
Pembrolizumab Administration[4]		X				X			X			X			X		X				
mFOLFOX7 (Arm 3) or FOLFIRI (Arm 4) Administration		X			X		X		X		X		X		X	X		X			
Clinical Procedures/ Assessments																						
Adverse Events Monitoring	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Full Physical Examination	X	X[5]				X[5]			X			X			X		X		X	X	
Height	X																					
Weight	X	X				X			X			X			X		X		X	X	
Vital Signs (respiratory rate, blood pressure, pulse, temperature)[6]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
12-Lead Electrocardiogram	X																					
ECOG Performance Status	X	X[5]				X			X			X			X		X		X	X	

	Screening Phase	Treatment Phase Cycle = 21 days																	End of Treatment	Post treatment Phase	
Treatment Cycle/Title	Screening	Cycle 1				Cycle 2[1]			Cycle 3[1]			Cycle 4[1]			Odd Number Cycles[1] (Cycle 5, 7, 9 etc.)		Even Number Cycles[1] (Cycle 6, 8, 10 etc.)		Discon	Safety Follow-up Visit	Survival Follow-up[23]
Cycle Day		1	2	8	15	1	8	15	1	8	15	1	8	15	1	15	1	8		30 days after last dose	Every 12 weeks
Scheduling Window (Days)	-28 to -1			±3	±3		±3	±3		±3	±3		±3	±3		±3		±3			
Survival Status[22]		<--->																			X
Efficacy Procedures/ Assessments																					
Tumor Imaging and irRECIST Response Assessment[7]		X										X[7]									
Laboratory Procedures/ Assessments –Analysis by Local Lab																					
Complete blood count (CBC) with differential	X[8]	X[5]		X	X	X[5]	X		X[5]		X	X[5]	X		X[5]	X	X[5]	X	X	X	
PT/INR and aPTT	X[8]																				
Chemistry Panel	X[8]	X[5]		X	X	X[5]	X		X[5]		X	X[5]	X		X[5]	X	X[5]	X	X	X	
CEA Testing	X[8]	X[5]				X[5]			X[5]			X[5]			X[5]		X[5]				
Lactate dehydrogenase (LDH), gamma-glutamyl transferase (GGT)	X[8]	X[5]				X[5]			X[5]			X[5]			X[5]		X[5]				

	Screening Phase	Treatment Phase Cycle = 21 days																	End of Treatment	Post treatment Phase	
Treatment Cycle/Title	Screening	Cycle 1				Cycle 2[1]			Cycle 3[1]			Cycle 4[1]			Odd Number Cycles[1] (Cycle 5, 7, 9 etc.)		Even Number Cycles[1] (Cycle 6, 8, 10 etc.)		Discon	Safety Follow-up Visit	Survival Follow-up[23]
Cycle Day		1	2	8	15	1	8	15	1	8	15	1	8	15	1	15	1	8		30 days after last dose	Every 12 weeks
Scheduling Window (Days)	-28 to -1			±3	±3		±3	±3		±3	±3		±3	±3		±3		±3			
Pregnancy Test – Urine Serum β-human chorionic gonadotropin (β-hCG), if applicable[9]	X	X																			
Urinalysis	X[8]					X[5]						X[5]					X[5]		X	X	
Thyroid Function (thyroxine [T4], triiodothyronine [T3], thyroid stimulating hormone [TSH])	X	X[5]				X[5]			X[5]			X[5]			X[5]		X[5]		X	X	
BRAF Status[24]	X																				
HIV, Hepatitis B and C[10]	X																				
Laboratory Procedures/ Assessments-Analysis to be Performed by Central Lab																					
Anti-MK-4280 Antibodies[11]		X				X			X			X					X[11]			X	

	Screening Phase	Treatment Phase Cycle = 21 days																	End of Treatment	Post treatment Phase	
Treatment Cycle/Title	Screening	Cycle 1				Cycle 2[1]			Cycle 3[1]			Cycle 4[1]			Odd Number Cycles[1] (Cycle 5, 7, 9 etc.)		Even Number Cycles[1] (Cycle 6, 8, 10 etc.)		Discon	Safety Follow-up Visit	Survival Follow-up[23]
Cycle Day		1	2	8	15	1	8	15	1	8	15	1	8	15	1	15	1	8		30 days after last dose	Every 12 weeks
Scheduling Window (Days)	-28 to -1			±3	±3		±3	±3		±3	±3		±3	±3		±3		±3			
Anti-Pembrolizumab Antibodies[11]		X				X			X			X					X[11]			X	
PK for Pembrolizumab and MK-4280[12, 13]		X	X	X	X	X	X	X	X			X	X	X			X		X	X	
PK for Oxaliplatin (Arm 3)[14]					X																
PK for Irinotecan (Arm 4)[14]					X																
PK for 5-FU[14]					X																
Blood for DNA Correlative Studies[15]		X				X													X		
Blood for RNA Correlative Studies[15]		X				X													X		
Blood for Genetic Analysis[16]		X																			
Blood for Exploratory Protein Analysis (serum)[15]		X				X													X		

	Screening Phase	Treatment Phase Cycle = 21 days																	End of Treatment	Post treatment Phase	
Treatment Cycle/Title	Screening	Cycle 1				Cycle 2[1]			Cycle 3[1]			Cycle 4[1]			Odd Number Cycles[1] (Cycle 5, 7, 9 etc.)		Even Number Cycles[1] (Cycle 6, 8, 10 etc.)		Discon	Safety Follow-up Visit	Survival Follow-up[23]
Cycle Day		1	2	8	15	1	8	15	1	8	15	1	8	15	1	15	1	8		30 days after last dose	Every 12 weeks
Scheduling Window (Days)	-28 to -1			±3	±3		±3	±3		±3	±3		±3	±3		±3		±3			
Pharmacodynamic receptor availability[17, 18]		X	X	X	X	X	X	X	X			X	X	X			X		X		
Lipase and Amylase[19]		X				X			X			X			X		X		X	X	
T-cell flow cytometry analysis[20]		X		X	X	X		X	X		X	X		X							
Tumor Tissue Collection																					
Archival or New Obtained Tumor Tissue[21]	X																				
Post Treatment Tumor Biopsy[22]				X																	

1. Trial treatment may be administered up to 3 days before or 5 days after the scheduled Day 1 of each cycle, beginning in Cycle 3. Cycle 2 Day 1 may be administered up to 5 days after the scheduled Day 1.
2. Documented informed consent must be obtained prior to performing any protocol-specific procedure. Tests 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.
3. Providing documented informed consent for Future Biomedical Research (FBR) is optional, and may be provided at any time during the subject's participation in the trial. Detailed instructions for the collection and management of FBR specimens are provided in the Procedure Manual.
4. Pembrolizumab is administered first and then, following a 30-minute interval, MK-4280 will be administered.
5. These samples and procedures required predose on Day 1 may be performed up to 72 hours prior to dosing. If Screening was performed ≤72 hours prior to dosing in Cycle 1, the results obtained at Screening can also be used for the Cycle 1, Day 1 predose values.
6. Vital signs (VS) to include temperature, pulse, respiratory rate, and blood pressure for all subjects. On Day 1 of Cycles 1-4, collect prior to dosing and at 2 hrs, 4 hrs, and 6 hrs (±10 mins for each) after start of the MK-4280 infusion. Beginning with Cycle 5, collect VS predose on Day 1 of each cycle for all subjects. .
7. Tumor imaging (computerized tomography [CT] scan or magnetic resonance imaging [MRI]) should be performed within 28 days of enrollment. Tumor imaging and response assessment are to be performed 9 weeks after first dose, then every 9 weeks until disease progression. Imaging assessments should be repeated every 9 weeks and follow calendar days and should not be adjusted

for delays in cycle starts. If institutional standard of care for imaging frequency differ from these guidelines, follow the institutional standard of care after confirming with the Sponsor. The same imaging technique should be used on a subject throughout the trial. Information for disease assessments may be requested and submitted for central review.

8. Laboratory tests at Screening are to be performed within 7 days prior to the first dose of study treatment.
9. For women of reproductive potential, a urine pregnancy test will be performed at Screening and within 72 hours of receiving the first dose of study medication. If urine pregnancy test cannot be confirmed as negative, a serum pregnancy test is required.
10. Include HCV RNA (qualitative) or Hepatitis C antibody, HBsAg, and HIV type 1 and type 2 (eg, HIV-1/-2 antibody screening test and evaluation of HIV viral load as needed).
11. MK-4280 and pembrolizumab ADA samples (predose; all subjects) will be drawn within 24 hours prior to start of infusion on Day 1 of Cycles 1-4, 6, and 8, and every 4 cycles thereafter.
12. Pembrolizumab and MK-4280 PK samples (predose) will be drawn within 24 hours prior to start of infusion on Day 1 of Cycles 1-4, 6, 8 and every 4 cycles thereafter.
13. Postdose pembrolizumab and MK-4280 PK samples will be drawn on Day 1 of Cycles 1, 2, 4, 6, and 8 at the end of the pembrolizumab infusion (+10 minutes; pembrolizumab PK assessed alone), at the end of MK-4280 infusion (+10 minutes), and 2 hrs after the start of the MK-4280 infusion (±10 minutes). Additional postdose pembrolizumab and MK-4280 PK samples in Cycles 1, 2, and 4 will be collected on Day 2 (Cycle 1 only), Day 8, and Day 15. PK samples will also be drawn at Discontinuation and at the Safety Follow-up Visit.
14. PK samples for oxaliplatin (Arm 3), irinotecan and its active metabolite SN-38 (Arm 4), and 5-FU (Arm 3 and Arm 4) will be collected pre-dose and at the end of their respective second infusions (+10 minutes, ie Day 15 of Cycle 1). Subjects must return to the study site when the 5-FU infusion ends (46-48 hours after Cycle 1 Day 15, ie on Day 17) to provide this post-infusion sample (+10 minutes).
15. Blood for correlative studies (RNA and DNA samples) and serum for exploratory protein analysis will be drawn prior to dosing on Day 1 of Cycle 1, on Day 1 of Cycle 2 (or Day 22 of Cycle 1 for subjects who do not receive a second dose of MK-4280), and at discontinuation. Detailed instructions for the collection and management of these samples are provided in the Procedure Manual.
16. This sample should be drawn for planned analysis of the association between genetic variants in DNA and drug response. If there is either a documented law or regulation prohibiting collection, or if the IRB/IEC does not approve the collection of the sample for these purposes, then this sample will not be collected at that site. If the sample is collected, leftover extracted DNA will be stored for FBR if the subject (or legally acceptable representative) provides documented informed consent for FBR. 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.
17. Pharmacodynamic receptor availability samples (predose) for all subjects will be drawn within 24 hours prior to start of infusion on Day 1 of Cycles 1-4, 6, 8, and every 4 cycles thereafter
18. Postdose pharmacodynamic receptor availability samples will be drawn on Day 1 of Cycles 1, 2, 4, 6, and 8 at the end of the pembrolizumab infusion (+10 minutes), at the end of the MK-4280 infusion (+10 minutes), and 2 hrs after the start of the MK-4280 infusion (±10 minutes). Additional postdose pharmacodynamic receptor availability samples in Cycles 1, 2, and 4 will be collected on Day 2 (Cycle 1 only), Day 8, and Day 15. Pharmacodynamic receptor availability samples will also be drawn at Discontinuation.
19. On Day 1 in Cycles 1-4, amylase and lipase samples should both be drawn predose and repeated 4 hours (±10 mins) after the start of the first infusion. Beginning with Cycle 5, amylase and lipase should be drawn predose on Day 1 for all subjects.
20. Predose T-cell flow cytometry analysis samples will be drawn from subjects within 24 hours prior to start of infusion on Day 1 of Cycles 1-4. Postdose samples will be drawn on Day 8 of Cycle 1 only and on Day 15 of Cycles 1-4. The Sponsor may direct certain sites to not perform this assessment if it is determined to be infeasible for logistical or administrative reasons.
21. Tumor tissue (archival or newly obtained biopsy) will be required at Screening for all subjects. PD-L1 testing will be performed but does not need to be completed during Screening. Prior MSI testing is required. If subjects have not had these tests previously performed, they should be performed by the local laboratory at Screening. Leftover tissue may also be saved for Future Biomedical Research if the subject provides documented informed consent for FBR.
22. Post treatment tumor biopsy is optional, but strongly encouraged, for all subjects in Cycle 1 between Day 8 and Day 15. Leftover tissue may also be saved for FBR if the subject provides documented informed consent for FBR.
23. After confirmed disease progression, or the start of new anticancer treatment; contacts are approximately every 12 weeks. 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).
24. For subjects with CRC only. If BRAF status is unknown at the time of screening, the site should submit sample for local testing. If local testing is not available and a subject's BRAF status is unknown, this procedure does not need to be performed.

6.3 Part B – Arm 6 Flow Chart

	Screening Phase	Treatment Phase Cycle = 21 days										End of Treatment	Post Treatment Phase	
Treatment Cycle/Title	Screening (Visit 1)	Cycle 1				Cycles 2-4[1]				Cycles 5-8[1]	Cycle 9 and Beyond[1]	Discon.	Safety Follow-up Visit	Survival Follow-up[2]
Cycle Day		1	2	8	15	1	8	15	9 weeks after 1st dose	1	1		30 days after last dose	Every 12 weeks
Scheduling Window (Days)	-28 to -1			±3	±3		±3	±3	±7				±7	±7
Administrative Procedures														
Informed Consent[3]	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	X	
Prior Oncology Treatment History	X													
MK-4280 Drug Administration		X				X				X	X			
Pembrolizumab Drug Administration[4]		X				X				X	X			
Lenvatinib Dispensed[5]		X				X				X	X			
Lenvatinib Container Returned						X				X	X	X		
Clinical Procedures/Assessments														
Adverse Events Monitoring	X	X	X	X	X	X	X	X		X	X	X	X	
Full Physical Examination (including oral examination)	X	X[6]				X[6]				X[6]	X[6]	X	X	

	Screening Phase	Treatment Phase Cycle = 21 days										End of Treatment	Post Treatment Phase	
Treatment Cycle/Title	Screening (Visit 1)	Cycle 1				Cycles 2-4[1]				Cycles 5-8[1]	Cycle 9 and Beyond[1]	Discon.	Safety Follow-up Visit	Survival Follow-up[2]
Cycle Day		1	2	8	15	1	8	15	9 weeks after 1st dose	1	1		30 days after last dose	Every 12 weeks
Scheduling Window (Days)	-28 to -1			±3	±3		±3	±3	±7				±7	±7
Height	X													
Weight	X	X				X				X	X	X	X	
Vital Signs (respiratory rate, blood pressure, pulse, temperature)[7]	X	X	X	X	X	X	X	X		X	X	X	X	
12-Lead Electrocardiogram[8]	X	X				X				X	X	X	X	
MUGA or ECHO for LVEF assessment	X											X		
ECOG Performance Status	X	X[6]				X[6]				X[6]	X[6]	X	X	
Survival Status[2]		←											→	X
Efficacy Procedures/Assessments														
Tumor Imaging and irRECIST Response Assessment[9]	X								X[9]	X[9]	X[9]			
Laboratory Procedures/Assessments –Analysis by Local Lab														
Complete blood count (CBC) with differential	X[10]	X[6,11]		X	X	X[6,11]	X			X[6,11]	X[6,11]	X	X	
PT/INR and aPTT	X[10]													
Chemistry Panel	X[10]	X[6,11]		X		X[6,11]	X			X[6,11]	X[6,11]	X	X	

	Screening Phase	Treatment Phase Cycle = 21 days										End of Treatment	Post Treatment Phase	
Treatment Cycle/Title	Screening (Visit 1)	Cycle 1				Cycles 2-4[1]				Cycles 5-8[1]	Cycle 9 and Beyond[1]	Discon.	Safety Follow-up Visit	Survival Follow-up[2]
Cycle Day		1	2	8	15	1	8	15	9 weeks after 1st dose	1	1		30 days after last dose	Every 12 weeks
Scheduling Window (Days)	-28 to -1			±3	±3		±3	±3	±7				±7	±7
CEA Testing[12]	X[10]	X[6]				X[12]				X[12]	X[12]			
Lactate dehydrogenase (LDH), gamma-glutamyl transferase (GGT)	X[10]	X[6]				X[6]				X[6]				
Pregnancy Test – Urine Serum β-human chorionic gonadotropin (β-hCG), if applicable[13]	X	X				X				X	X	X	X	
Urinalysis	X[10]													
Urine dipstick testing[14]	X[10]	X			X	X		X		X	X	X	X	
Thyroid Function (thyroxine [T4], triiodothyronine [T3], thyroid stimulating hormone [TSH])[15]	X	X[6]				X[6]				X[6]	X		X	
BRAF Status[16]	X													
HIV, Hepatitis B and C[17]	X													
Laboratory Procedures/Assessments-Analysis to be Performed by Central Lab														
Anti-MK-4280 Antibodies and Anti-Pembrolizumab Antibodies[18]		X				X				X	X		X	

	Screening Phase	Treatment Phase Cycle = 21 days										End of Treatment	Post Treatment Phase	
Treatment Cycle/Title	Screening (Visit 1)	Cycle 1				Cycles 2-4[1]				Cycles 5-8[1]	Cycle 9 and Beyond[1]	Discon.	Safety Follow-up Visit	Survival Follow-up[2]
Cycle Day		1	2	8	15	1	8	15	9 weeks after 1st dose	1	1		30 days after last dose	Every 12 weeks
Scheduling Window (Days)	-28 to -1			±3	±3		±3	±3	±7				±7	±7
PK for Pembrolizumab and MK-4280[19]		X	X	X	X	X				X	X	X	X	
PK for Lenvatinib[20]		X			X	X								
Blood for DNA Correlative Studies[21]		X				X						X		
Blood for RNA Correlative Studies[21]		X				X						X		
Blood for Genetic Analysis[22]		X												
Blood for Exploratory Protein Analysis (serum)[21]		X				X						X		
Pharmacodynamic receptor availability[23]	X	X	X	X	X	X				X	X	X		
Lipase and Amylase[24]	X	X				X				X	X	X	X	
T-cell flow cytometry analysis[25]		X		X	X	X		X						
Tumor Tissue Collection														
Archival or New Obtained Tumor Tissue[26]	X													
Post Treatment Tumor Biopsy[27]				X										

1. Trial treatment may be administered up to 3 days before or 3 days after the scheduled Day 1 of each cycle, beginning in Cycle 3. Cycle 2 Day 1 may be administered up to 3 days after the scheduled Day 1.
2. After confirmed disease progression, or the start of new anticancer treatment; contacts are approximately every 12 weeks. 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).

3. Documented informed consent must be obtained prior to performing any protocol-specific procedure. Tests 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.
4. Pembrolizumab is administered first and then, following a 30-minute interval, MK-4280 will be administered.
5. Lenvatinib will be administered 0 to 4 hours after completion of the MK-4280 administration. Lenvatinib will also be administered in the clinic on Cycle 1 Day 15 to allow for predose and postdose PK sample collections.
6. These samples and procedures required predose on Day 1 may be performed up to 72 hours prior to dosing. If Screening was performed ≤72 hours prior to dosing in Cycle 1, the results obtained at Screening can also be used for the Cycle 1, Day 1 predose values.
7. Vital signs (VS) to include temperature, pulse, respiratory rate, and blood pressure for all subjects. Blood pressure and pulse will be measured after the subject has been resting for 5 minutes. On Day 1 of Cycles 1-4, collect prior to dosing and at 2 hrs, 4 hrs, and 6 hrs (±10 mins for each) after start of the MK-4280 infusion. Beginning with Cycle 5, collect VS predose on Day 1 of each cycle.
8. Twelve-lead electrocardiogram (ECG) at screening, Day 1 of Cycle 1 and Cycle 2, Day 1 of every 4th cycle (12 weeks) thereafter (eg, Cycle 6, Cycle 10, Cycle 14, etc), Discontinuation, and the Safety Follow-up Visit. ECG at Cycle 1, Day 1 and Cycle 2, Day 1 should be performed approximately 2 hours post-lenvatinib dose. For high-risk patients (Section 7.1.2.5), conduct ECG monitoring every cycle. If lenvatinib is discontinued, ECGs are only required at the Discontinuation and Safety Follow-up visits.
9. Tumor imaging (computerized tomography [CT] scan or magnetic resonance imaging [MRI]) should be performed within 28 days of enrollment. Tumor imaging and response assessment are to be performed 9 weeks after first dose, then every 9 weeks until disease progression. Imaging assessments should be repeated every 9 weeks and follow calendar days and should not be adjusted for delays in cycle starts. If institutional standard of care for imaging frequency differ from these guidelines, follow the institutional standard of care after confirming with the Sponsor. The same imaging technique should be used on a subject throughout the trial. Information for disease assessments may be requested and submitted for central review.
10. Laboratory tests at Screening are to be performed within 7 days prior to the first dose of study treatment.
11. On Day 1 in Cycles 1-4, CBC with differential and the Chemistry Panel should be drawn prior to dosing.
12. CEA will be assessed during screening and predose at every other cycle beginning with Cycle 1 (C1, C3, C5, etc.).
13. For women of reproductive potential, a urine pregnancy test will be performed at Screening and within 24 hours of receiving the first dose of study medication. If more than 24 hours have elapsed prior to the first dose of study intervention, another pregnancy test is required prior to starting study intervention. If urine pregnancy test cannot be confirmed as negative, a serum pregnancy test is required.
14. Urine dipstick testing is to be performed at screening, Day 1 and Day 15 of Cycle 1 and Cycle 2, Day 1 of every cycle thereafter, and at the Discontinuation and Safety Follow-up visits. Urinalysis may be used if the use of urine dipsticks is not feasible.
15. Thyroid function testing is to be performed at screening, Cycle 1 Day 1 and then Day 1 of every other cycle, and at the post treatment Safety Follow-up Visit.
16. If BRAF status is unknown at the time of screening, the site should submit sample for local testing. If local testing is not available and a subject's BRAF status is unknown, this procedure does not need to be performed.
17. Include HCV RNA (qualitative) or Hepatitis C antibody, HBsAg, and HIV type 1 and type 2 (eg, HIV-1/-2 antibody screening test and evaluation of HIV viral load as needed).
18. Pembrolizumab and MK-4280 ADA samples (predose) will be drawn within 24 hours prior to start of infusion on Day 1 of Cycles 1-4, 6, and 8, and every 4 cycles thereafter.
19. Pembrolizumab and MK-4280 PK samples (predose) will be drawn from subjects within 24 hours prior to start of infusion on Day 1 of Cycles 1-4, 6, and 8, and every 4 cycles thereafter. Postdose pembrolizumab and MK-4280 PK samples will be drawn on Day 1 of Cycle 1 at the end of the pembrolizumab infusion (+10 minutes; pembrolizumab PK assessed alone), at the end of MK-4280 infusion (+10 minutes), and 2 hrs after the start of the MK-4280 infusion (±10 minutes). Additional postdose pembrolizumab and MK-4280 PK samples in Cycle 1 will be collected on Day 2, Day 8, and Day 15. PK samples will also be drawn at Discontinuation and at the Safety Follow-up Visit.
20. Lenvatinib PK samples will be drawn on Cycle 1 Day 1 (between 0.5 hr to 4 hrs and 6 to 10 hours postdose), on Cycle 1 Day 15 (predose and between 2 to 12 hours postdose), and on Cycle 2 Day 1 (predose and between 0.5 hr to 4 hrs and 6 to 10 hours postdose). No predose sampling on Cycle 1 Day 1. All predose samples should be collected within 2 hours of lenvatinib dosing. Postdose samples are not needed if lenvatinib administration is skipped.
21. Blood for correlative studies (RNA and DNA samples) and serum for exploratory protein analysis will be drawn prior to dosing on Day 1 of Cycle 1, on Day 1 of Cycle 2 (or Day 22 of Cycle 1 for subjects who do not receive a second dose of MK-4280), and at discontinuation. Detailed instructions for the collection and management of these samples are provided in the Procedure Manual.
22. This sample should be drawn for planned analysis of the association between genetic variants in DNA and drug response. If there is either a documented law or regulation prohibiting collection, or if the IRB/IEC does not approve the collection of the sample for these purposes, then this sample will not be collected at that site.
23. Pharmacodynamic receptor availability samples (predose) will be drawn within 24 hours prior to start of infusion on Day 1 of Cycles 1-4, 6, 8, and every 4 cycles thereafter. Postdose pharmacodynamic receptor availability samples will be drawn on Day 1 of Cycle 1 at the end of the pembrolizumab infusion (+10 minutes), at the end of the MK-4280 infusion (+10 minutes), and 2 hrs after the start of the MK-4280 infusion (±10 minutes). Additional postdose pharmacodynamic receptor availability samples in Cycle 1 will be collected on Day 2, Day 8, and Day 15. Pharmacodynamic receptor availability samples will also be drawn at Discontinuation.
24. On Day 1 in Cycles 1-4, amylase and lipase samples should both be drawn predose and repeated 4 hours (±10 mins) after the start of the first infusion. Beginning with Cycle 5, amylase and

lipase should be drawn predose on Day 1.

25. Predose T-cell flow cytometry analysis samples will be drawn within 24 hours prior to start of infusion on Day 1 of Cycles 1-4. Postdose samples will be drawn on Day 8 of Cycle 1 only and on Day 15 of Cycles 1-4. The Sponsor may direct certain sites to not perform this assessment if it is determined to be infeasible for logistical or administrative reasons.
26. Tumor tissue (archival or newly obtained biopsy) will be required at Screening. PD-L1 testing will be performed but does not need to be completed during Screening. Prior MSI testing is also required. If subjects have not had these tests previously performed, they should be performed by the local laboratory at Screening.
27. Post treatment tumor biopsy is optional, but strongly encouraged, in Cycle 1 between Day 8 and Day 15.

6.4 Crossover Flow Chart

Subjects who discontinue MK-4280 in Arm 1 of Part B due to confirmed disease progression per irRECIST 1.1 may, at the investigator's discretion and after consultation with the Sponsor, crossover to Arm 2 and receive MK-4280 in combination with pembrolizumab. The list and schedule of procedures to be performed are provided in the following flow chart.

	Treatment Phase Cycle = 21 days				End of Treatment	Post Treatment Phase	
Treatment Cycle/Title	Cycle 1		Cycles ≥ 2[1]		Discon.	Safety Follow-up Visit	Survival Follow-up[2]
Cycle Day	1	8	1	Every 9 weeks		30 days after last dose	Every 12 weeks
Scheduling Window (Days)		±3		±7		±7	±7
Administrative Procedures							
Concomitant Medication Review	X	X	X		X	X	
MK-4280 Drug Administration	X		X				
Pembrolizumab Drug Administration[3]	X		X				
Clinical Procedures/Assessments							
Adverse Events Monitoring	X	X	X		X	X	
Full Physical Examination	X[4]		X[4]		X	X	
Weight	X		X		X	X	
Vital Signs (respiratory rate, blood pressure, pulse, temperature)[5]	X[5]	X	X[5]		X	X	
12-Lead Electrocardiogram	X[4]					X	
ECOG Performance Status	X[4]		X[4]		X	X	
Survival Status[2]	<----------						X

	Treatment Phase Cycle = 21 days				End of Treatment	Post Treatment Phase	
Treatment Cycle/Title	Cycle 1		Cycles ≥ 2[1]		Discon.	Safety Follow-up Visit	Survival Follow-up[2]
Cycle Day	1	8	1	Every 9 weeks		30 days after last dose	Every 12 weeks
Scheduling Window (Days)		±3		±7		±7	±7
Efficacy Procedures/Assessments							
Tumor Imaging and irRECIST Response Assessment[6]	X[7]			X[7]			
Laboratory Procedures/Assessments –Analysis by Local Lab							
Complete blood count (CBC) with differential	X[4, 7]	X	X[4]		X	X	
PT/INR and aPTT	X						
Chemistry Panel	X[4, 7]	X	X[4, 7]		X	X	
CEA Testing (subjects in Part B with CRC only)	X[4]		X[4]				
Lactate dehydrogenase (LDH), gamma-glutamyl transferase (GGT)	X[4]						
Thyroid Function (thyroxine [T4], triiodothyronine [T3], thyroid stimulating hormone [TSH])[8]	X[4]		X[4]			X	
Laboratory Procedures/Assessments-Analysis to be Performed by Central Lab							
PK for Pembrolizumab and MK-4280[9, 10]	X[10]	X	X		X	X	
Anti-MK-4280 Antibodies[9]	X		X			X	
Anti-Pembrolizumab Antibodies[9]	X		X			X	
Pharmacodynamic receptor availability[11, 12]	X[12]	X	X		X		

	Treatment Phase Cycle = 21 days				End of Treatment	Post Treatment Phase	
Treatment Cycle/Title	Cycle 1		Cycles ≥ 2[1]		Discon.	Safety Follow-up Visit	Survival Follow-up[2]
Cycle Day	1	8	1	Every 9 weeks		30 days after last dose	Every 12 weeks
Scheduling Window (Days)		±3		±7		±7	±7
Lipase and Amylase[13]	X		X		X	X	
Biopsy[14]	X						

1. Trial treatment may be administered up to 3 days before or 5 days after the scheduled Day 1 of each cycle, beginning in Cycle 3. Cycle 2 Day 1 may be administered up to 5 days after the scheduled Day 1. Note that cycle numbering resets during crossover. Subjects may receive up to 35 cycles of combination treatment regardless of how many cycles of monotherapy treatment they received.
2. After confirmed disease progression, or the start of new anticancer treatment; contacts are approximately every 12 weeks. 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).
3. Pembrolizumab is administered first and then, following a 30-minute interval, MK-4280 will be administered.
4. These samples and procedures required predose on Day 1 may be performed up to 72 hours prior to dosing.
5. Vital signs (VS) to include temperature, pulse, respiratory rate, and blood pressure for all subjects. On Day 1 of Cycles 1-4, collect prior to dosing and at 2 hrs, 4 hrs, and 6 hrs (±10 mins for each) after start of the MK-4280 infusion. Beginning with Cycle 5, collect VS predose on Day 1 of each cycle for all subjects.
6. If ≥4 weeks have passed between the scan used to confirm disease progression (and allow crossover) and Day 1 of Cycle 1, imaging should be repeated and these results should become the new baseline images. Tumor imaging and response assessment are to be performed 9 weeks after first dose, then every 9 weeks until disease progression. Imaging assessments should be repeated every 9 weeks and follow calendar days and should not be adjusted for delays in cycle starts. If institutional standard of care for imaging frequency differ from these guidelines, follow the institutional standard of care after confirming with the Sponsor. The same imaging technique should be used on a subject throughout the trial. Information for disease assessments may be requested and submitted for central review.
7. On Day 1 in Cycles 1-4, CBC with differential and the Chemistry Panel should be drawn prior to dosing
8. Thyroid function testing is to be performed starting in Cycle 1 and then every other cycle and at the post treatment Safety Follow-up Visit.
9. Pembrolizumab and MK-4280 PK samples (predose) and ADA samples (predose) will be drawn from subjects within 24 hours prior to start of infusion on Day 1 of Cycles 1-4, 6, 8 and every 4 cycles thereafter. Pembrolizumab and MK-4280 ADA samples will also be drawn at the Safety Follow-up Visit.
10. Postdose pembrolizumab and MK-4280 PK samples will be drawn on Day 1 of Cycle 1 at the end of the pembrolizumab infusion (+10 minutes; pembrolizumab PK assessed alone), at the end of MK-4280 infusion (+10 minutes), and 2 hrs after the start of the MK-4280 infusion (±10 minutes). Additional postdose pembrolizumab and MK-4280 PK samples in Cycle 1 will be collected on Day 8. PK samples will also be drawn at Discontinuation and at the Safety Follow-up Visit.
11. Pharmacodynamic receptor availability samples (predose) for all subjects will be drawn within 24 hours prior to start of infusion on Day 1 of Cycles 1-4, 6, 8, and every 4 cycles thereafter.
12. Postdose pharmacodynamic receptor availability samples will be drawn on Day 1 of Cycle 1 at the end of the pembrolizumab infusion (+10 minutes), at the end of the MK-4280 infusion (+10 minutes), and 2 hrs after the start of the MK-4280 infusion (±10 minutes). Additional postdose pharmacodynamic receptor availability samples in Cycle 1 will be collected on Day 8. Pharmacodynamic receptor availability samples will also be drawn at Discontinuation.
13. On Day 1 in Cycles 1-4, amylase and lipase samples should both be drawn predose and repeated 4 hours (±10 mins) after the start of the first infusion. Beginning with Cycle 5, amylase and lipase should be drawn predose on Day 1.
14. An optional, but strongly encouraged, biopsy should be performed for subjects before they receive the first dose of crossover therapy. Leftover tissue may also be saved for FBR if the subject provides documented informed consent for FBR.

6.5 Second Course - Part A - Arm 1 and Arm 2; Part B - Arm 1, Arm 2A , Arm 2B, Arm 2C, and Arm 5 Flow Chart

	Treatment Phase Cycle = 21 days										End of Treatment	Post-Treatment Phase	
Treatment Cycle/Title	Cycle 1				Cycles 2-4[1]				Cycles 5-8[1]	Cycle 9 and Beyond[1]	Discon.	Safety Follow-up Visit	Survival Follow-up[15]
Cycle Day	1	2	8	15	1	8	15	9 weeks after 1st dose	1	1		30 days after last dose	Every 12 weeks
Scheduling Window (Days)			±3	±3		±3	±3	±7				±7	±7
Administrative Procedures													
Informed Consent[2]	X												
Inclusion/Exclusion Criteria	X												
Prior and Concomitant Medication Review	X	X	X	X	X	X	X		X	X	X	X	
MK-4280 Drug Administration (Arm 1 and Arm 2 only)	X				X				X	X			
Pembrolizumab Drug Administration[3] (Arm 2 only)	X				X				X	X			
MK-4280A Drug Administration (Arm 5 only)	X				X				X	X			
Clinical Procedures/Assessments													
Adverse Events Monitoring	X	X	X	X	X	X	X		X	X	X	X	
Full Physical Examination	X[4]				X[4]				X[4]	X[4]	X	X	
Weight	X				X				X	X	X	X	
Vital Signs (respiratory rate, blood pressure, pulse, temperature)[5]	X	X	X	X	X	X	X		X	X	X	X	

	Treatment Phase Cycle = 21 days										End of Treatment	Post-Treatment Phase	
Treatment Cycle/Title	Cycle 1				Cycles 2-4[1]				Cycles 5-8[1]	Cycle 9 and Beyond[1]	Discon.	Safety Follow-up Visit	Survival Follow-up[15]
Cycle Day	1	2	8	15	1	8	15	9 weeks after 1st dose	1	1		30 days after last dose	Every 12 weeks
Scheduling Window (Days)			±3	±3		±3	±3	±7				±7	±7
12-Lead Electrocardiogram[6]	X[4]				X[4]							X	
ECOG Performance Status	X[4]				X[4]				X[4]	X[4]	X	X	
Survival Status[14]	←											→	X
Efficacy Procedures/Assessments													
Tumor Imaging and irRECIST Response Assessment[7]								X[7]	X[7]	X[7]			
Laboratory Procedures/Assessments – Analysis by Local Lab													
Complete blood count (CBC) with differential	X[8,9]		X		X[4,9]	X			X[4,9]	X[4,9]	X	X	
PT/INR and aPTT[11]	X												
Chemistry Panel	X[4,9]		X		X[4,9]	X			X[4,9]	X[4,9]	X	X	
CEA Testing (subjects in Part B with CRC only)[12]	X[8]				X[12]				X[12]	X[12]			
Lactate dehydrogenase (LDH), gamma-glutamyl transferase (GGT)	X[4]				X[4]				X[4]				
Pregnancy Test – Urine Serum β-human chorionic gonadotropin (β-hCG), if applicable[10]	X												
Urinalysis[11]	X												

	Treatment Phase Cycle = 21 days										End of Treatment	Post-Treatment Phase	
Treatment Cycle/Title	Cycle 1				Cycles 2-4[1]				Cycles 5-8[1]	Cycle 9 and Beyond[1]	Discon.	Safety Follow-up Visit	Survival Follow-up[15]
Cycle Day	1	2	8	15	1	8	15	9 weeks after 1st dose	1	1		30 days after last dose	Every 12 weeks
Scheduling Window (Days)			±3	±3		±3	±3	±7				±7	±7
Thyroid Function (thyroxine [T4], triiodothyronine [T3], thyroid stimulating hormone [TSH])[13]	X[4]				X[4]				X[4]	X		X	
HIV, Hepatitis B and C[14]													

1. Trial treatment may be administered up to 3 days before or 5 days after the scheduled Day 1 of each cycle, beginning in Cycle 3. Cycle 2 Day 1 may be administered up to 5 days after the scheduled Day 1.
2. Documented informed consent must be obtained prior to performing any protocol-specific procedure. Tests 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.
3. In Arm 2 of Part A and Part B, pembrolizumab is administered first and then, following a 30-minute interval, MK-4280 will be administered.
4. These samples and procedures required predose on Day 1 may be performed up to 72 hours prior to dosing.
5. Vital signs (VS) to include temperature, pulse, respiratory rate, and blood pressure for all subjects. On Day 1 of Cycles 1-4, collect prior to dosing and at 2 hrs, 4 hrs, and 6 hrs (±10 mins for each) after start of the MK-4280 or MK-4280A infusion. Beginning with Cycle 5, collect VS predose on Day 1 of each cycle for all subjects.
6. Twelve-lead electrocardiogram (ECG) should be performed at for all subjects and repeated only for subjects in Arm 1 of Part A and Arm 5 of Part B prior to and within 30 minutes after the end of the MK-4280 or MK-4280A infusion in Cycles 1-4, and at the Safety Follow-up Visit.
7. If ≥4 weeks have passed between the scan used to confirm disease progression (and allow retreatment in second course) and Day 1 of Cycle 1, imaging should be repeated and these results should become the new baseline images. Tumor imaging and response assessment are to be performed 9 weeks after first dose, then every 9 weeks until disease progression. Imaging assessments should be repeated every 9 weeks and follow calendar days and should not be adjusted for delays in cycle starts. If institutional standard of care for imaging frequency differ from these guidelines, follow the institutional standard of care after confirming with the Sponsor. The same imaging technique should be used on a subject throughout the trial. Information for disease assessments may be requested and submitted for central review.
8. Performed locally within 7 days before first dose. After C1, collect within 3 days prior to dosing.
9. On Day 1 in Cycles 1-4, CBC with differential and the Chemistry Panel should be drawn prior to dosing.
10. For women of reproductive potential, a urine pregnancy test will be performed at Screening and within 72 hours of receiving the first dose of study medication. If urine pregnancy test cannot be confirmed as negative, a serum pregnancy test is required.
11. Laboratory tests to be performed within 7 days prior to the first dose of study treatment.
12. For subjects in Part B with CRC, CEA will be assessed predose at every other cycle beginning with Cycle 1 (C1, C3, C5, etc.).
13. Thyroid function testing is to be performed starting in Cycle 1 and then every other cycle and at the post-treatment Safety Follow-up Visit.
14. Include HCV RNA (qualitative) or Hepatitis C antibody, HBsAg, and HIV type 1 and type 2 (eg, HIV-1/-2 antibody screening test and evaluation of HIV viral load as needed).
15. After confirmed disease progression, or the start of new anticancer treatment; contacts are approximately every 12 weeks. Updated survival status may be requested by the Sponsor at any time during the course of the study. Upon Sponsor notification, all subjects who do not/will not have a scheduled study visit or study contact during the Sponsor-defined time period will be contacted for their survival status (excluding subjects that have a death event previously recorded).

6.6 Second Course - Part B - Arm 3 and Arm 4 Flow Chart

	Treatment Phase Cycle = 21 days																	End of Treatment	Post-treatment Phase	
Treatment Cycle/Title	Cycle 1				Cycle 2[1]			Cycle 3[1]			Cycle 4[1]			Odd Number Cycles[1] (Cycle 5, 7, 9 etc.)		Even Number Cycles[1] (Cycle 6, 8, 10 etc.)		Discon	Safety Follow-up Visit	Survival Follow-up[13]
Cycle Day	1	2	8	15	1	8	15	1	8	15	1	8	15	1	15	1	8		30 days after last dose	Every 12 weeks
Scheduling Window (Days)			±3	±3		±3	±3		±3	±3		±3	±3		±3		±3			
Administrative Procedures																				
Informed Consent[2]	X																			
Inclusion/Exclusion Criteria	X																			
Prior and Concomitant Medication Review	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
MK-4280 Administration	X				X			X			X			X		X				
Pembrolizumab Administration[3]	X				X			X			X			X		X				
mFOLFOX7 (Arm 3) or FOLFIRI (Arm 4) Administration[4]	X			X		X		X		X		X		X	X		X			
Clinical Procedures/ Assessments																				
Adverse Events Monitoring	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	

	Treatment Phase Cycle = 21 days																	End of Treatment	Post-treatment Phase	
Treatment Cycle/Title	Cycle 1				Cycle 2[1]			Cycle 3[1]			Cycle 4[1]			Odd Number Cycles[1] (Cycle 5, 7, 9 etc.)		Even Number Cycles[1] (Cycle 6, 8, 10 etc.)		Discon	Safety Follow-up Visit	Survival Follow-up[13]
Cycle Day	1	2	8	15	1	8	15	1	8	15	1	8	15	1	15	1	8		30 days after last dose	Every 12 weeks
Scheduling Window (Days)			±3	±3		±3	±3		±3	±3		±3	±3		±3		±3			
Full Physical Examination	X[5]				X[5]			X			X			X		X		X	X	
Weight	X				X			X			X			X		X		X	X	
Vital Signs (respiratory rate, blood pressure, pulse, temperature)[6]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
12-Lead Electrocardiogram	X																			
ECOG Performance Status	X[5]				X			X			X			X		X		X	X	
Survival Status[13]	←----------→																			X
Efficacy Procedures/ Assessments																				
Tumor Imaging and irRECIST Response Assessment[7]	X										X[7]									

	Treatment Phase Cycle = 21 days																	End of Treatment	Post-treatment Phase	
Treatment Cycle/Title	Cycle 1				Cycle 2[1]			Cycle 3[1]			Cycle 4[1]			Odd Number Cycles[1] (Cycle 5, 7, 9 etc.)		Even Number Cycles[1] (Cycle 6, 8, 10 etc.)		Discon	Safety Follow-up Visit	Survival Follow-up[13]
Cycle Day	1	2	8	15	1	8	15	1	8	15	1	8	15	1	15	1	8		30 days after last dose	Every 12 weeks
Scheduling Window (Days)			±3	±3		±3	±3		±3	±3		±3	±3		±3		±3			
Laboratory Procedures/ Assessments –Analysis by Local Lab																				
Complete blood count (CBC) with differential	X[8,5]		X	X	X[5]	X		X[5]		X	X[5]	X		X[5]	X	X[5]	X	X	X	
PT/INR and aPTT[9]	X																			
Chemistry Panel	X[9,5]		X	X	X[5]	X		X[5]		X	X[5]	X		X[5]	X	X[5]	X	X	X	
CEA Testing	X[8,5]				X[5]			X[5]			X[5]			X[5]		X[5]				
Lactate dehydrogenase (LDH), gamma-glutamyl transferase (GGT)	X[5]				X[5]			X[5]			X[5]			X[5]		X[5]				
Pregnancy Test – Urine Serum β-human chorionic gonadotropin (β-hCG), if applicable[10]	X																			
Urinalysis	X[9]				X[5]						X[5]					X[5]		X	X	

	Treatment Phase Cycle = 21 days																	End of Treatment	Post-treatment Phase	
Treatment Cycle/Title	Cycle 1				Cycle 2[1]			Cycle 3[1]			Cycle 4[1]			Odd Number Cycles[1] (Cycle 5, 7, 9 etc.)		Even Number Cycles[1] (Cycle 6, 8, 10 etc.)		Discon	Safety Follow-up Visit	Survival Follow-up[13]
Cycle Day	1	2	8	15	1	8	15	1	8	15	1	8	15	1	15	1	8		30 days after last dose	Every 12 weeks
Scheduling Window (Days)			±3	±3		±3	±3		±3	±3		±3	±3		±3		±3			
Thyroid Function (thyroxine [T4], triiodothyronine [T3], thyroid stimulating hormone [TSH])	X[5]				X[5]			X[5]			X[5]			X[5]		X[5]		X	X	
HIV, Hepatitis B and C[12]																				

1. Trial treatment may be administered up to 3 days before or 5 days after the scheduled Day 1 of each cycle, beginning in Cycle 3. Cycle 2 Day 1 may be administered up to 5 days after the scheduled Day 1.
2. Documented informed consent must be obtained prior to performing any protocol-specific procedure. Tests 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.
3. Pembrolizumab is administered first and then, following a 30-minute interval, MK 4280 will be administered.
4. Continuation or resumption of same chemotherapy as received in the First Course Treatment Phase may be administered in the Second Course Phase at the discretion of the investigator. Note that chemotherapy different from that received in the First Course Treatment Phase is not permitted.
5. These samples and procedures required predose on Day 1 may be performed up to 72 hours prior to dosing.
6. Vital signs (VS) to include temperature, pulse, respiratory rate, and blood pressure for all subjects. On Day 1 of Cycles 1-4, collect prior to dosing and at 2 hrs, 4 hrs, and 6 hrs (±10 mins for each) after start of the MK-4280 infusion. Beginning with Cycle 5, collect VS predose on Day 1 of each cycle for all subjects. .
7. If ≥4 weeks have passed between the scan used to confirm disease progression (and allow retreatment in second course) and Day 1 of Cycle 1, imaging should be repeated and these results should become the new baseline images. Tumor imaging and response assessment are to be performed 9 weeks after first dose, then every 9 weeks until disease progression. Imaging assessments should be repeated every 9 weeks and follow calendar days and should not be adjusted for delays in cycle starts. If institutional standard of care for imaging frequency differ from these guidelines, follow the institutional standard of care after confirming with the Sponsor. The same imaging technique should be used on a subject throughout the trial. Information for disease assessments may be requested and submitted for central review.
8. Performed locally within 7 days prior to the first dose. After C1, collect within 3 days before dosing.
9. Laboratory tests are to be performed within 7 days prior to the first dose of study treatment.
10. For women of reproductive potential, a urine pregnancy test will be performed at Screening and within 72 hours of receiving the first dose of study medication. If urine pregnancy test cannot be confirmed as negative, a serum pregnancy test is required.
11. Laboratory tests to be performed within 7 days prior to the first dose of study treatment
12. Include HCV RNA (qualitative) or Hepatitis C antibody, HBsAg, and HIV type 1 and type 2 (eg, HIV-1/-2 antibody screening test and evaluation of HIV viral load as needed).
13. After confirmed disease progression, or the start of new anticancer treatment; contacts are approximately every 12 weeks. Updated survival status may be requested by the Sponsor at any time during the course of the study. Upon Sponsor notification, all subjects who do not/will not have a scheduled study visit or study contact during the Sponsor-defined time period will be contacted for their survival status (excluding subjects that have a death event previously recorded).

6.7 Second Course - Part B – Arm 6 Flow Chart

	Treatment Phase Cycle = 21 days										End of Treatment	Post-Treatment Phase	
Treatment Cycle/Title	Cycle 1				Cycles 2-4[1]				Cycles 5-8[1]	Cycle 9 and Beyond[1]	Discon.	Safety Follow-up Visit	Survival Follow-up[2]
Cycle Day	1	2	8	15	1	8	15	9 weeks after 1st dose	1	1		30 days after last dose	Every 12 weeks
Scheduling Window (Days)			±3	±3		±3	±3	±7				±7	±7
Administrative Procedures													
Informed Consent[3]	X												
Inclusion/Exclusion Criteria	X												
Prior and Concomitant Medication Review	X	X	X	X	X	X	X		X	X	X	X	
MK-4280 Drug Administration	X				X				X	X			
Pembrolizumab Drug Administration[4]	X				X				X	X			
Lenvatinib Dispensed[5]	X				X				X	X			
Lenvatinib Container Returned					X				X	X	X		
Clinical Procedures/Assessments													
Adverse Events Monitoring	X	X	X	X	X	X	X		X	X	X	X	
Full Physical Examination (including oral examination)	X[6]				X[6]				X[6]	X[6]	X	X	
Weight	X				X				X	X	X	X	
Vital Signs (respiratory rate, blood pressure, pulse, temperature)[7]	X	X	X	X	X	X	X		X	X	X	X	
12-Lead Electrocardiogram[8]	X				X				X	X	X	X	

	Treatment Phase Cycle = 21 days										End of Treatment	Post-Treatment Phase	
Treatment Cycle/Title	Cycle 1				Cycles 2-4[1]				Cycles 5-8[1]	Cycle 9 and Beyond[1]	Discon.	Safety Follow-up Visit	Survival Follow-up[2]
Cycle Day	1	2	8	15	1	8	15	9 weeks after 1st dose	1	1		30 days after last dose	Every 12 weeks
Scheduling Window (Days)			±3	±3		±3	±3	±7				±7	±7
MUGA or ECHO for LVEF assessment[9]	X										X		
ECOG Performance Status	X[6]				X[6]				X[6]	X[6]	X	X	
Survival Status[2]	←									→			X
Efficacy Procedures/Assessments													
Tumor Imaging and irRECIST Response Assessment[10]								X[9]	X[9]	X[9]			
Laboratory Procedures/Assessments – Analysis by Local Lab													
Complete blood count (CBC) with differential	X[11,12]		X	X	X[6,12]	X			X[6,12]	X[6,12]	X	X	
PT/INR and aPTT[15]	X												
Chemistry Panel	X[11,12]		X		X[6,12]	X			X[6,12]	X[6,12]	X	X	
CEA Testing[13]	X[6]				X[13]				X[13]	X[13]			
Lactate dehydrogenase (LDH), gamma-glutamyl transferase (GGT)	X[6]				X[6]				X[6]				
Pregnancy Test – Urine Serum β-human chorionic gonadotropin (β-hCG), if applicable[14]	X				X				X	X	X	X	
Urinalysis[15]	X												
Urine dipstick testing[9,16]	X			X	X		X		X	X	X	X	

	Treatment Phase Cycle = 21 days										End of Treatment	Post-Treatment Phase	
Treatment Cycle/Title	Cycle 1				Cycles 2-4[1]				Cycles 5-8[1]	Cycle 9 and Beyond[1]	Discon.	Safety Follow-up Visit	Survival Follow-up[2]
Cycle Day	1	2	8	15	1	8	15	9 weeks after 1st dose	1	1		30 days after last dose	Every 12 weeks
Scheduling Window (Days)			±3	±3		±3	±3	±7				±7	±7
Thyroid Function (thyroxine [T4], triiodothyronine [T3], thyroid stimulating hormone [TSH])[17]	X[6]				X[6]				X[6]	X		X	
HIV, Hepatitis B and C[18]													

1. Trial treatment may be administered up to 3 days before or 3 days after the scheduled Day 1 of each cycle, beginning in Cycle 3. Cycle 2 Day 1 may be administered up to 3 days after the scheduled Day 1.
2. After confirmed disease progression, or the start of new anticancer treatment; contacts are approximately every 12 weeks. 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).
3. Documented informed consent must be obtained prior to performing any protocol-specific procedure. Tests 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.
4. Pembrolizumab is administered first and then, following a 30-minute interval, MK-4280 will be administered.
5. Lenvatinib is allowed during Second Course at the discretion of the investigator. Antineoplastic therapy different from lenvatinib is not permitted. Lenvatinib will be administered 0 to 4 hours after completion of the MK-4280 administration.
6. These samples and procedures required predose on Day 1 may be performed up to 72 hours prior to dosing.
7. Vital signs (VS) to include temperature, pulse, respiratory rate, and blood pressure for all subjects. Blood pressure and pulse will be measured after the subject has been resting for 5 minutes. On Day 1 of Cycles 1-4, collect prior to dosing and at 2 hrs, 4 hrs, and 6 hrs (±10 mins for each) after start of the MK-4280 infusion. Beginning with Cycle 5, collect VS predose on Day 1 of each cycle.
8. Twelve-lead electrocardiogram (ECG) at screening, Day 1 of Cycle 1 and Cycle 2, Day 1 of every 4th cycle (12 weeks) thereafter (eg, Cycle 6, Cycle 10, Cycle 14, etc), Discontinuation, and the Safety Follow-up Visit. ECG at Cycle 1, Day 1 and Cycle 2, Day 1 should be performed approximately 2 hours post-lenvatinib dose. For high-risk patients (Section 7.1.2.5), conduct ECG monitoring every cycle. If lenvatinib is discontinued, ECGs are only required at the Discontinuation and Safety Follow-up visits. If Lenvatinib was not administered in second course then ECG is only required at Cycle 1, Day 1 and Safety Follow-up.
9. Only to be performed if lenvatinib is administered during Second Course.
10. If ≥4 weeks have passed between the scan used to confirm disease progression (and allow retreatment in second course) and Day 1 of Cycle 1, imaging should be repeated and these results should become the new baseline images. Tumor imaging and response assessment are to be performed 9 weeks after first dose, then every 9 weeks until disease progression. Imaging assessments should be repeated every 9 weeks and follow calendar days and should not be adjusted for delays in cycle starts. If institutional standard of care for imaging frequency differ from these guidelines, follow the institutional standard of care after confirming with the Sponsor. The same imaging technique should be used on a subject throughout the trial. Information for disease assessments may be requested and submitted for central review.
11. Performed locally within 7 days before first dose. After C1, collect within 3 days before dosing.
12. On Day 1 in Cycles 1-4, CBC with differential and the Chemistry Panel should be drawn prior to dosing.

	Treatment Phase Cycle = 21 days										End of Treatment	Post-Treatment Phase	
Treatment Cycle/Title	Cycle 1				Cycles 2-4[1]				Cycles 5-8[1]	Cycle 9 and Beyond[1]	Discon.	Safety Follow-up Visit	Survival Follow-up[2]
Cycle Day	1	2	8	15	1	8	15	9 weeks after 1st dose	1	1		30 days after last dose	Every 12 weeks
Scheduling Window (Days)			±3	±3		±3	±3	±7				±7	±7

13. CEA will be assessed during screening and predose at every other cycle beginning with Cycle 1 (C1, C3, C5, etc.).
14. For women of reproductive potential, a urine pregnancy test will be performed within 24 hours of receiving the first dose of study medication. If more than 24 hours have elapsed prior to the first dose of study intervention, another pregnancy test is required prior to starting study intervention. If urine pregnancy test cannot be confirmed as negative, a serum pregnancy test is required.
15. Laboratory tests to be performed within 7 days prior to the first dose of study treatment
16. Urine dipstick testing is to be performed at screening, Day 1 and Day 15 of Cycle 1 and Cycle 2, Day 1 of every cycle thereafter, and at the Discontinuation and Safety Follow-up visits. Urinalysis may be used if the use of urine dipsticks is not feasible.
17. Thyroid function testing is to be performed at screening, Cycle 1 Day 1 and then Day 1 of every other cycle, and at the post-treatment Safety Follow-up Visit.
18. Include HCV RNA (qualitative) or Hepatitis C antibody, HBsAg, and HIV type 1 and type 2 (eg, HIV-1/-2 antibody screening test and evaluation of HIV viral load as needed).

7.0 TRIAL PROCEDURES

7.1 Trial Procedures

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

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

7.1.1 Administrative Procedures

7.1.1.1 Informed Consent

The investigator or qualified designee must obtain documented informed consent from each potential subject or their legally acceptable representative prior to participating in this clinical trial or Future Biomedical Research. If there are changes to the subject's status during the trial (e.g., health or age of majority requirements), the investigator or qualified designee must ensure the appropriate documented informed consent is in place.

7.1.1.1.1 General Informed Consent

Informed consent given by the subject or their legally acceptable representative must be documented on a consent form. The form must include the trial protocol number, trial protocol title, dated signature, and agreement of the participant (or his/her legally acceptable representative) and of the person conducting the consent discussion.

A copy of the signed and dated informed consent form should be given to the subject (or their legally acceptable representative) before participation in the trial.

The initial informed consent form, any subsequent revised 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 or the subject's legally acceptable representative's dated signature.

Specifics about the trial and the trial population are to be included in the trial informed consent form.

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, or the subject's legally acceptable representative, answer all of his/her questions, and obtain documented informed consent before performing any procedure related to Future Biomedical Research. A copy of the informed consent will be given to the subject before performing any procedure related to Future Biomedical Research.

Future Biomedical Research will not be applicable to Arm 6 or Cohort F.

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

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

7.1.1.4 Medical History

A medical history will be obtained by the investigator or qualified designee. Medical history will include all active conditions, and any condition diagnosed within the prior 10 years that are considered clinically significant by the investigator. Details regarding the disease for which the subject has been enrolled in the trial will be recorded separately and should not be listed in medical history.

7.1.1.5 Prior and Concomitant Medications Review

7.1.1.5.1 Prior Medications

The investigator or qualified designee will review prior medication use, including any protocol-specified washout requirement, and record prior medication taken by the subject within 30 days before starting the trial. Treatment for the disease for which the subject has been enrolled in this trial will be recorded separately and should not be listed in prior medications.

7.1.1.5.2 Concomitant Medications

The investigator or qualified designee will record medication, if any, taken by the subject during the trial and through the 30-day Safety Follow-up Visit. After the Safety Follow-up Visit, record all medications related to reportable SAEs and ECIs as defined in Section 7.2.

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.

7.1.1.6 Assignment of Screening Number

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

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

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

7.1.1.7 Assignment of Treatment/Randomization Number

Subjects in Cohort E of Part B will be randomly allocated to 1 of 2 doses of MK-4280 and will receive a treatment/randomization number accordingly. If Arms 1, 2C and 5 for 3L+ CRC subjects are enrolling at the same time, subjects will be assigned in an alternating fashion across the open arms at the study level through IVRS.

All other eligible subjects will be allocated, by non-random assignment, and will receive a treatment/randomization number.

The treatment/randomization number identifies the subject for all procedures occurring after treatment allocation/randomization. For subjects that are being allocated to their treatment, and not 'randomized', the unique number is still termed a randomization number throughout the protocol for operational purposes. Allocation to either Arm 1 or Arm 2 of Part A, and enrollment and/or randomization in Part B, will be managed by the Sponsor through an IVRS/IWRS.

Once a treatment/randomization number is assigned to a subject, it can never be re-assigned to another subject.

A single subject cannot be assigned more than 1 treatment/randomization number.

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

Interruptions from the protocol specified treatment(s) for ≥12 weeks require consultation between the investigator and the Sponsor and written documentation of the collaborative decision on subject management.

If there are interruptions in the study intervention schedule or infusion/injection was stopped, the details of and reason for any interruption of study intervention or infusion/injection cessation will be documented in the participant's medical record. Refer to Section 5.2.6 for Dose Modification and Toxicity Management Guidelines.

For subjects in Arm 6, lenvatinib compliance will be calculated by the Sponsor based on the drug accountability documented by the site staff and monitored by the Sponsor/designee. The objective is 100% compliance and investigators and their staff should evaluate compliance at each visit and take appropriate steps to optimize compliance.

7.1.1.9 Administration of Study Treatments

MK-4280 and pembrolizumab (or MK-4280A) will be administered using intravenous infusion. The Pharmacy Manual contains specific instructions for the preparation and administration of the infusion solutions.

Designated site personnel will be responsible for preparing and administering MK-4280 and pembrolizumab (or MK-4280A), and will be required to record limited information during each infusion (eg, infusion date/time, lot number and expiry date for product administered, total dose/volume administered). See Pharmacy Manual for further details.

In Arm 2 of Part A and Part B, pembrolizumab is administered first and then, following a 30-minute interval, MK-4280 will be administered.

In Arm 3 and Arm 4, pembrolizumab is administered first and then, following a 30-minute interval, MK-4280 will be administered. At visits where MK-4280, pembrolizumab, and chemotherapy are to be administered, chemotherapy will be administered in accordance with their approved labeling and in keeping with local clinical practice 30 minutes after the end of the MK-4280 infusion. Every attempt should be made to record limited information during each infusion (eg, infusion date/time, lot number and expiry date for product administered, total dose/volume administered) as per local guidelines. More details can be found in the Pharmacy Manual.

In Arm 6 of Part B, pembrolizumab is administered first and then, following a 30-minute interval, MK-4280 will be administered. Lenvatinib will be taken orally with water (with or without food) at approximately the same time each day in 21-day cycles. However, on visit days when pembrolizumab and MK-4280 are also administered, lenvatinib will be administered 0 to 4 hours after the MK-4280 infusion is complete.

If a lenvatinib dose is missed and cannot be taken within 12 hours, then that dose should be skipped and the next dose should be taken at the usual time of administration.

Subjects in Arm 1 of Part B who discontinue MK-4280 due to confirmed disease progression per irRECIST may be allowed to crossover to Arm 2 (see Section 5.2.5). The subject may receive up to 35 cycles of combination treatment (irrespective of how many cycles of monotherapy treatment they received).

7.1.1.10 Disease Details and Treatments

7.1.1.10.1 Disease Details

The investigator or qualified designee will obtain prior and current details regarding disease status.

7.1.1.10.2 Prior Oncology Treatment History

The investigator or qualified designee will record all prior anti-cancer treatments including systemic treatments, radiation and surgeries radiations and surgeries regardless of time prior to first dose of trial treatment.

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 according to NCI CTCAE Version 4.0. Toxicities will be characterized in terms of seriousness, causality, toxicity grade, and action taken with regard to trial treatment.

This is a dose-escalation trial to establish the MTD/MAD of MK-4280 monotherapy and an RP2D for MK-4280 when given in combination with pembrolizumab; therefore, each dose escalation will be based on the safety and tolerability experienced by subjects at each dose level. The safety and tolerability of each cohort for the DLT evaluation period will be reviewed prior to the start of the next cohort in each arm. The Sponsor and the principal investigators will review the safety and tolerability of each trial treatment, the appropriateness of dose escalation, when each cohort is completed and the next cohort is opened for enrollment. Frequency of these communications will depend on the enrollment of each cohort, as well as any potential new information regarding a safety concern in this trial or other relevant trials.

As a Phase 1 trial, there is no plan for an external safety reviewer. Data from individual subjects will be closely followed on an ongoing basis by the principal investigator and the Sponsor.

7.1.2.2 Full Physical Exam

The investigator or qualified designee will perform a complete physical exam during the screening period. Clinically significant findings from the screening exam should be recorded as medical history.

A full physical exam should be repeated according to the frequency defined in Section 6.0 – Trial Flow Chart. After the first dose of study treatment, new clinically significant abnormal findings should be recorded as AEs.

For subjects receiving lenvatinib on Arm 6: A complete physical examination including oral examination will be conducted by an investigator or medically qualified designee (consistent with local requirements) per institutional standard.

7.1.2.3 Vital Signs, Height, and Weight

The investigator or qualified designee will take vital signs for all study subjects at Screening, and on Day 1 of Cycles 1-4 prior to dosing, and at 2 hours, 4 hours, and 6 hours after the start of the MK-4280 (or MK-4280A) infusion. Subjects in Arm 2C, Arm 5, and Arm 6 will also be monitored for 6 hours after the start of the MK-4280 (or MK-4280A) infusion for signs of infusion reaction in Cycles 1-4. Beginning with Cycle 5, vital signs are to be collected prior to dosing on Day 1 of each cycle for all subjects, and at the Safety Follow-up Visit as specified in the Trial Flow Chart. Vital signs should include temperature, pulse, respiratory rate, blood pressure (BP), and weight at the frequency defined in Section 6.0 – Trial Flow Chart.

Height will be obtained at Screening only.

For subjects receiving lenvatinib on Arm 6:

- BP and heart rate will be measured after the subject has been resting for 5 minutes. All BP measurements should be performed on the same arm, preferably by the same person.
- Only 1 BP measurement is needed for subjects with systolic BP <140 mm Hg and diastolic BP <90 mm Hg. If the subject's first BP measurement of the current assessment is elevated (ie, systolic BP ≥140 mm Hg or diastolic BP ≥90 mm Hg), the BP measurement should be repeated at least 5 minutes later. One BP assessment is defined as the mean value of 2 measurements at least 5 minutes apart. If the BP assessment (ie, the mean of the 2 BP measurements obtained at least 5 minutes apart) shows an elevated BP (systolic BP ≥140 mm Hg or diastolic BP ≥90 mm Hg), a confirmatory assessment should be obtained at least 30 minutes later by performing 2 measurements (at least 5 minutes apart) to yield a mean value.
- If required, subjects will have BP measured between clinic visits. If the subject does not return to the study site for this BP measurement, BP may be measured, for example, at home or at a local pharmacy, and the results will be reviewed with the investigator or designee. The investigator/site may provide a diary as a tool to aid the subject in collecting BP evaluations between clinic visits. The Sponsor will not provide diaries to the site. If BP result raises concerns, the investigator may require additional follow-up, including an on-site BP re-test, or other clinically appropriate intervention(s).

7.1.2.4 Eastern Cooperative Oncology Group (ECOG) Performance Status

The investigator or qualified designee will assess the ECOG performance status as the time points specified in the Section 6.0 – Trial Flow Chart.

7.1.2.5 Electrocardiogram

A 12-lead ECG will be performed by the investigator or qualified designee at the time points outlined in Section 6.0 – Trial Flow Chart.

For subjects receiving lenvatinib on Arm 6:

Complete, standardized, 12-lead ECG recordings that permit all 12 leads to be displayed on a single page with an accompanying lead II rhythm strip below the customary 3 × 4 lead format are to be used. In addition to a rhythm strip, a minimum of 3 full complexes should be recorded from each lead simultaneously. Subjects must be in the recumbent position for a period of 5 minutes prior to the ECG. The Fridericia correction method for calculating QTc will be used.

An ECG abnormality may meet the criteria of an AE as described in this protocol (see Section 7.2) and the CRF Completion Guidelines. In these instances, the AE corresponding to the ECG abnormality will be recorded on the appropriate CRF.

QTc prolongation has been seen in some lenvatinib studies. Monitor electrocardiograms every cycle (as specified in Section 6.3 – Arm 6 Flow Chart) in patients with congenital long QT syndrome, congestive heart failure, bradyarrhythmias, or those who are taking drugs known to prolong the QT interval, including Class Ia and III antiarrhythmics. Refer to the lenvatinib IB.

7.1.2.6 Echocardiogram or Multiple Gated Acquisition Scan

For subjects receiving lenvatinib on Arm 6, a MUGA scan (using technetium-based tracer) or an echocardiogram will be performed to assess left ventricular ejection fraction (LVEF) as designated in the SoA (Section 6.3). MUGA or echocardiogram scans should be performed locally in accordance with the institution's standard practice. MUGA scans are the preferred modality; however, whichever modality is used for an individual subject at baseline should be repeated for all subsequent LVEF assessments for that subject. LVEFs as assessed by the institution will be entered onto the CRF. Investigator assessment will be based upon institutional reports.

7.1.2.7 Pregnancy Testing

Pregnancy testing:

- Pregnancy testing requirements for study inclusion are described in Section 5.1.2.
- Additional serum or urine pregnancy tests may be performed, as determined necessary by the investigator or required by local regulation, to establish the absence of pregnancy at any time during the subject's participation in the study.

Arm 6 only:

- Pregnancy testing (urine or serum as required by local regulations) should be conducted at monthly intervals during intervention.
- Pregnancy testing (urine or serum as required by local regulations) should be conducted at the end of relevant systemic exposure and correspond with the time frame for female participant contraception in 5.1.2.

7.1.2.8 Disease Assessments

Initial imaging (CT scans or MRI) must be performed within 28 days prior to the first dose of treatment, and should be repeated every 9 weeks (±7 days) from the first dose of treatment until confirmed disease progression, the start of new anticancer therapy, withdrawal of consent, death, or end of the study, whichever comes first.

The same imaging technique should be performed at each time point.

Information for disease assessments may be requested and submitted for central review.

Response will be assessed using RECIST 1.1 criteria by investigator assessment. However, clinical decisions as to whether discontinue study treatment should be made using irRECIST criteria along with clinical judgement.

Immunotherapeutic agents, such as MK-4280 and pembrolizumab may produce antitumor effects by potentiating endogenous cancer-specific immune response. The response patterns seen with such an approach may extend beyond the typical time course of responses seen with typical cytotoxic agents, and can manifest a clinical response after an initial increase in tumor burden or even the appearance of new lesions. Therefore, the subject should not be discontinued from the trial unless the initial assessment of PD is confirmed at least 4 weeks later (Section 4.2.3.1).

Subjects who have initial evidence of radiological PD by RECIST 1.1 after starting study treatment, should, at the discretion of the investigator, continue on study treatment until repeat imaging is obtained ≥4 weeks later to confirm PD. This clinical judgement decision should be based on the subject's overall clinical condition, including performance status, clinical symptoms, and laboratory data. Clinical stability is defined as the following:

(1) Absence of symptoms and signs indicating clinically significant progression of disease, including worsening of laboratory values

(2) No decline in ECOG performance status

(3) Absence of rapid progression of disease

(4) Absence of progressive tumor at critical anatomical sites (eg, spinal cord compression)

Any subject deemed clinically unstable should be discontinued from trial treatment and is not required to have repeat imaging for PD confirmation.

In determining whether or not the tumor burden has increased or decreased on the follow-up scan per RECIST 1.1, the local site investigator should consider target and nontarget lesions, as well as any incremental new lesion(s).

Progressive disease will be confirmed at repeat imaging if ANY of the following occur:

- Tumor burden remains ≥20% and there is at least a 5 mm absolute increase compared to the nadir
- Nontarget disease resulting in initial PD is qualitatively worse
- New lesion resulting in initial PD is qualitatively worse
- Additional new lesion(s) are identified since the last evaluation

- Additional new nontarget progression is identified since the last evaluation

For subjects who crossover Part B from Arm 1 to Arm 2C due to confirmed disease progression, the following criteria apply:

- The imaging results used for determination of disease progression and crossover (confirmatory scans, if performed) should become the new baseline imaging results from which subsequent progression is to be determined.
- Imaging for subjects who crossover should continue per the regular imaging schedule (every 9 weeks calculated from first dose of study treatment and not adjusted for delays)
- Management of crossover subjects will be identical to the management of new subjects entering Arm 2C of the study (ie, combination treatment should be discontinued once disease progression is documented and, if applicable, confirmed per irRECIST 1.1)
- All participants who have completed the first course may be eligible for second course of treatment after Sponsor consultation if there is investigator-determined progressive disease after initial treatment has been completed. Please refer to Sections 5.2.8, 6.5, 6.6, and 6.7 for additional details for imaging in second course.

7.1.2.9 Tumor Tissue Collection and Biomarker Assessment

Subjects will be requested to provide a tumor sample (archival or newly obtained pretreatment sample) as specified in the Procedure Manual. Sample collection, storage, and shipment instructions for correlative study samples, archival tumor samples, and newly obtained biopsy specimens will be provided in the Procedure Manual.

For all subjects in Part B, PD-L1 assessment will be performed but does not need to take place during the screening period.

For subjects in Part B with HNSCC (of oropharyngeal origin, only), HPV testing by p16 IHC, polymerase chain reaction (PCR), or fluorescent in situ hybridization is required before or during screening. For subjects in Part B with gastric cancer, HER2/neu testing via IHC and EBV testing via Epstein–Barr virus-encoded small RNAs (EBER1) in situ hybridization are required before or during screening. For subjects in Part B with gastric cancer or CRC, MSI testing by IHC or PCR is required before or during screening.

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 pretrial to posttrial visits), including approximate blood/tissue volumes drawn/collected by visit and by sample type per subject can be found in the Procedures Manual.

7.1.3.1 Laboratory Evaluations (Hematology, Chemistry, and Urinalysis)

Laboratory tests for hematology, chemistry, urinalysis and others are specified in Table 8.

Table 8 Laboratory Tests

Hematology	**Chemistry**	**Urinalysis/Urine Dipstick Testing[f]**	**Other**
Hematocrit	Albumin	Blood	Blood for correlative studies
Hemoglobin	Alkaline phosphatase	Glucose	β-hCG[a]
Platelet count	ALT	Protein	Blood for genetics
White blood cells (WBC) (total and differential)	AST	Specific gravity	PT (INR)[d]
Red blood cells (RBC)	Bicarbonate or carbon dioxide (CO_2)[b]	Microscopic exam, if abnormal results are noted	aPTT/PTT[d]
Absolute neutrophil count	Calcium	Urine pregnancy test[a]	TSH (T3, T4, TSH)[e]
	Chloride		CEA
	Creatinine		BRAF
	Glucose		
	Phosphorus		
	LDH and GGT		
	Potassium		
	Sodium		
	Total bilirubin		
	Direct bilirubin, if total bilirubin is elevated above the upper limit of normal		
	Total protein		
	Blood urea nitrogen		
	Urea[c]		
	Uric Acid		
	Magnesium[g]		

a. Perform on women of childbearing potential only. Urine pregnancy test is preferred. If the urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required.
b. If these tests are not done as part of standard of care in a particular region then these tests do not need to be performed.
c. Blood Urea Nitrogen is preferred; if not available urea may be tested.
d. Coagulation factors (PT/INR and aPTT/PTT) should be tested as part of the screening procedures for all subjects. Any subject receiving anticoagulant therapy should have coagulation factors monitored closely throughout the trial.
e. Total T3 is preferred; if not available free T3 may be tested.
f. For subjects in Arm 6, if urine protein is ≥2+ (≥100 mg/dL) (first occurrence or a subsequent increase in severity of urine dipstick or urinalysis proteinuria occurring on the same lenvatinib dose level), then a 24-hour urine collection or an immediate spot urine protein to-creatinine (UPCR) test should be done to quantify the 24-hour urine protein excretion. A 24 hour urine collection (initiated as soon as possible and at least within 72 hours) to verify the grade of proteinuria is required when UPCR is ≥2.4.
g. For subjects in Arm 6 only.

Laboratory tests for Screening should be performed within 7 days prior to the first dose of study treatment. After Cycle 1, predose laboratory tests can be performed up to 72 hours prior to dosing. Results must be reviewed by the investigator of qualified designee and found to be acceptable prior to each dose of study treatment.

For subjects in Arm 6, CBC with differential and clinical chemistry results must be reviewed before administration of study treatment. Electrolytes such as potassium, calcium, and magnesium should be monitored and abnormalities, when considered clinically significant, should be corrected in all subjects before starting study treatment.

7.1.3.2 Pharmacokinetic/Pharmacodynamic Evaluations

7.1.3.2.1 Blood Collection for Analysis

Sample collection, storage, and shipment instructions for blood and plasma samples will be provided in the study Procedures Manual. For subjects in Arms 2-6 of Part A and Part B, only one set of PK samples needs to be collected to assay for both MK-4280 and pembrolizumab.

To evaluate the immunogenicity and exposure of pembrolizumab, MK-4280, mFOLFOX7, FOLFIRI, and lenvatinib in these indications, sample collections for analysis of ADA and PK are currently planned as shown in the Trial Flowchart. Blood samples for PK and ADA collected may be stored only at this time. Further analysis may be performed if required. If ongoing PK, PD, and/or ADA sampling is deemed to be unnecessary by the Sponsor, it may be reduced or discontinued.

7.1.3.3 Planned Genetic Analysis Sample Collection

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

7.1.3.4 Future Biomedical Research Sample Collection

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

DNA for future research.

Leftover archival or newly obtained tumor tissue for future research.

Leftover RNA and serum for future research.

7.1.4 Other Procedures

7.1.4.1 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 final trial visit should be performed at the time of discontinuation. Any adverse events which are present at the time of discontinuation/withdrawal should be followed in accordance with the safety requirements outlined in Section 7.2 - Assessing and Recording Adverse Events.

7.1.4.1.1 Withdrawal From Future Biomedical Research

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

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

7.1.4.2 Blinding/Unblinding

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

7.1.4.3 Calibration of Equipment

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

7.1.5 Visit Requirements

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

7.1.5.1 Screening

Approximately 28 days prior to randomization, potential subjects will be evaluated to determine that they fulfill the entry requirements as set forth in Section 5.1.

Screening procedures may be repeated after consultation with the Sponsor.

Documented informed consent must be obtained prior to performing any protocol-specific procedure. 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:

- Screening laboratory tests are to be performed within 7 days prior to the first dose of trial treatment.
- For women of reproductive potential, a urine pregnancy test will be performed within 72 hours prior to first dose of trial treatment. If urine pregnancy results cannot be confirmed as negative, a serum pregnancy test, performed by the local study site laboratory, will be required.
- For Arm 6 only: All women who are being considered for participation in Arm 6 of the study, and who are not surgically sterilized or postmenopausal, must be tested for pregnancy within 24 hours of the first dose of study intervention. If a urine test is positive or not evaluable, a serum test will be required.

7.1.5.2 Treatment Visit Period

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

After a screening phase of up to 28 days, eligible subjects will be assigned by either randomization or nonrandom allocation to a specific cohort. MK-4280, pembrolizumab, MK-4280A, mFOLFOX7, FOLFIRI treatment, and lenvatinib will be administered as outlined in Section 5.2 - Trial Treatment(s). After the EOT, all subjects will be followed for 30 days for AEs. Subjects in Arm 1 of Part A and Part B will also be followed for 30 days for SAEs, whereas subjects in Arms 2-6 of Part A and Part B will be followed for 90 days for SAEs.

7.1.5.3 Post-Trial

7.1.5.3.1 Safety Follow-up Visit

The mandatory Safety Follow-up Visit should be conducted approximately 30 days after the last dose of trial treatment or before the initiation of a new anticancer treatment, whichever comes first. Subjects with an AE of Grade 2 or higher will be further followed until the resolution of the AE to Grade 0-1 or until beginning a new anticancer therapy, whichever occurs first. Subjects who are eligible for retreatment in second course (see Section 5.2.8 – Second Course of Study Treatment) may have up to 2 safety follow-up visits, one after the initial Treatment Period and one after the Second Course Phase.

7.1.5.3.2 Survival Follow-up

Subjects who experience confirmed disease progression or start a new anticancer therapy will move into the Survival Follow-up Phase and should be contacted approximately every 12 weeks to assess for survival status until death, withdrawal of consent, or the end of the trial, whichever occurs first.

7.1.5.4 Survival Status

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

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

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 unfavorable 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.

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

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

Adverse events will not be collected for subjects during the pre-screening period (for determination of archival tissue status) as long as that subject has not undergone any protocol-specified procedure or intervention. If the subject requires a blood draw, fresh tumor biopsy etc., the subject is first required to provide consent to the main study and AEs will be captured according to guidelines for standard AE reporting.

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

For purposes of this trial, an overdose will be defined as any dose exceeding the prescribed dose for pembrolizumab by at least 1000 mg (5 times the dose), 20% or more above the prescribed dose for MK-4280 or MK-4280A, and any dose above the protocol-prescribed dose of lenvatinib if associated with an adverse event. No specific information is available on the treatment of overdose of pembrolizumab, MK-4280, MK-4280A, or lenvatinib. In the event of overdose, pembrolizumab, MK-4280, MK-4280A, or lenvatinib should be discontinued and the subject should be observed closely for signs of toxicity. Appropriate supportive treatment should be provided if clinically indicated.

Sponsor does not recommend specific treatment for an overdose. Decisions regarding dose interruptions or modifications will be made by the investigator in consultation with the Sponsor Clinical Director based on the clinical evaluation of the participant.

There is no specific antidote for an overdose of lenvatinib. Due to its high degree of plasma protein binding, lenvatinib is not expected to be dialyzable. Adverse reactions in patients receiving single doses of lenvatinib as high as 40 mg were similar to those in clinical studies at the recommended dose for differentiated thyroid cancer, RCC, and HCC.

Refer to the approved prescribing information and local practice guidelines regarding the definition of and treatment for an overdose of mFOLFOX7 or FOLFIRI.

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).

7.2.1.1 Definitions of Medication Error, Misuse, and Abuse

Medication error

This is an unintended failure in the drug treatment process that leads to or has the potential to lead to harm to the patient.

Misuse

This refers to situations where the medicinal product is intentionally and inappropriately used not in accordance with the terms of the product information.

Abuse

This corresponds to the persistent or sporadic, intentional excessive use of a medicinal product for a perceived psychological or physiological reward or desired nontherapeutic effect.

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 subject provides documented informed consent but before treatment allocation/randomization must be reported by the investigator if they cause the subject to be excluded from the trial, or are the result of a protocol-specified intervention, including but not limited to washout or discontinuation of usual therapy, diet, placebo treatment or a procedure. Pregnancies and lactations that occur from the time of treatment allocation/randomization through 120 days following cessation of study treatment (or 30 days following cessation of study 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 9 for additional details regarding each of the above criteria.

Progression of the cancer under study is not considered an adverse event unless it results in hospitalization or death.

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

For the time period beginning at treatment allocation/randomization through 90 days following cessation of study treatment (or 30 days following cessation of study 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, whether or not related to the Sponsor's product, must be reported within 24 hours to the Sponsor either by electronic media or paper. Electronic reporting procedures can be found in the EDC data entry guidelines. Paper reporting procedures can be found in the Investigator Trial File Binder (or equivalent).

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

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

7.2.3.2 Events of Clinical Interest

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

For the time period beginning when the subject provides documented informed consent until treatment allocation/randomization, any ECI, or follow up to an ECI, that occurs to any subject must be reported within 24 hours to the Sponsor if it causes the subject to be excluded from the trial, or is the result of a protocol-specified intervention, including but not

limited to washout or discontinuation of usual therapy, diet, placebo treatment or a procedure.

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

Events of clinical interest for this trial include:

a. 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.

b. 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).

7.2.4 Evaluating Adverse Events

An investigator who is a qualified physician will evaluate all adverse events with respect to the elements outlined in Table 9. The investigator's assessment of causality is required for each adverse event. Refer to Table 9 for instructions in evaluating adverse events.

An investigator who is a qualified physician will evaluate all adverse events according to the NCI Common Terminology for Adverse Events (CTCAE), version 4. Any adverse event which changes CTCAE grade over the course of a given episode will have each change of grade recorded on the adverse event case report forms/worksheets.

All adverse events regardless of CTCAE grade must also be evaluated for seriousness. Investigators need to document if an SAE was associated with a medication error, misuse, or abuse.

For studies in which multiple agents are administered as part of a combination regimen, the investigator may attribute each adverse event causality to the combination regimen or to a single agent of the combination. In general, causality attribution should be assigned to the combination regimen (i.e., to all agents in the regimen). However, causality attribution may be assigned to a single agent if in the investigator's opinion, there is sufficient data to support full attribution of the adverse experience to the single agent.

Table 9 Evaluating Adverse Events

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

V4.0 CTCAE Grading	**Grade 1**	**Mild; asymptomatic or mid symptoms; clinical or diagnostic observations only; intervention not indicated.**
	Grade 2	**Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL.**
	Grade 3	**Severe or medically significant but not immediately life-threatening; hospitalization or prolongation or hospitalization indicated; disabling; limiting self-care ADL.**
	Grade 4	**Life threatening consequences; urgent intervention indicated.**
	Grade 5	**Death related to AE**
Seriousness	A serious adverse event is any adverse event occurring at any dose or during any use of Sponsor's product that:	
	†**Results in death**; or	
	†**Is life threatening; or** places the subject, in the view of the investigator, at immediate risk of death from the event as it occurred (Note: This does not include an adverse event that, had it occurred in a more severe form, might have caused death.); or	
	†**Results in a persistent or significant disability/incapacity** (substantial disruption of one's ability to conduct normal life functions); or	
	†**Results in or prolongs an existing inpatient hospitalization** (hospitalization is defined as an inpatient admission, regardless of length of stay, even if the hospitalization is a precautionary measure for continued observation. (Note: Hospitalization for an elective procedure to treat a pre-existing condition that has not worsened is not a serious adverse event. A pre-existing condition is a clinical condition that is diagnosed prior to the use of a MSD product and is documented in the patient's medical history.); or	
	†**Is a congenital anomaly/birth defect** (in offspring of subject taking the product regardless of time to diagnosis);or	
	Is a new **cancer** (that is not a condition of the study) **(**although not serious per ICH definition, is reportable to the Sponsor within 24 hours to meet certain local requirements); **or**	
	Is an overdose (whether accidental or intentional). Any adverse event associated with an overdose is considered a serious adverse event for collection purposes. An overdose that is not associated with an adverse event is considered a non-serious event of clinical interest and must be reported within 24 hours.	
	Other important medical events that may not result in death, not be life threatening, or not require hospitalization may be considered a serious adverse event when, based upon appropriate medical judgment, the event may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed previously (designated above by a †).	
Duration	Record the start and stop dates of the adverse event. If less than 1 day, indicate the appropriate length of time and units	
Action taken	Did the adverse event cause the Sponsor's product to be discontinued?	
Relationship to Sponsor's Product	Did the Sponsor's product cause the adverse event? The determination of the likelihood that the Sponsor's product caused the adverse event will be provided by an investigator who is a qualified physician. The investigator's signed/dated initials on the source document or worksheet that supports the causality noted on the AE form, ensures that a medically qualified assessment of causality was done. This initialed document must be retained for the required regulatory time frame. The criteria below are intended as reference guidelines to assist the investigator in assessing the likelihood of a relationship between the test drug and the adverse event based upon the available information. **The following components are to be used to assess the relationship between the Sponsor's product and the AE**; the greater the correlation with the components and their respective elements (in number and/or intensity), the more likely the Sponsor's product caused the adverse event (AE):	
	Exposure	Is there evidence that the subject was actually exposed to the Sponsor's product such as: reliable history, acceptable compliance assessment (pill count, diary, etc.), expected pharmacologic effect, or measurement of drug/metabolite in bodily specimen?
	Time Course	Did the AE follow in a reasonable temporal sequence from administration of the Sponsor's product? Is the time of onset of the AE compatible with a drug-induced effect (applies to trials with investigational medicinal product)?
	Likely Cause	Is the AE not reasonably explained by another etiology such as underlying disease, other drug(s)/vaccine(s), or other host or environmental factors

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

7.2.5 Sponsor Responsibility for Reporting Adverse Events

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

7.3 TRIAL GOVERNANCE AND OVERSIGHT

7.3.1 Scientific Advisory Committee

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

8.0 STATISTICAL ANALYSIS PLAN

This Section outlines the statistical analysis plan (SAP) strategies and procedures for the primary and key secondary analyses of the study. Exploratory and other non-confirmatory analyses will be outlined in a separate supplemental Statistical Analysis Plan (sSAP).

This study was developed in collaboration with a SAC. The SAC is comprised of both Sponsor and non-Sponsor scientific experts who provide scientific and strategic guidance on various aspects of the clinical trial and/or development, which may include study design, interpretation of study results, and subsequent peer-reviewed scientific publications.

Changes to analyses made after the protocol has been finalized, but prior to database lock, will be documented in the 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

This Section contains a brief summary of the statistical analyses for this trial. Full detail is found in the subsequent Sections.

Study Design Overview	Phase 1/1b Trial of MK-4280 as Monotherapy, in Combination with Pembrolizumab, in combination with Pembrolizumab and either mFOLFOX7, FOLFIRI or lenvatinib, and as a co-formulated product with pembrolizumab (MK-4280A) in Subjects With Advanced Solid Tumors. A 3+3 design in Part A to identify preliminary MTD; TPI design for dose confirmation and efficacy expansion cohorts for combination therapy (HNSCC and CRC), a randomized dose finding cohort (gastric cancer), MK-4280 monotherapy cohorts (CRC and gastric) and a MK-4280A cohort in Part B.
Analysis Populations	Safety (Primary): All-Subjects-as-Treated (ASaT) PK (Secondary): Per-Protocol (PP) Efficacy (Secondary & Exploratory): Full Analysis Set (FAS)
Primary Endpoint(s)	Safety: DLTs

Key Secondary Endpoints	PK parameters of single-agent MK-4280, MK-4280 in combination with pembrolizumab, in combination with pembrolizumab and either mFOLFOX7, FOLFIRI or lenvatinib, and as a co-formulated product with pembrolizumab; PK profile of pembrolizumab in combination with MK-4280 with or without mFOLFOX7, FOLFIRI or lenvatinib, and as part of MK-4280A ORR measured by RECIST 1.1 as assessed by investigator review
Statistical Methods for Key Efficacy/Immunogenicity/ Pharmacokinetic Analyses	Serum concentrations of MK-4280 in each arm will be summarized by planned visit and time for each dose separately; PK parameters will be summarized by dose. For each tumor type separately, the point estimate and 95% confidence interval (CI) for ORR will be evaluated in subjects treated with MK-4280 monotherapy, in combination with pembrolizumab (sequential administration and co-formulated product) or in combination with pembrolizumab and either mFOLFOX7, FOLFIRI or lenvatinib, using exact binomial distribution. A between dose comparison for ORR in the gastric combination therapy cohort will be conducted.
Treatment Assignment	In Part A, subjects are allocated to increasing doses of single-agent MK-4280 and MK-4280 coadministered with pembrolizumab without randomization centrally through IVRS; the study is open-label. In Part B Arm 2, subjects with gastric cancer will be randomized in a 1:1 fashion through IVRS to 1 of 2 doses of MK-4280 in combination with a fixed dose of pembrolizumab. Enrollment to Arm 3 or Arm 4 will be guided by a subject's eligibility for one arm or the other or, if eligible for both arms, will be determined by investigator choice. If any of Arms 1, 2C and 5 in Part B for 3L+ CRC subjects are enrolling at the same time, subjects will be assigned in an alternating fashion across the open arms at the study level through IVRS. Otherwise, all other subjects in Part B will receive the same treatment within their assigned arm and therefore will not be randomized; an IVRS will be used to control enrollment.
Statistical Methods for Key Safety Analyses	Summary statistics (counts, percentage, mean, standard deviation, etc.) will be provided for the safety endpoints as appropriate. The estimate of the DLT rate among subjects treated with the recommended MK-4280 Phase 2 dose when used in combination with pembrolizumab, and in combination with pembrolizumab and either mFOLFOX7, FOLFIRI or lenvatinib, and the 80% Bayesian Credible Interval for the estimate will be provided.
Interim Analyses	Safety will be monitored by cumulative data reviews throughout the trial. Data will be examined on a continuous basis to allow for dose-escalation decisions using the 3+3 design in Part A and dose-confirmation decisions using the TPI design in Part B. An interim analysis for efficacy will be performed for the CRC and PD-1-treatment-naïve HNSCC combination cohorts in Part B to determine tumor-specific cohort expansion to a maximum of 40 (HNSCC) or 100 (CRC) subjects. Safety and efficacy data will be monitored for the 2 different doses of MK-4280 administered with pembrolizumab in the gastric cancer cohort on a continuous basis to aid in internal decision making and to determine if an additional 20 subjects with gastric cancer will be enrolled to receive MK-4280 monotherapy at the RP2D.
Multiplicity	No multiplicity adjustment is planned in this Phase 1/1b study.

Sample Size and Power	The sample size of the dose escalation and dose confirmation/efficacy expansion (Parts A and B) depends on the observed DLT profiles of MK-4280 monotherapy and MK-4280 coadministered with pembrolizumab. A target sample size of 576 subjects will be used for study planning purposes.

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 conducted as an open-label trial, ie, subjects, investigators, and Sponsor personnel will be aware of subject treatment assignments after each subject is enrolled and treatment is assigned.

8.3 Hypotheses/Estimation

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

8.4 Analysis Endpoints

Efficacy and safety endpoints are listed below, followed by the descriptions of the derivations of selected endpoints.

8.4.1 Efficacy/Immunogenicity/Pharmacokinetics Endpoints

Objective response rate in subjects treated with MK-4280 alone, in combination with pembrolizumab, or in combination with pembrolizumab and either mFOLFOX7, FOLFIRI or lenvatinib is a secondary endpoint of the trial and is defined as the proportion of subjects in the analysis population who experience complete response (CR) or partial response (PR) using RECIST 1.1 criteria as assessed by investigator review. Other efficacy endpoints (eg, Duration of Response [DOR], progression-free survival [PFS], Overall Survival [OS]) or the use of irRECIST 1.1 criteria are exploratory endpoints in this trial and will be defined in the sSAP.

Pharmacokinetic endpoints include serum concentrations of MK-4280, pembrolizumab, and lenvatinib, and derived PK parameters.

For the comparison of MK-4280 and pembrolizumab pharmacokinetics administered as a co-formulated product (MK-4280A, Cohort A, Arm 5) with that of its individual components administered sequentially (Cohort A, Arm 2C), the pharmacokinetic endpoints of interest are $AUC_{0\text{-}21days}$ and C_{max} from the first cycle. Additional PK parameters such as $AUC_{0\text{-}\infty}$ and soluble LAG-3 exposure parameters such as $AUC_{0\text{-}21days}$ from the first cycle administration of MK-4280A and MK-4280 administered in sequential combination with pembrolizumab are also of interest.

To characterize the pharmacokinetics in subjects from China, pharmacokinetic endpoints include serum concentrations of MK-4280 and pembrolizumab, and derived PK parameters:

- Single dose parameters: $AUC_{0\text{-}21days}$, C_{max}, T_{max}, and $t_{1/2}$.

- Multiple dose parameters: C_{trough}, $AUC_{0\text{-}21days}$, and C_{max} at steady state, accumulation ratio.

8.4.2 Safety Endpoints

The primary safety endpoint is DLT. Safety will be monitored by cumulative data reviews throughout the trial. The toxicities and grades experienced by subjects who have received study treatment, including AEs and SAEs, will be summarized. Of particular interest are infusion related reactions and immune-related AEs. Other safety measures evaluated in all parts of the study include laboratory safety assessments, ECGs, vital signs, and physical examinations.

8.4.3 Derivations of Safety Endpoints

Description of safety measures is provided in Section 7.1.

8.5 Analysis Populations

8.5.1 Safety Analysis Populations

The ASaT population will be used for the analysis of safety data in this study. The ASaT population consists of all subjects who received at least 1 dose of study treatment. In case of treatment administration errors, subjects will be analyzed according to the treatment they actually received. For DLT evaluation, ASaT subjects that were observed for safety for 21 days after the first dose of assigned treatment or experienced a DLT prior to 21 days after the first dose of assigned treatment will be used.

At least 1 laboratory or vital sign measurement obtained subsequent to at least 1 dose of study treatment is required for inclusion in the analysis of each specific parameter. To assess change from baseline, a baseline measurement is also required.

8.5.2 Pharmacokinetic Analysis Populations

The PP population will be used for the PK analyses and target engagement. The PP population consists of all subjects who comply with the protocol sufficiently to ensure that these data will be likely to exhibit the effects of treatment, according to the underlying scientific model. Compliance covers such considerations as exposure to treatment, availability of measurements and absence of major protocol violations. Major protocol violators will be identified to the extent possible prior to database lock by individuals responsible for data collection/compliance, and its analysis and interpretation. Any subjects or data values excluded from analysis will be identified, along with their reason for exclusion, in the CSR. At the end of the study, all subjects who are compliant with the study procedure as aforementioned and have available data from at least 1 treatment will be included in the analysis dataset.

8.5.3 Efficacy Analysis Populations

The FAS population will be used for the analysis of secondary and exploratory efficacy data in this trial. The FAS population consists of all subjects with a baseline scan with measurable

disease by investigator assessment who were administered a dose of study treatment regardless of dose level.

8.6 Statistical Methods

This Section describes the statistical methods that address the primary and secondary objectives. Methods related to exploratory endpoints will be described in the sSAP.

8.6.1 Statistical Methods for Safety Analyses

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

Dose limiting toxicities will be listed, and DLTs and AEs will be summarized as counts and frequencies for each MK-4280 dose level administered as monotherapy, in combination with pembrolizumab, or in combination with pembrolizumab and either mFOLFOX7, FOLFIRI or lenvatinib that had at least 3 subjects treated and listed for other dose levels. The estimate of the DLT rate among subjects treated with the preliminary RP2D and the 80% Bayesian credible interval based on a prior distribution of Beta (1,1) for the estimate will be provided.

Laboratory assessments, vital signs, and other safety endpoints will be summarized as appropriate.

In addition, the broad clinical and laboratory AE categories consisting of the percentage of subjects with any AE, a drug-related AE, an SAE, an AE that is both drug-related and serious, and who discontinued due to an AE will be summarized for dose levels with at least 3 subjects treated and listed for other doses.

Data from subjects who experienced disease progression in the Part B monotherapy arm and crossed over into the combination arm will be presented separately.

Data from subjects in Arm 3, Arm 4 and Arm 6 will be summarized separately.

The difference and 95% CI for the rates of infusion related reactions and immune related AEs between MK-4280 administered as a co-formulated product with pembrolizumab (MK-4280A, Arm 5) and MK-4280 and pembrolizumab administered sequentially (Arm 2C, equivalent dose to Arm 5) will be calculated.

8.6.2 Statistical Methods for Efficacy Analyses

Clinical responses will be listed for subjects in Part A for both the MK-4280 monotherapy arm and the MK-4280 in combination with pembrolizumab arm by dose level.

For the secondary endpoint of ORR, the point estimate and 95% CI will be evaluated separately in Part B subjects treated with MK-4280 monotherapy, in combination with pembrolizumab (separately for co-formulated product or following sequential administration), and in combination with pembrolizumab and either mFOLFOX7, FOLFIRI or lenvatinib at the RP2D for each tumor cohort separately, using an exact method based on binomial distribution (Clopper-Pearson interval).

A comparison will be conducted for ORR between the 2 doses of MK-4280 in combination with pembrolizumab administered in the gastric cancer cohort. Miettinen and Nurminen's

method will be used to estimate the treatment difference between the 2 doses and its 95% CI. Other exploratory endpoints may also be compared between doses (eg, DOR, PFS). Data from subjects who experienced disease progression in the Part B monotherapy gastric arm and crossed over into the combination arm will be summarized separately and will not be included in the dose comparison analysis.

8.6.3 Summaries of Baseline Characteristics, Demographics, and Other Analyses

8.6.3.1 Demographic and Baseline Characteristics

The number and percentage of subjects screened, randomized/allocated, the primary reasons for screening failure, and the primary reason for discontinuation will be displayed. Demographic variables, baseline characteristics, primary and secondary diagnoses, and prior and concomitant therapies will be summarized.

8.6.3.2 Pharmacokinetics and Pharmacodynamics Modeling Analysis

Serum concentrations of MK-4280 in each arm, serum concentrations of pembrolizumab in each arm, and plasma concentrations of lenvatinib in Arm 6 will be summarized by planned visit and time for each dose separately. Pharmacokinetic parameters will be summarized by dose. Pharmacokinetic data from subjects from China (Cohort F, Arm 5) will be summarized separately to characterize the PK in this group. Descriptive statistics will be provided for each dose with at least 3 subjects; for other doses, the results will be listed. These analyses will be done on an ongoing basis throughout the study and at the end of the study.

The data from the study will be used to quantitatively explore the relationships among pharmacokinetics, target engagement, exploratory biomarkers, and tumor response measurements.

8.6.4 Statistical Methods for Biocomparability Analyses

To compare the pharmacokinetics between MK-4280A and that of its individual components administered sequentially, pharmacokinetic data from Cohort A, Arm 5 (MK-4280A) and Arm 2C (CRC subjects receiving MK-4280 and pembrolizumab sequentially at the equivalent dose of Arm 5) will be used.

Individual MK-4280 $AUC_{0\text{-}21days}$ and C_{max} values from Cycle 1 will be natural log-transformed and analyzed separately in ANCOVA models with effects for treatment, body weight and baseline sLAG-3. Additional covariates deemed significant during PK analysis may also be considered. A 90% CI for the difference in treatment means on the log scale will be calculated using the mean square error from the model and referencing a t-distribution for each endpoint. These confidence limits will be exponentiated to obtain the 90% CI for the ratio of geometric means (MK-4280 from MK-4280A / MK-4280 administered sequentially with pembrolizumab) for MK-4280 $AUC_{0\text{-}21days}$ and C_{max}. Pembrolizumab $AUC_{0\text{-}21days}$ and C_{max} from Cycle 1 will be analyzed in a similar fashion. Additional PK parameters such as $AUC_{0\text{-}\infty}$ and soluble LAG-3 exposure parameters ($AUC_{0\text{-}21days}$) from Cycle 1 may also be analyzed in a similar manner.

8.7 Interim Analyses

In this study there will be no hypothesis testing. Safety data will be examined on a continuous basis to allow for dose-escalation and dose-confirmation decisions.

In Part B, Arm 2A of the study, an interim analysis will be performed for the CRC and PD-1-treatment-naïve HNSCC cohorts receiving MK-4280 in combination with pembrolizumab. For these tumor cohorts, after 10 subjects have been enrolled and have at least 1 post-baseline scan assessment, the ORR will be evaluated. If an individual cohort experiences an ORR of 20% or greater (ie, at least 2 of 10 subjects), this cohort will be expanded to enroll a maximum of 30 (PD-1-treatment-naïve HNSCC) or 90 (CRC) additional subjects, for a maximum of 40 or 100 subjects in the particular cohort. Enrollment to these cohorts will not be paused in the time period between when 10 subjects have been enrolled and when the interim analysis is performed. If fewer than 2 of 10 subjects experience an objective response in a given cohort, the totality of data will be evaluated to decide whether or not to continue enrollment in that cohort. The operating characteristics of the interim analysis rule are provided in Table 10.

Table 10 Operating Characteristics of Interim Analysis Rule for Each Tumor Type

True ORR	Probability of ≤1 of 10 Subjects Respond
10%	0.74
15%	0.54
20%	0.38
25%	0.24
30%	0.15
35%	0.09
40%	0.05
45%	0.02
50%	0.01

To aid in internal decision making, an interim analysis of efficacy may be performed comparing the 2 doses of MK-4280 in combination with pembrolizumab (Part B, Arm 2A, 2B) administered in the gastric cancer cohort after approximately 25 subjects per dose have been enrolled and have at least 1 post-baseline scan.

Additionally, if antitumor activity is observed in this cohort (≥8 of 40 subjects with an objective response, irrespective of dose) an additional 20 subjects with gastric cancer will be enrolled to receive MK-4280 monotherapy at the RP2D. The operating characteristics of the interim analysis rule are provided in Table 11. If this predetermined ORR is not observed, the Sponsor will evaluate all available data before determining whether to enroll these additional subjects or not.

Table 11 Operating Characteristics of Interim Analysis Rule for Determining Conduct of Gastric Cancer Monotherapy Cohort

True ORR for the Combination	Probability Gastric Cancer Monotherapy Cohort Conducted (≥8 of 40 Combination Subjects Respond)
10%	0.04
15%	0.24
20%	0.56
25%	0.82
30%	0.94

8.8 Multiplicity

There will be no multiplicity control in this study.

8.9 Sample Size and Power Calculations

8.9.1 Dose Escalation and Dose Confirmation

The primary purpose of the dose-escalation and dose-confirmation parts of the trial is to investigate the safety and tolerability of MK-4280 monotherapy, MK-4280 in combination with pembrolizumab, and MK-4280 in combination with pembrolizumab and either mFOLFOX7, FOLFIRI or lenvatinib in adult subjects with advanced solid tumors (Part A and first 14 subjects in the PD-1-treatment-naïve HNSCC and CRC cohorts in Part B Arm 2A, and Arm 3, Arm 4 and Arm 6 in Part B) and to establish RP2Ds for MK-4280 in combination with pembrolizumab and in combination with pembrolizumab and either mFOLFOX7, FOLFIRI or lenvatinib.

The final number of subjects enrolled in the dose-escalation and dose-confirmation parts of the study will depend on the empirical safety (DLT) observations, in particular, at what dose the 3+3 design is triggered and what dose is identified as the preliminary RP2D. Sample sizes for a few possible scenarios as well as the estimated time required to enroll all subjects and the time required to determine the preliminary RP2D are provided below. The time required to estimate the preliminary RP2D is the time from the first subject's first dose to the end of the 3-week observation period following the first dose of the last subject enrolled in the dose confirmation part. The study duration is derived as the time from the first subject's first dose to the end of 2-year treatment period following the enrollment of the last Part B subject.

Scenario 1. No DLTs during Part A. For MK-4280, in a scenario where no DLTs are encountered during the dose escalation and dose confirmation parts so that Part A continues to the highest dose in Table 3 for both arms, the sample size to determine the preliminary RP2D is 44 subjects (15 in each of the 2 arms of Part A and the first 14 subjects enrolled in Part B Arm 2A who are dosed via the TPI design).

It will take a minimum of 21 weeks to enroll and observe for DLTs in MK-4280 monotherapy and combination subjects in Part A. Total follow-up for the Part A, Arm 2 subjects treated with pembrolizumab would be 104 weeks plus an additional 90 days to observe subjects with SAEs. The duration for Part A, then, is approximately 125 weeks or slightly greater than 2 ½ years.

Part B includes up to a total of 516 subjects. The first 14 subjects in the PD-1-treatment-naïve HNSCC and CRC cohorts enrolled to Part B Arm 2A will be used to further refine the MK-4280 plus pembrolizumab RP2D through the TPI design. The first 14 subjects in each of Arm 3, Arm 4 and Arm 6 from Part B will be used to refine the MK-4280 plus pembrolizumab plus either mFOLFOX7, FOLFIRI or lenvatinib RP2D through the TPI design. It will take approximately 20 months to enroll all subjects for Part B.

Scenario 2: Flat DLT dose-response. Suppose dose escalation in Part A, Arm 1 and Arm 2, continues to the highest dose with flat dose-response so that all 5 doses (including the top one) are given to 6 subjects each. Also suppose that the top dose is confirmed as the preliminary RP2D dose without de-escalation in Part B. Thus, the sample size to determine the preliminary RP2D for MK-4280 plus pembrolizumab is 74 subjects (30 in each of Arm 1 and Arm 2 in Part A and the first 14 subjects enrolled in Part B Arm 2A who are dosed via the TPI design, i.e., 30+30+14=74).

Part B includes up to a total of 516 subjects. The first 14 subjects in the PD-1-treatment-naïve HNSCC and CRC cohorts enrolled to Part B Arm 2A will be used to further refine the MK-4280 plus pembrolizumab RP2D through the TPI design. The first 14 subjects in each of Arm 3, Arm 4 and Arm 6 from Part B will be used to refine the MK-4280 plus pembrolizumab plus either mFOLFOX7, FOLFIRI or lenvatinib RP2D through the TPI design. It will take approximately 20 months to enroll all subjects for Part B.

Any dose de-escalations and/or re-escalations in Part B will increase the sample size in these examples.

8.9.2 Precision of the DLT Rate at Preliminary RP2D

Since the TPI approach will be used during the dose confirmation part of the study (Part B Arm 2A), the estimated DLT rate, and its 80% Bayesian Credibility Interval will be calculated from the posterior distribution of the DLT rate at the preliminary RP2D using the model specified in the TPI approach. If 40 subjects are finally dosed at the MK-4280 plus pembrolizumab RP2D during the efficacy expansion for a given tumor type, the estimated DLT rate and its 80% credibility interval should be similar to one of the rows in Table 12. This table also applies for the N=40 subjects dosed at the RP2D of MK-4280 plus pembrolizumab plus lenvatinib (Arm 6). Table 13 presents similar calculations for N=20 subjects dosed at the RP2D for MK-4280 plus pembrolizumab plus either mFOLFOX7 or FOLFIRI.

Table 12 Precision of the Estimated DLT Rates at MK-4280 Plus Pembrolizumab RP2D

Number of Subjects Dosed at RP2D	Number of DLT Events	Estimated DLT Rate	Lower Bound of 80% credibility interval	Upper Bound of 80% credibility interval
40	4	0.10	0.061	0.186
40	6	0.15	0.098	0.243
40	8	0.20	0.137	0.298
40	10	0.25	0.178	0.351
40	12	0.30	0.221	0.402
40	14	0.35	0.264	0.453
Assume non-informative prior distribution of DLT.				

Table 13 Precision of the Estimated DLT Rates at MK-4280 Plus Pembrolizumab Plus Either mFOLFOX7 or FOLFIRI RP2D

Number of Subjects Dosed at RP2D	Number of DLT Events	Estimated DLT Rate	Lower Bound of 80% credibility interval	Upper Bound of 80% credibility interval
20	2	0.10	0.054	0.237
20	3	0.15	0.087	0.295
20	4	0.20	0.123	0.350
20	5	0.25	0.160	0.402
20	6	0.30	0.200	0.453
20	7	0.35	0.240	0.502
Assume non-informative prior distribution of DLT.				

8.9.3 Efficacy Expansion

Table 14, Table 15 and Table 16 show the ORR estimate and the 95% CI (Clopper-Pearson interval) for various sample sizes among the Part B expansion cohorts or additions to cohorts under protocol amendments.

Table 14 Estimate and 95% CI of ORR (N=40)

Number of Responses (PR/CR)	Observed ORR	95% CI of ORR
3	7.5%	(1.6%, 20.4%)
4	10.0%	(2.8%, 23.7%)
5	12.5%	(4.2%, 26.8%)
6	15.0%	(5.7%, 29.8%)
7	17.5%	(7.3%, 32.8%)
8	20.0%	(9.1%, 35.6%)
9	22.5%	(10.8%, 38.5%)
10	25.0%	(12.7%, 41.2%)
11	27.5%	(14.6%, 43.9%)
12	30.0%	(16.6%, 46.5%)
13	32.5%	(18.6%, 49.1%)
14	35.0%	(20.6%, 51.7%)

Number of Responses (PR/CR)	Observed ORR	95% CI of ORR
15	37.5%	(22.7%, 54.2%)
16	40.0%	(24.9%, 56.7%)

Table 15 Estimate and 95% CI of ORR (N=60)

Number of Responses (PR/CR)	Observed ORR	95% CI of ORR
5	8.3%	(2.8%, 18.4%)
6	10.0%	(3.8%, 20.5%)
7	11.7%	(4.8%, 22.6%)
8	13.3%	(5.9%, 24.6%)
9	15.0%	(7.1%, 26.6%)
10	16.7%	(8.3%, 28.5%)

Table 16 Estimate and 95% CI of ORR (N=100)

Number of Responses (PR/CR)	Observed ORR	95% CI of ORR
8	8.0%	(3.5%, 15.2%)
9	9.0%	(4.2%, 16.4%)
10	10.0%	(4.9%, 17.6%)
11	11.0%	(5.6%, 18.8%)
12	12.0%	(6.4%, 20.0%)
13	13.0%	(7.1%, 21.2%)
14	14.0%	(7.9%, 22.4%)
15	15.0%	(8.6%, 23.5%)
16	16.0%	(9.4%, 24.7%)

Though no hypothesis testing will be performed, with 40 subjects per dose level in the gastric cancer cohort, the study has 80% power to detect a ~30% difference in ORR (for example, 55% versus 25%) at alpha=5% (1-sided) between 2 dose levels.

In the Part B MK-4280 monotherapy arms (Arm 1), 20 subjects will be enrolled in each cohort (CRC and gastric, if conducted). If the true ORR is either 5% or 10% for a given cancer type, then the chance of observing at least 1 responder among the 20 subjects will be 64% or 88%, respectively. For each cohort, if there are 0 responses, then there is 88% power to rule out a true ORR >10%.

8.9.4 Pharmacokinetic Comparison Between MK-4280A (Co-formulated Product) and MK-4280 and Pembrolizumab Administered Sequentially

The following precision calculations are based on assumed true between subject standard deviations of 0.429 and 0.463 for MK-4280 ln-$AUC_{0\text{-}21days}$ and ln-C_{max}, respectively, and 0.339 and 0.398 for pembrolizumab ln-$AUC_{0\text{-}21days}$ and ln-C_{max}, respectively. These estimates are based on currently available Cycle 1 pharmacokinetic data from subjects in this study who received either MK-4280 200 mg or 700 mg and pembrolizumab 200 mg.

With 40 subjects receiving MK-4280A (Cohort A, Arm 5), and 40 subjects from Part B Arm 2C receiving the equivalent dose of Arm 5:

MK-4280 $AUC_{0\text{-}21days}$: The half-width of the 90% CI for the ratio of geometric means (MK-4280 from MK-4280A / MK-4280 administered sequentially with pembrolizumab) on the log scale will be 0.159. The lower and upper 90% confidence limits for the ratio of geometric means will be given by OBS/1.17 and OBS*1.17, where OBS is the observed ratio. Thus, for example, if the observed ratio was 1, the 90% CIwould be (0.85, 1.17).

MK-4280 C_{max}: The half-width of the 90% CIfor the ratio of geometric means (MK-4280 from MK-4280A / MK-4280 administered sequentially with pembrolizumab) on the log scale will be 0.172. The lower and upper 90% confidence limits for the ratio of geometric means will be given by OBS/1.19 and OBS*1.19, where OBS is the observed ratio. Thus, for example, if the observed ratio was 1, the 90% CIwould be (0.84, 1.19).

Pembrolizumab $AUC_{0\text{-}21days}$: The half-width of the 90% CIfor the ratio of geometric means (Pembrolizumab from MK-4280A / Pembrolizumab administered sequentially with MK-4280) on the log scale will be 0.126. The lower and upper 90% confidence limits for the ratio of geometric means will be given by OBS/1.13 and OBS*1.13, where OBS is the observed ratio. Thus, for example, if the observed ratio was 1, the 90% CIwould be (0.88, 1.13).

Pembrolizumab C_{max}: The half-width of the 90% CIfor the ratio of geometric means (Pembrolizumab from MK-4280A / Pembrolizumab administered sequentially with MK-4280) on the log scale will be 0.148. The lower and upper 90% confidence limits for the ratio of geometric means will be given by OBS/1.16 and OBS*1.16, where OBS is the observed ratio. Thus, for example, if the observed ratio was 1, the 90% CIwould be (0.86, 1.16).

8.10 Subgroup Analyses

Within each tumor cohort, analyses of the efficacy endpoint ORR will be conducted by baseline PD-L1 status, separately for the monotherapy and combination arms.

8.11 Compliance (Medication Adherence)

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

8.12 Extent of Exposure

A subject's extent of exposure to MK-4280 is defined as the total number of doses of MK-4280 the subject received. A subject's extent of exposure to pembrolizumab is defined as the total number of doses of pembrolizumab the subject received.

Extent of exposure will be summarized for all MK-4280 and MK-4280 in combination with pembrolizumab dose levels with at least 3 subjects enrolled, and listed for other dose levels.

9.0 LABELING, PACKAGING, STORAGE AND RETURN OF CLINICAL SUPPLIES

9.1 Investigational Product

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

Clinical Supplies will be provided by the Sponsor as summarized in Table 17.

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 17 Product Descriptions

Product Name & Potency	Dosage Form	IMP or NIMP[2]
MK-4280 50 mg/vial (25 mg/mL)	Solution for Infusion	IMP
MK-4280 200 mg/vial (25 mg/mL)	Solution for Infusion	IMP
Pembrolizumab (MK-3475) 50 mg/vial	Lyophilized Powder for IV Injection/Infusion	IMP
Pembrolizumab (MK-3475) 100 mg/4 mL[1]	Solution for Infusion[1]	IMP
MK-4280A (20 mg/mL MK-4280 and 5 mg/mL pembrolizumab for a total protein content of 25 mg/mL)	Solution for Infusion	IMP
Lenvatinib (MK-7902) 10 mg	Capsule	IMP
Lenvatinib (MK-7902) 4 mg	Capsule	IMP

1. Solution will not be supplied at initiation of the trial. It is considered a backup formulation only.
2. Defining Investigational Medicinal Product (IMP) and Non- Investigational Medicinal Product (NIMP) is based on guidance issued by the European Commission. Regional and/or Country differences of the definition of IMP/NIMP may exist. In these circumstances, local legislation is followed.

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

Any commercially available product not included in Table 17 will be provided by the trial site, subsidiary or designee. Every attempt should be made to source these supplies from a single lot/batch number. The trial site is responsible for recording the lot number, manufacturer, and expiry date for any locally purchased product as per local guidelines unless otherwise instructed by the Sponsor.

9.2 Packaging and Labeling Information

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

9.3 Clinical Supplies Disclosure

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.

10.0 ADMINISTRATIVE AND REGULATORY DETAILS

10.1 Confidentiality

10.1.1 Confidentiality of Data

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

10.1.2 Confidentiality of Subject Records

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

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

10.1.3 Confidentiality of Investigator Information

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

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

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

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

10.1.4 Confidentiality of IRB/IEC Information

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

10.2 Compliance with Financial Disclosure Requirements

Financial Disclosure requirements are outlined in the US Food and Drug Administration Regulations, Financial Disclosure by Clinical Investigators (21 CFR Part 54). It is the

Sponsor's responsibility to determine, based on these regulations, whether a request for Financial Disclosure information is required. It is the investigator's/subinvestigator's responsibility to comply with any such request.

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

10.3 Compliance with Law, Audit and Debarment

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

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

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

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

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

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

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

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

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

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

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

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

anticipated review process, thorough understanding of clinical trial methods, appropriate enrollment of subject cohort, timely achievement of trial milestones). The Protocol CI must be a participating trial investigator.

10.4 Compliance with Trial Registration and Results Posting Requirements

Under the terms of the Food and Drug Administration Modernization Act (FDAMA) and the Food and Drug Administration Amendments Act (FDAAA), the Sponsor of the trial is solely responsible for determining whether the trial and its results are subject to the requirements for submission to the Clinical Trials Data Bank, http://www.clinicaltrials.gov. MSD, as Sponsor of this trial, will review this protocol and submit the information necessary to fulfill these requirements. MSD entries are not limited to FDAMA/FDAAA mandated trials. Information posted will allow subjects to identify potentially appropriate trials for their disease conditions and pursue participation by calling a central contact number for further information on appropriate trial locations and trial site contact information.

By signing this protocol, the investigator acknowledges that the statutory obligations under FDAMA/FDAAA are that of the Sponsor and agrees not to submit any information about this trial or its results to the Clinical Trials Data Bank.

10.5 Quality Management System

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

10.6 Data Management

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

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

10.7 Publications

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

relevant regulatory authority decisions on the trial drug have been made with regard to pediatric-related regulatory filings. MSD will post a synopsis of trial results for approved products on www.clinicaltrials.gov by 12 months after the last subject's last visit for the primary outcome, 12 months after the decision to discontinue development, or product marketing (dispensed, administered, delivered or promoted), whichever is later.

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

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

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

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

11.0 LIST OF REFERENCES

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12.0 APPENDICES

12.1 Code of Conduct for Clinical Trials

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

I. Introduction

A. Purpose

MSD Sharp & Dohme LLC, Rahway, NJ, USA (MSD), through its subsidiaries, conducts clinical trials worldwide to evaluate the safety and effectiveness of our products. As such, we are committed to designing, implementing, conducting, analyzing and reporting these trials in compliance with the highest ethical and scientific standards. Protection of subject safety is the overriding concern in the design of clinical trials. In all cases, MSD 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 MSD irrespective of the party (parties) employed for their execution (e.g., contract research organizations, collaborative research efforts). This Code is not intended to apply to trials 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 MSD.

II. Scientific Issues

A. Trial Conduct

1. Trial Design

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

MSD selects investigative sites based on medical expertise, access to appropriate subjects, adequacy of facilities and staff, previous performance in MSD trials, as well as budgetary considerations. Prior to trial initiation, sites are evaluated by MSD 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. MSD reviews clinical data for accuracy, completeness and consistency. Data are verified versus source documentation according to standard operating procedures. Per MSD policies and procedures, if 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, MSD 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.

MSD'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. MSD 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 MSD 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 MSD clinical trial.

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

C. Confidentiality

MSD is committed to safeguarding 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 MSD's policy to compensate investigators (or the sponsoring institution) in a fair manner for the work performed in support of MSD trials. MSD does not pay incentives to enroll 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.

MSD does not pay for subject referrals. However, MSD 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 MSD, 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 MSD trials will indicate MSD as a source of funding.

C. Funding for Travel and Other Requests

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

V. Investigator Commitment

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

12.2 Collection and Management of Specimens for Future Biomedical Research

1. Definitions

a. Biomarker: A biological molecule found in blood, other body fluids, or tissues that is a sign of a normal or abnormal process or of a condition or disease. A biomarker may be used to see how well the body responds to a treatment for a disease or condition.[1]

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

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

d. DNA: Deoxyribonucleic acid.

e. RNA: Ribonucleic acid.

2. Scope of Future Biomedical Research

The specimens collected in this trial as outlined in Section 7.1.3.4 – 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 Future Biomedical Research.

b. Informed Consent

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

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

c. eCRF Documentation for Future Biomedical Research Specimens

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

d. Future Biomedical Research Specimen Collections

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

4. Confidential Subject Information for Future Biomedical Research

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

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

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

5. Biorepository Specimen Usage

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

6. Withdrawal From Future Biomedical Research

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

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

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

7. Retention of Specimens

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

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

8. Data Security

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

9. Reporting of Future Biomedical Research Data to Subjects

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

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

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

10. Future Biomedical Research Study Population

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

11. Risks Versus Benefits of Future Biomedical Research

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

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

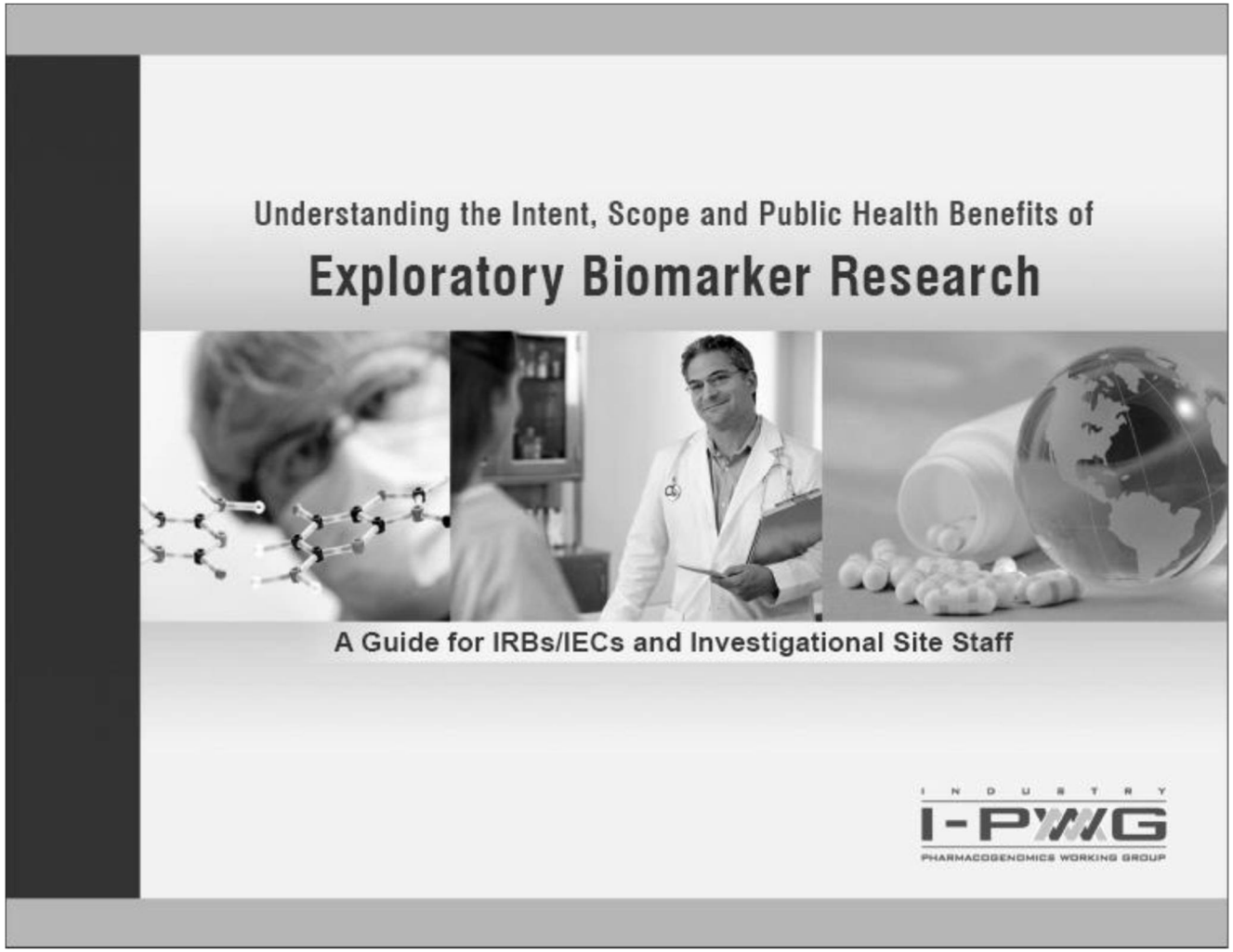
12. Questions

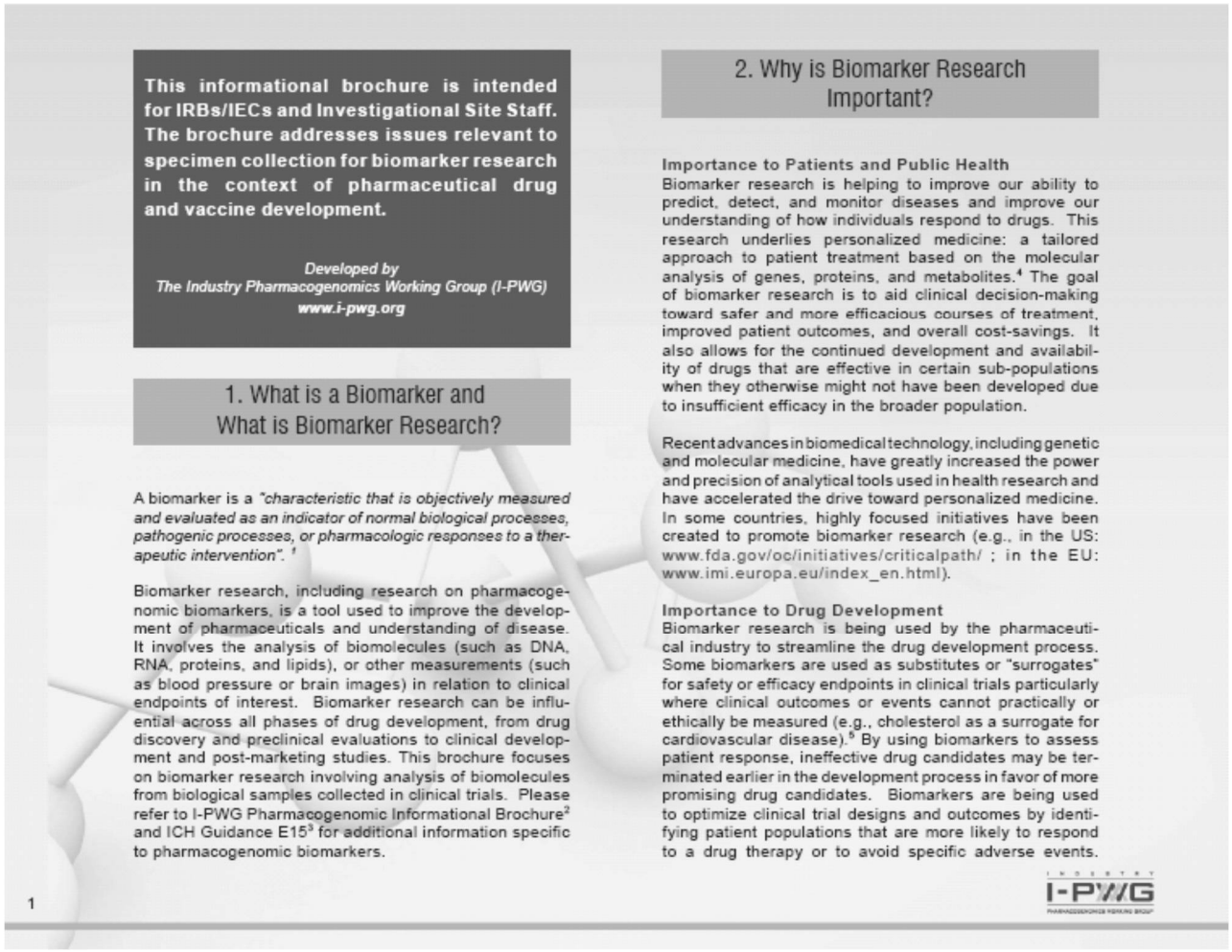
Any questions related to the future biomedical research should be e-mailed directly to clinical.specimen.management@MSD.com.

13. References

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

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





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

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

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

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

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

2. Why is Biomarker Research Important?

Importance to Patients and Public Health

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

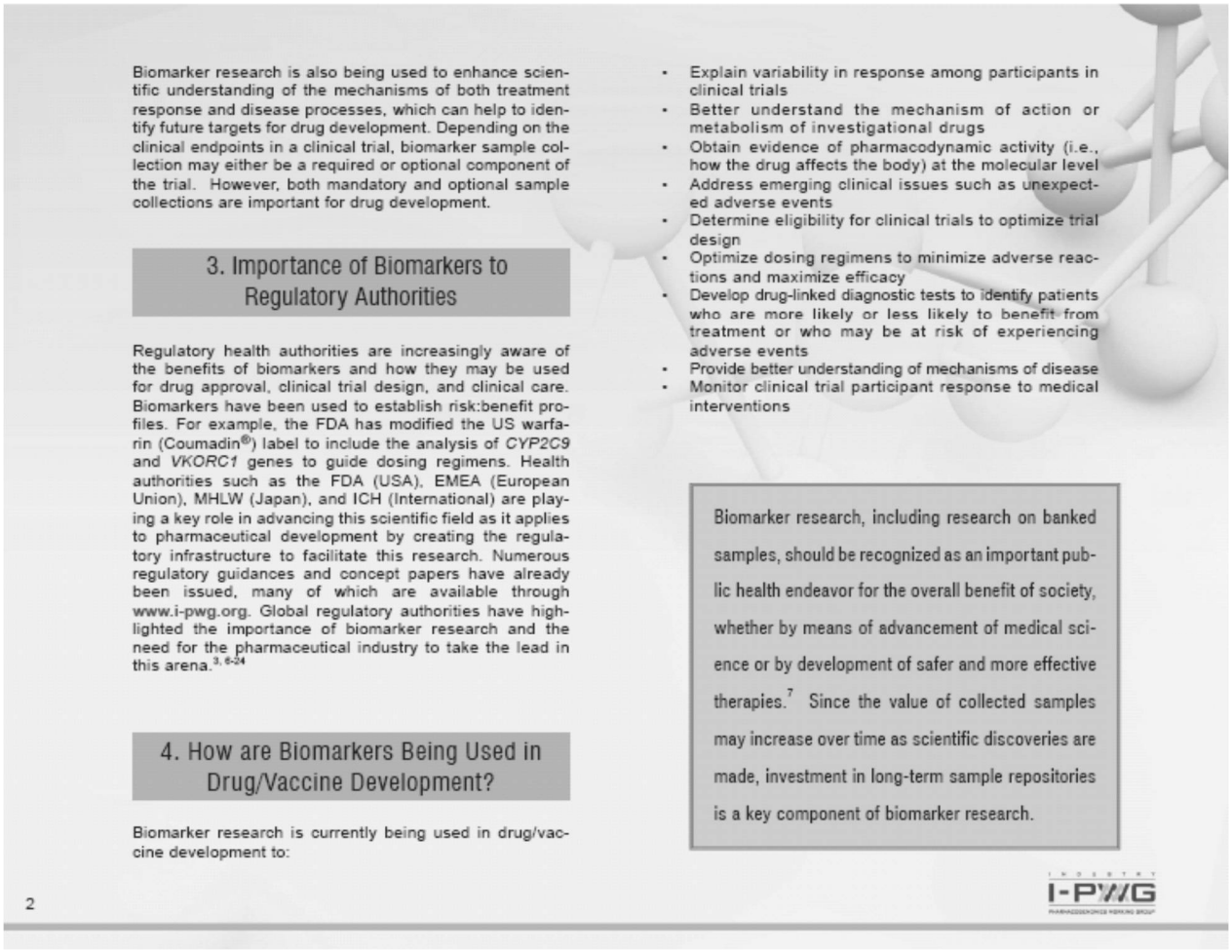
Recent advances in biomedical technology, including genetic and molecular medicine, have greatly increased the power and precision of analytical tools used in health research and have accelerated the drive toward personalized medicine. In some countries, highly focused initiatives have been created to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

Importance to Drug Development

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

I-PWG

1


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.
2
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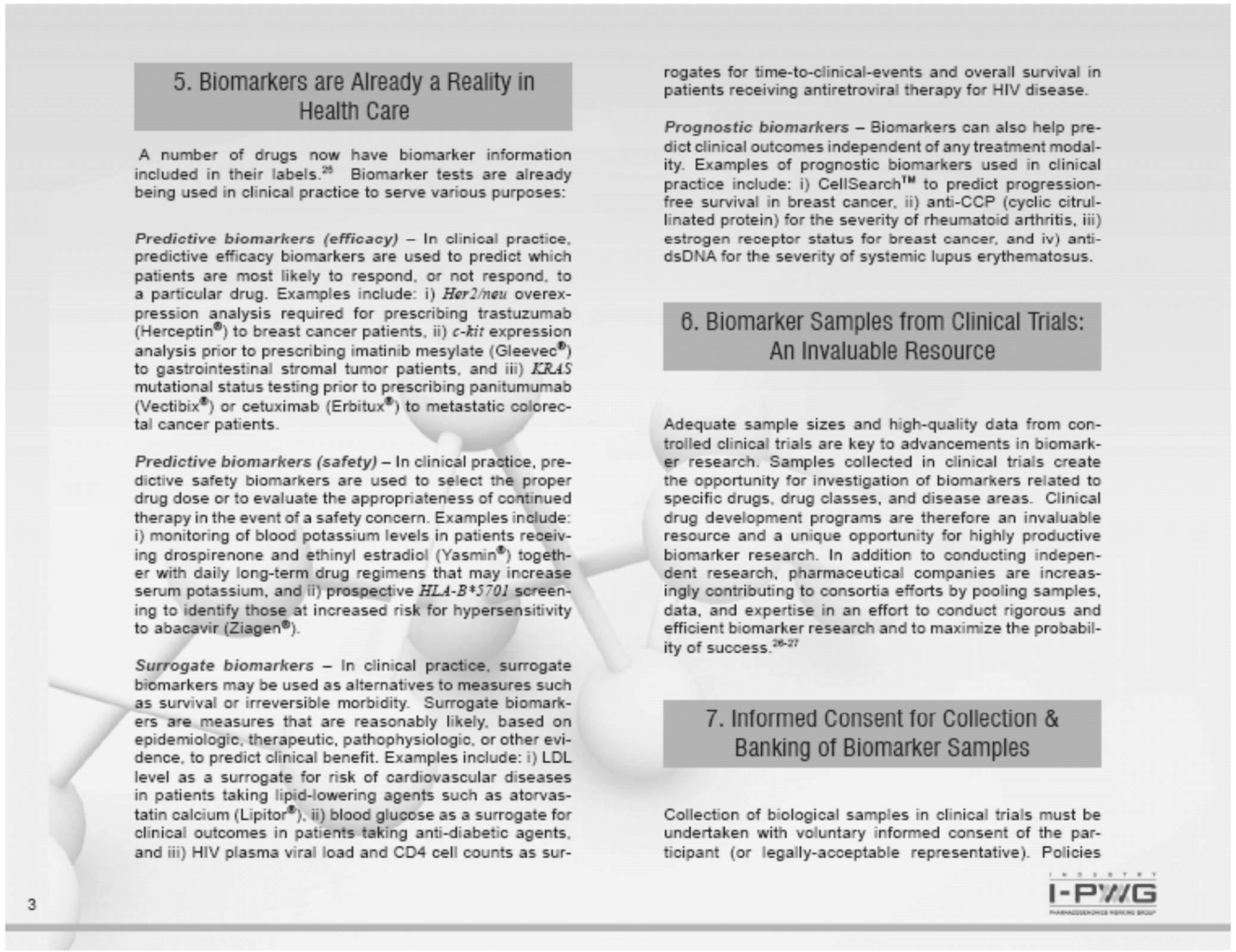

5. Biomarkers are Already a Reality in Health Care

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

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

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

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

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

6. Biomarker Samples from Clinical Trials: An Invaluable Resource

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

7. Informed Consent for Collection & Banking of Biomarker Samples

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

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

Optional vs. Required Subject Participation

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

Consent for Future Research Use

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

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

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

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

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

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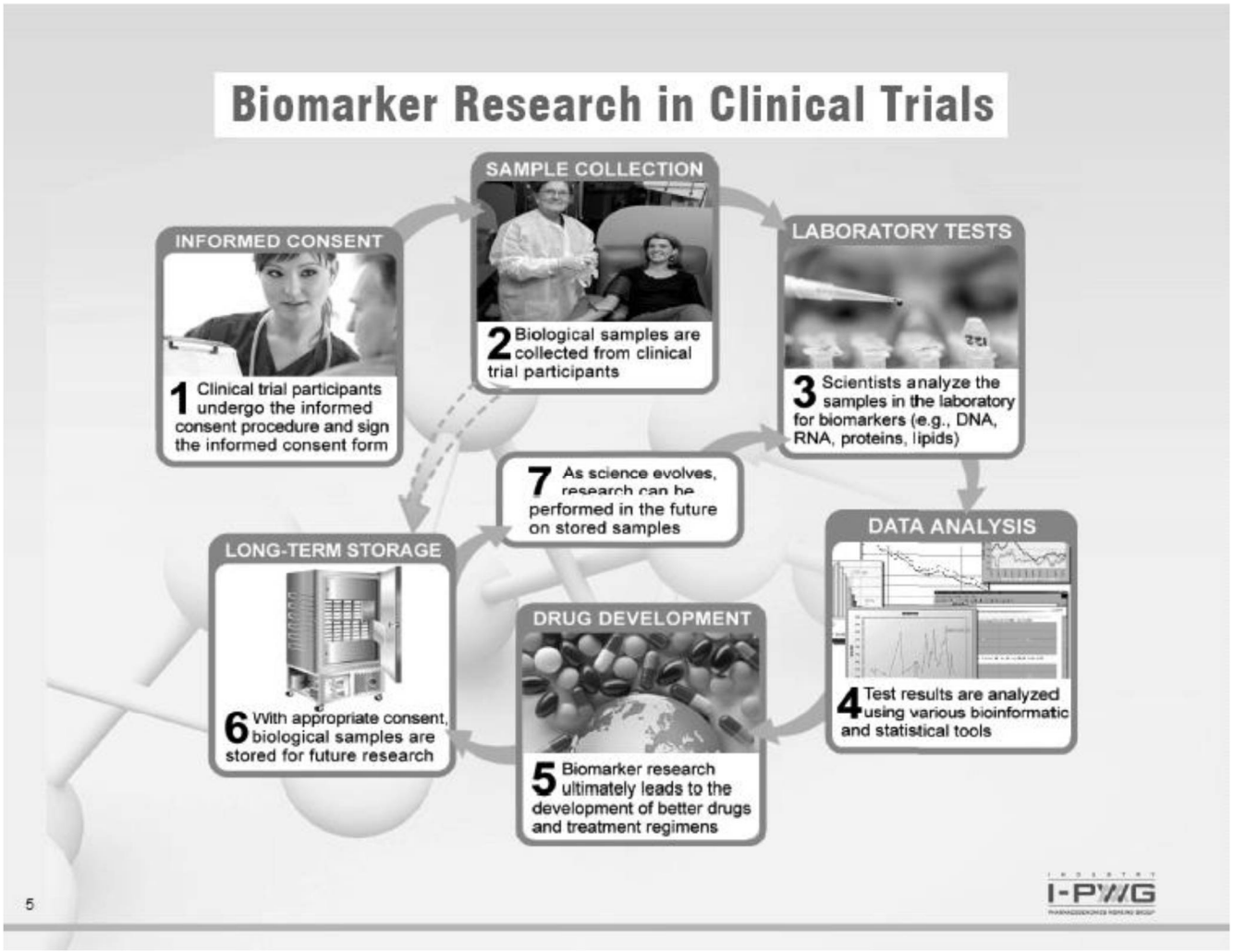
Biomarker Research in Clinical Trials
SAMPLE COLLECTION
2 Biological samples are collected from clinical trial participants
LABORATORY TESTS
3 Scientists analyze the samples in the laboratory for biomarkers (e.g., DNA, RNA, proteins, lipids)
INFORMED CONSENT
1 Clinical trial participants undergo the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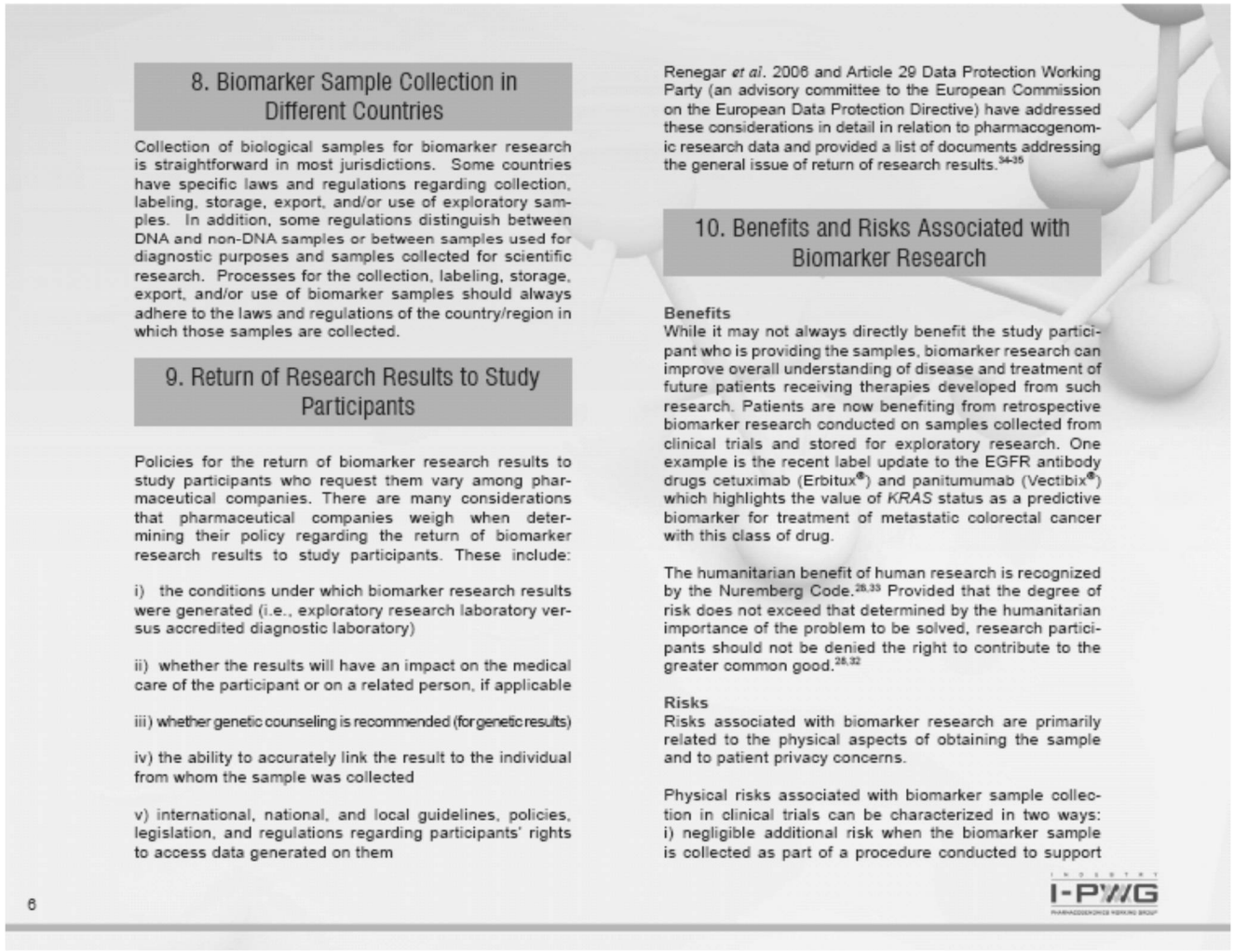

8. Biomarker Sample Collection in Different Countries

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

9. Return of Research Results to Study Participants

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

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

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

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

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

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

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

10. Benefits and Risks Associated with Biomarker Research

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

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

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

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

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

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

11. Privacy, Confidentiality, and Patient Rights

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

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

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

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

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

12.Where to Get More Information?

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

13. What is I-PWG?

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

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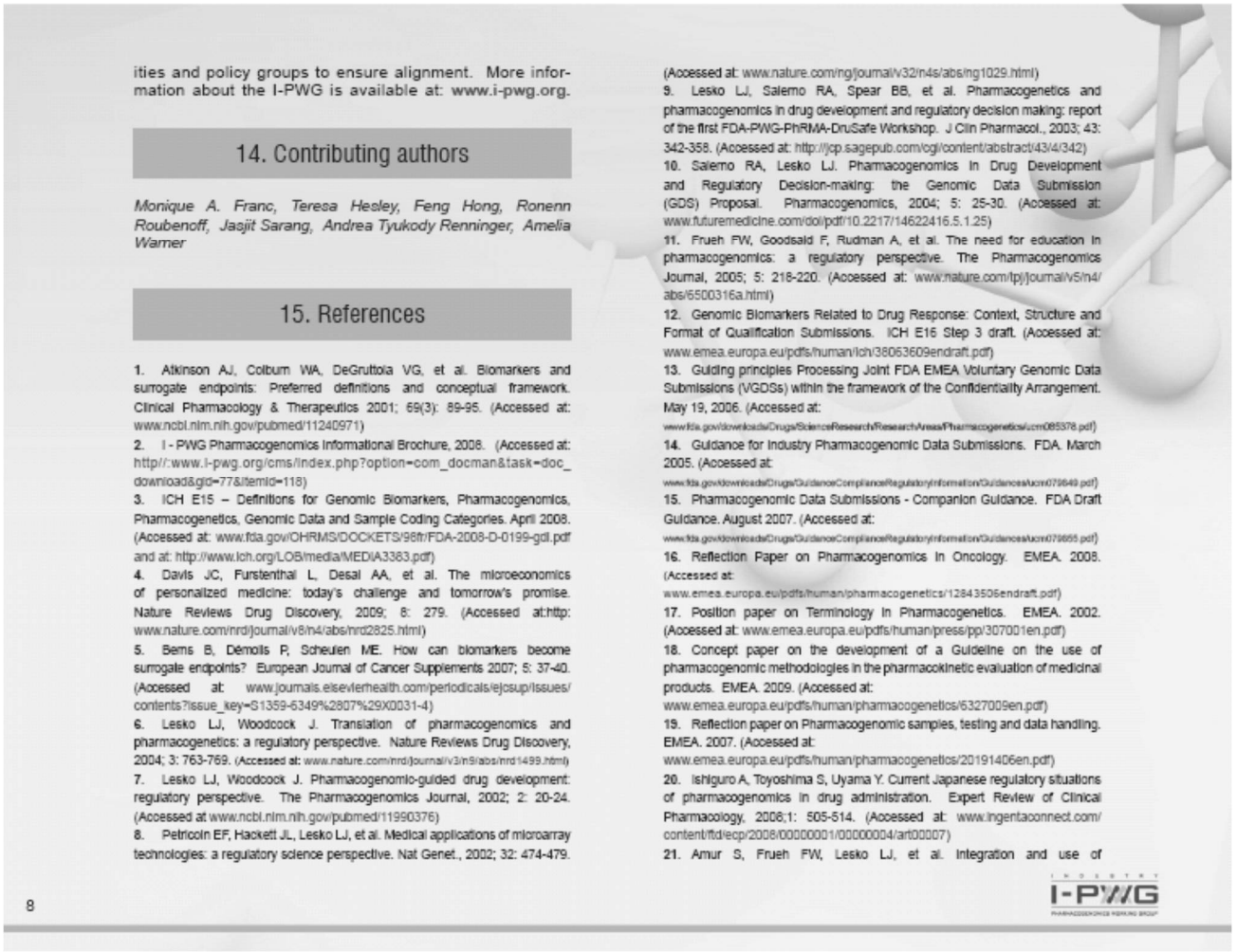

ities and policy groups to ensure alignment. More information about the I-PWG is available at: www.i-pwg.org.

14. Contributing authors

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

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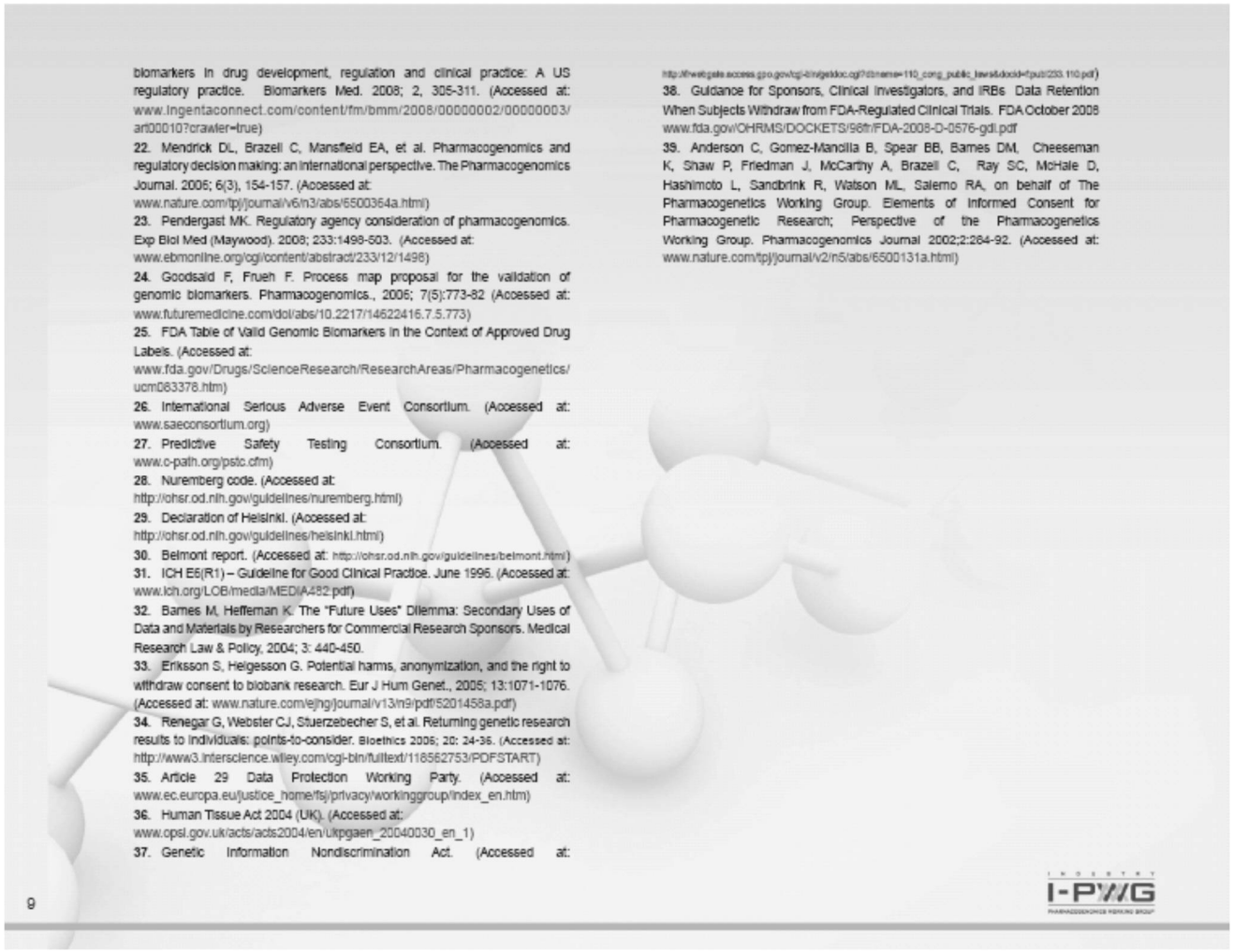

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12.4 ECOG Performance Status

Grade	Description
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (e.g., light housework, office work).
2	In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead

* As published in Am. J. Clin. Oncol.: *Oken, M.M., Creech, R.H., Tormey, D.C., Horton, J., Davis, T.E., McFadden, E.T., Carbone, P.P.: Toxicity And Response Criteria Of The Eastern Cooperative Oncology Group. Am J Clin Oncol 5:649-655, 1982.* The Eastern Cooperative Oncology Group, Robert Comis M.D., Group Chair.

12.5 Common Terminology Criteria for Adverse Events V4.0 (CTCAE)

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

12.6 List of Abbreviations and Definitions of Terms

Abbreviation or Term	Definition
β-hCG	serum β-human chorionic gonadotropin
%CV	percent coefficient of variation
ADA	antidrug antibody
AE	adverse event
ALT	alanine aminotransferase
ANC	absolute neutrophil count
ANCOVA	analysis of covariance
aPTT	activated partial thromboplastin time
ASaT	all-subjects-as-treated
AST	aspartate aminotransferase
BCG	*Bacillus* Calmette-Guérin
BICR	blinded independent central radiology
BOR	best overall response
CBC	complete blood count
CD	cluster of differentiation
CD3ζ	CD3 zeta
CEA	carcinoembryonic antigen
CI	confidence interval
CL	clearance
C_{max}	maximum serum concentration
CNS	central nervous system
CO_2	carbon dioxide
CR	complete response / complete remission
CRC	colorectal cancer
CrCl	creatinine clearance
CSR	clinical study report
CT	computerized tomography
CTCAE	common terminology criteria for adverse events
CTFG	Clinical Trial Facilitation Group
CTLA-4	cytotoxic T-lymphocyte-associated protein 4
DCR	disease control rate
DKA	diabetic ketoacidosis
DLT	dose limiting toxicity
dMMR	mismatch repair deficient
DNA	deoxyribonucleic acid
DOR	duration of response
EBER1	Epstein–Barr virus-encoded small RNA
EBV	Epstein-Barr virus
ECI	event of clinical interest
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EDC	electronic data capture
EOT	end of treatment

Abbreviation or Term	Definition
EPO	erythropoietin
ERC	ethics review committee
FAS	Full Analysis Set
FBR	future biomedical research
FDA	Food & Drug Administration
FGF	fibroblast growth factor
FGFR	fibroblast growth factor receptor
FIH	first-in-human
FOLFIRI	irinotecan/leucovorin/5-FU
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
GEJ	gastric-esophageal junction
GFR	glomerular filtration rate
GGT	gamma-glutamyl transferase
GI	gastrointestinal
HBsAg	hepatitis B surface antigen
HCC	hepatocellular carcinoma
HCV	hepatitis C virus
HER2/neu	human epidermal growth factor receptor 2
HIV	Human Immunodeficiency Virus
HNSCC	head and neck squamous cell cancer
HPV	human papillomavirus
HRT	hormone replacement therapy
HUVEC	human umbilical vein endothelial cell
IB	Investigator Brochure
ICF	informed consent form
ICH	International Conference on Harmonization
IEC	independent ethics committee
IFN-γ	interferon gamma
Ig	immunoglobulin
IHC	immunohistochemistry
IL	interleukin
IMP	Investigational Medicinal Product
IMR	immunomodulatory receptor
INR	international normalized ratio
IO	immune-oncology
irAE	immune-related adverse event
IRB	institutional review board
irRECIST	immune-related response evaluation criteria in solid tumors
ITIM	immunoreceptor tyrosine-based inhibition motif
ITSM	immunoreceptor tyrosine-based switch motif
IUD	intrauterine device
IV	intravenous
IVRS	interactive voice response system
IWRS	integrated web response system

Abbreviation or Term	Definition
LAG-3	lymphocyte-activation gene 3
LDH	lactate dehydrogenase
mAB	monoclonal antibody
MAD	maximum administered dose
mFOLFOX7	oxaliplatin/leucovorin/5-FU
MHC	major histocompatibility complex
MRI	magnetic resonance imaging
mRNA	messenger RNA
MSI	microsatellite instability
MSI-H	microsatellite instability-high
MSS	microsatellite stable
MTD	maximum tolerated dose
N/A	not applicable
NCI	National Cancer Institute
NHP	nonhuman primate
NIMP	Non-Investigational Medicinal Product
NOAEL	no-observed-adverse-effect level
NSAID	non-steroidal anti-inflammatory drug
NSCLC	non-small cell lung cancer
ONJ	osteonecrosis of the jaw
ORR	objective response rate
OTC	over-the-counter
PBMC	peripheral blood mononuclear cell
PCR	polymerase chain reaction
PD	progressive disease
PFS	progression-free survival
PI	probability interval
PK	pharmacokinetic
PKCθ	protein kinase C-theta
PO	orally
PP	per-protocol
PR	partial response
PSN	peripheral sensory neuropathy
PT	prothrombin time
PTT	partial thromboplastin time
Q2W	every 2 weeks
Q3W	every 3 weeks
RAG	recombination-activating gene
RBC	red blood cell
RCC	renal cell carcinoma
RECIST	response evaluation criteria in solid tumors
RNA	ribonucleic acid
RP2D	recommended Phase 2 dose
RTK	receptor tyrosine kinase
SAC	scientific advisory committee

Abbreviation or Term	Definition
SAE	serious adverse event
SAP	statistical analysis plan
SGOT	serum glutamic oxaloacetic transaminase
SGPT	serum glutamic pyruvic transaminase
sLAG-3	soluble LAG-3
SOC	standard of care
sSAP	supplemental statistical analysis plan
T1DM	type 1 diabetes mellitus
T3	triiodothyronine
T4	thyroxine
TAM	tumor-associated macrophage
TCR	T-cell receptor
TKI	tyrosine kinase inhibitor
TNF-α	tumor necrosis factor-alpha
T_{reg}	regulatory T-cell
TPI	toxicity probability interval
TPS	tumor proportion score
TSH	thyroid stimulating hormone
ULN	upper limit of normal
VEGF	vascular endothelial growth factor
VEGFR	vascular endothelial growth factor receptor
VS	vital signs
WBC	white blood cell
ZAP70	zeta-chain-associated protein kinase

12.7 Country-specific Requirements

12.7.1 China

Section 2.1 Trial Design

After enrollment of the global portion of the study is complete, the study may remain open to enrollment in China alone until the target number of participants in China has been enrolled to meet local regulatory requirements

12.7.2 Japan

Japan has country-specific requirements for the protocol which are summarized below.

Section 5.1.2 - Inclusion Criterion 1d:

To be eligible for enrollment into the gastric cancer cohort of Part B, in addition to meeting the criteria in Inclusion Criterion 1d, the subject must also satisfy the following requirement:

The subject must have no available therapy that may convey clinical benefit.

Section 5.2.4 – Definition of Dose Limiting Toxicity:

In addition to all DLTs listed, the following will be considered a DLT for subjects in Japan:

Thrombocytopenia if associated with bleeding that requires a platelet transfusion.

Section 5.5.2 – Prohibited Concomitant Medications/Procedures:

In addition to all prohibited concomitant medications/procedures listed, the following is a prohibited concomitant medication for subjects in Japan:

Prophylactic use of granulocyte colony-stimulating factor (G-CSF) during the DLT observation period is not permitted.

Section 6.0 and 7.1.2 – Trial Flow Chart & Clinical Procedures/Assessments

In addition to all procedures and assessments listed, the following procedures should be performed as indicated for subjects in Japan:

Japan-specific Trial Flow Chart (for All Arms)

	Screening Phase	Treatment Phase Cycle = 21 days										End of Treat-ment	Post-Treatment Phase	
Treatment Cycle/Title	Screening (Visit 1)	Cycle 1				Cycles 2-4				Cycles 5-8	Cycle 9 and Beyond	Discon.	Safety Follow-up Visit	Survival Follow-up[27]
Cycle Day		1	2	8	15	1	8	15	9 weeks after 1st dose	1	1		30 days after last dose	Every 12 weeks
Scheduling Window (Days)	-28 to -1			±3	±3		±3	±3	±7				±7	±7
Clinical Procedures/Assessments														
Pulse Oximetry (SpO_2)	X	X	X	X	X	X	X	X		X	X	X	X	
CBC with differential					X									
Chemistry Panel					X									

For subjects in Japan only, pulse oximetry will be performed using local standard procedures by the investigator or qualified designee at the time points outlined in Table above.

For subjects in Japan only, CBC with differential and Chemistry Panel samples will be collected on C1D15, in addition to all scheduled timepoints in Section 6.0.

Clinical Study Conduct System

The clinical study conduct system in Japanese is included in the accompanying documents. The contents are as follows:

1. Sponsor

1.1 Name and Address of Sponsor

1.2 Sponsor's Representative

1.3 Medical Expert

1.4 Field Monitor (CRA) Representative

2. Contract Research Organization

2.1 External Monitoring Agency

2.2 Patient Registration Center

2.3 MSD Emergency Center

2.4 Central Laboratory Testing Facilities

3. Investigators

4. Japan Enrollment Policy

12.7.3 Germany

Throughout the Protocol

Legally Acceptable Representative

Persons of legal age, who are incapable of comprehending the nature, significance and implications of the clinical trial and of determining their will, are excluded from the trial at German sites; therefore, all references to a participant's "legally acceptable representative" in the protocol are not applicable for participants in Germany.

Exclusion of MUGA (multigated-acquisition) scans

Starting from Protocol version 10, Section 5.1.3 (Subject exclusion criteria) and 7.1.2 (Clinical Procedures/Assessments) as well as other sections of the protocol refer to MUGA scans or ECHO scans for LVEF assessments. As per protocol, MUGA or echocardiogram scans should be performed locally in accordance with the institution's standard practice.

This is to clarify that in Germany MUGA scans are not standard practice and were not notified to the Federal Office for Radiation Protection (BfS). Therefore, only ECHO scans will be done at the German sites. No MUGA scans will be done in Germany.

12.8 Section 6.3 Part B – Arm 6 Flow Chart

SAEs will be monitored for 120 days after the last dose of study intervention.

Pregnancy testing will be continued for 120 days after the last dose of study intervention, regardless of initiation of subsequent anticancer therapy.

Section 5.1.3 Subject Exclusion Criteria

- Has a known history of human immunodeficiency virus (HIV) infection. HIV testing is required at Screening.
- Has a known history of Hepatitis B (defined as Hepatitis B surface antigen [HBsAg] reactive) or known active Hepatitis C virus (defined as HCV RNA [qualitative] is detected) infection. Testing for Hepatitis B or Hepatitis C is required at Screening.

12.8.1 Canada

Please refer to the current lenvatinib product monograph for management of AEs associated with lenvatinib administration.

Section 5.2.6.3.9 Management of Gastrointestinal Perforation or Fistula Formation

Lenvatinib should be discontinued in any subject who develops gastrointestinal perforation of any grade or ≥Grade 3 fistula.

12.9 Contraceptive Guidance

12.9.1 Definitions

Women of Childbearing Potential (WOCBP)

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

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

Women in the following categories are not considered WOCBP:

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

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

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

12.9.2 Contraception Requirements

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

13.0 SIGNATURES

13.1 Sponsor's Representative

TYPED NAME	
TITLE	
SIGNATURE	
DATE SIGNED	

13.2 Investigator

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

TYPED NAME	
TITLE	
SIGNATURE	
DATE SIGNED	