Official Protocol Title:	A Phase 1b Study to Evaluate the Safety and Tolerability of MK-8353 in combination with Pembrolizumab in Patients with Advanced Malignancies
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TITLE:

A Phase 1b Study to Evaluate the Safety and Tolerability of MK-8353 in combination with Pembrolizumab in Patients with Advanced Malignancies

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DOCUMENT HISTORY

Document	Date of Issue	Overall Rationale
Amendment 07	28-JUN-2021	To update the dose modification and toxicity management guidelines for irAEs.
Amendment 06	24-AUG-2020	Added 2 dose levels to Arm B to further evaluate MTD.
Amendment 05	08-NOV-2018	The primary reasons for this amendment were to, 1) update the participant population to include microsatellite-stable CRC disease rather than an unselected CRC, 2) provide an additional MK-8353 dose level in Arms B, C, and D, and 3) incorporate new language to support flexible dosing.
Amendment 04	22-FEB-2018	The primary reasons for this amendment were to, 1) provide clarification regarding Arm D DLT evaluation period, 2) provide clarification regarding Arm D run-in period and subsequent cycles, and 3) expanded the dose modification guidelines to include supportive care, monitoring, and follow-up.
Amendment 03	29-AUG-2017	The primary reasons for this amendment were to, 1) align multiple sections within the protocol with modifications applied to treatment Arms, 2) provide informative immunological assay information based on results observed in animal studies, 3) update specific inclusion and exclusion criteria, 4) update Table 8 and Table 12, and 3) provide a Flow Chart specific to Arm D.

Document	Date of Issue	Overall Rationale
Amendment 02	11-AUG-2017	The primary reasons for this amendment were to modify text, tables, and figures in support of adding treatment arms and dose levels in all arms for MK-8353 dose escalation, also adding doses and schedules for potential exploration in Part 2.
Amendment 01	17-APR-2017	The primary reasons for this amendment were to, 1) modify text, tables, and figures in support of adding 2 additional optional treatment arms, additional doses in Arm A, also added doses and schedules for potential exploration in Part 2, 2) provide updated language in various sections and table to remove redundancy and provide clarity, and 3) provide updates to the Study Flow Chart to reflect modification to study design and to also provide clarification
Original Protocol	26-SEP-2016	Not applicable

SUMMARY OF CHANGES

PRIMARY REASON(S) FOR THIS AMENDMENT:

Section Number	Section Title	Description of Change	Rationale
5.2.2.2	Immune-Related Events and Dose Modification (Withhold, Treat, Discontinue)	The dose modification and toxicity management guidelines for irAEs and table were updated.	The dose modification and toxicity management guidelines for irAEs and table were updated as requested by the U.S. FDA in an effort to harmonize the presentation of safety information across all FDA-approved PD-1/L1 antibody prescribing information.

ADDITIONAL CHANGE(S) FOR THIS AMENDMENT:

No additional changes.

1 TRIAL SUMMARY

Abbreviated Title	Phase 1b Study of MK-8353 + Pembrolizumab in Subjects with Advanced Malignancies
Sponsor Product Identifiers	MK-8353 and pembrolizumab
Trial Phase	Phase 1b
Clinical Indication	Treatment of Advanced Solid Tumors with a Focus on non-MSI-H/dMMR Colorectal Cancer ≥Second Line
Trial Type	Interventional
Type of control	No treatment control
Route of administration	Oral (MK-8353) and intravenous (Pembrolizumab)
Trial Blinding	Unblinded Open-label
Treatment Groups	Part 1: Dose escalation and confirmation (modified toxicity probability interval design) **Arm A (MK-8353: twice daily [bid] continuous):** Dose level (DL)1: MK-8353 350 mg bid + Pembrolizumab 200 mg once every 3 weeks (q3w) DL1A: MK-8353 50 mg bid + Pembrolizumab 200 mg q3w DL2A: MK-8353 50 mg + 100 mg + Pembrolizumab 200 mg q3w (total daily dose of 150 mg MK-8353) DL3A: MK-8353 100 mg bid + Pembrolizumab 200 mg q3w DL4A: MK-8353 150 mg bid + Pembrolizumab 200 mg q3w DL5A: MK-8353 200 mg bid + Pembrolizumab 200 mg q3w DL6A: MK-8353 300 mg bid + Pembrolizumab 200 mg q3w **Arm B (MK-8353: once daily [qd] continuous):** DL1B: MK-8353 50 mg qd + Pembrolizumab 200 mg q3w DL2B: MK-8353 100 mg qd + Pembrolizumab 200 mg q3w DL3B: MK-8353 150 mg qd + Pembrolizumab 200 mg q3w DL4B: MK-8353 200 mg qd + Pembrolizumab 200 mg q3w DL5B: MK-8353 300 mg qd + Pembrolizumab 200 mg q3w DL6B: MK-8353 400 mg qd + Pembrolizumab 200 mg q3w DL7B: MK-8353 600 mg qd + Pembrolizumab 200 mg q3w DL8B: MK-8353 900 mg qd + Pembrolizumab 200 mg q3w DL9B: MK-8353 1200 mg qd + Pembrolizumab 200 mg q3w **Optional Arm C (MK-8353: qd 1 week on/1 week off)** DL1C: MK-8353 50 mg qd + Pembrolizumab 200 mg q3w DL2C: MK-8353 100 mg qd + Pembrolizumab 200 mg q3w DL3C: MK-8353 150 mg qd + Pembrolizumab 200 mg q3w DL4C: MK-8353 200 mg qd + Pembrolizumab 200 mg q3w DL5C: MK-8353 300 mg qd + Pembrolizumab 200 mg q3w DL6C: MK-8353 400 mg qd + Pembrolizumab 200 mg q3w DL7C: MK-8353 600 mg qd + Pembrolizumab 200 mg q3w

	Optional Arm D (MK-8353: qd monotherapy run-in then continuous) DL1D: MK-8353 50 mg qd + Pembrolizumab 200 mg q3w DL2D: MK-8353 100 mg qd + Pembrolizumab 200 mg q3w DL3D: MK-8353 150 mg qd + Pembrolizumab 200 mg q3w DL4D: MK-8353 200 mg qd + Pembrolizumab 200 mg q3w DL5D: MK-8353 300 mg qd + Pembrolizumab 200 mg q3w DL6D: MK-8353 400 mg qd + Pembrolizumab 200 mg q3w DL7D: MK-8353 600 mg qd + Pembrolizumab 200 mg q3w Note: Doses of MK-8353 at 10 and 30 mg might be explored in Arms A, B, C, and/or D, based on the safety profile and pharmacokinetic (PK) data observed at the higher doses. Part 2: Cohort expansion MK-8353 at Recommended Phase 2 Dose(s) + Pembrolizumab 200 mg q3w (several schedules and doses could be explored)
Number of trial subjects	Approximately 182 subjects will be enrolled.
Estimated duration of trial	The Sponsor estimates that the trial will require approximately 42 months from the time the first subject signs the informed consent until the last subject's last study-related phone call or visit.
Duration of Participation	Each subject will participate in the trial for approximately 28 months, from the time the subject signs the informed consent form through the final contact. After a screening phase of up to 28 days, each subject will receive assigned treatment for up to approximately 24 months. After the end of treatment, each subject will be followed for a minimum of 30 days (serious adverse events will be collected for 90 days), or until initiation of a new anticancer treatment, whichever occurs first. Subjects will be treated until disease progression, unacceptable toxicity, or the withdrawal of consent, or for approximately 24 months, and will be treated thereafter at the discretion of the physician.
Randomization Ratio	N/A

A list of abbreviations used in this document can be found in Section 12.8.

Pembrolizumab will be used throughout the protocol to refer to KEYTRUDA™ or MK-3475 as supplied by the Sponsor.

2 TRIAL DESIGN

2.1 Trial Design

This is a multicenter, worldwide, open-label, nonrandomized, Phase 1b study of MK-8353 in combination with pembrolizumab in subjects with advanced solid tumors with a focus on subjects with ≥ second line advanced non-MSI-H/dMMR colorectal cancer (CRC).

This study will evaluate the safety, tolerability, and preliminary efficacy of MK-8353 when administered in combination with pembrolizumab. There are 2 parts in this study, dose escalation and confirmation (Part 1) and cohort expansion (Part 2).

For each subject, RAS/RAF mutations and proficient versus deficient mismatch repair (pMMR vs. dMMR) status will be required for enrolling in the study. Archived tumor samples or newly obtained biopsies will be obtained during the screening period for assessment of these mutations and for biomarker evaluation.

In Part 1, the modified toxicity probability interval (mTPI) design [1] will be used to identify and confirm the recommended Phase 2 dose(s) (RP2D[s]) of MK-8353 in combination with a fixed dose of pembrolizumab in subjects with advanced malignancies. Subjects will be enrolled in 1 of 2 arms to receive MK-8353 in combination with pembrolizumab at a fixed dose of 200 mg, during 21-day cycles for approximately 24 months of treatment. In Arm A and Arm B, MK-8353 will be administered continuously at a starting dose of 50 mg twice daily (bid), or 50 mg once daily (qd), respectively (refer to Section 4.2.2). Enrollment will alternate between arms.

Initially, the protocol started at a dose of 350 mg bid of MK-8353 in combination with pembrolizumab and several dose levels for escalation from this initial dose were planned; however, 3 of the 4 subjects who received MK-8353 at 350 mg bid developed a Grade 3 rash and MK-8353 was discontinued at this dose for these 4 subjects (refer to Section 4.1.3.1).

The protocol was then amended (Amendment 1) to restart at a lower dose (100 mg bid) of MK-8353 in combination with pembrolizumab (Arm A) with a potential de-escalation dose of 50 mg bid; several dose levels for escalation were planned. The subject enrolled at 100 mg bid of MK-8353 in combination with pembrolizumab developed several Grade 3 toxicities, including Grade 3 rash, and the next subjects were enrolled at 50 mg bid of MK-8353 in combination with pembrolizumab (refer to Section 4.1.3.1.).

Under Amendment 3, Arm A is to start at 50 mg bid of MK-8353 and Arm B was added and is to be enrolled in parallel to Arm A. In addition, 2 optional arms, Arm C (in which MK-8353 is to be administered 1 week on/1 week off at a starting dose of 50 mg qd in combination with pembrolizumab), and Arm D (in which MK-8353 is to be administered first as monotherapy during a 2-week run-in at a starting dose of 50 mg qd, and then followed by continuous administration in combination with pembrolizumab at a dose of 50 mg qd). Lower doses of MK-8353 could be implemented in the event of unacceptable toxicities or based on PK measurements in Arm A or Arm B. Doses of MK-8353 at 10 mg and 30 mg could also be explored in Arms C or D (refer to Section 5.2). Additional doses between all described doses may be added based on reported toxicities upon agreement between the investigators and the Sponsor.

Barring dose-limiting toxicities (DLTs), additional subjects are to be enrolled and dose-finding is to proceed, according to an algorithm based on the mTPI method, targeting a dose with a 30% DLT rate for the combination therapy to determine the RP2D. Up to approximately 142 subjects evaluable for safety and tolerability are to be enrolled according to the mTPI method. The final number of subjects enrolled in Part 1 will depend on the empirical safety observations (ie, DLTs), and the dose and schedule ultimately identified as the RP2D using the mTPI design.

In Part 2, up to approximately 40 subjects with advanced non-MSI-H/dMMR CRC, who received at least 1 and up to 5 prior lines of therapy, will be enrolled at the RP2D(s) of the combination treatment in the expansion cohort to further evaluate safety and efficacy. Several doses and schedules of MK-8353 in combination with pembrolizumab may be

explored in separate cohorts in Part 2. Based on previous studies, approximately 50% of enrolled subjects are expected to present with a KRAS mutant MMR proficient CRC. Preliminary efficacy will be evaluated using overall response rate (ORR) assessed by the investigator based on the Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST 1.1) as a secondary objective. The duration of response (DOR), disease control rate (DCR), and progression-free survival (PFS) based on RECIST 1.1 as assessed by the investigator, as well as overall survival (OS) will be also evaluated as exploratory objectives.

Although there will not be any formal hypothesis testing in this study, an interim look at the data may be conducted to enable future trial planning and dosing decisions. In Part 2, a futility check will be performed after the first ~18 evaluable subjects in each cohort are enrolled. If no responses are observed, the trial may be stopped early.

Subjects will be monitored carefully for the development of adverse events (AEs), and for clinical and/or radiographic evidence of disease progression according to RECIST 1.1; however immune-related RECIST (irRECIST) could be used by the investigator for treatment decision. In subjects who have initial evidence of radiological progressive disease by RECIST 1.1, it will be at the discretion of the investigator whether or not to continue a subject on study treatment until repeat imaging is obtained. This clinical judgment decision should be based on the subject's overall clinical condition, including performance status, clinical symptoms, and laboratory data. Subjects may continue to receive study treatment until tumor assessment is repeated ≥4 weeks later in order to confirm progressive disease by irRECIST per site assessment.

Adverse events will be evaluated by the investigator, according to criteria outlined in the National Cancer Institute (NCI) Common Toxicity Criteria for Adverse Events (CTCAE), version 4.0, to establish the safety and tolerability of MK-8353 when administered in combination with pembrolizumab as per the primary objective of this study.

There will be no intrasubject dose escalation for subjects enrolled in this study. The definition of DLTs and criteria for dose modification of MK-8353 are outlined in Sections 5.2.1.5 and 5.2.2. Pembrolizumab will be administered at a fixed dose of 200 mg once every 3 weeks (q3w), which will not be modified.

Subjects may receive study treatment (MK-8353 and pembrolizumab) for up to 35 cycles in Arms A, B, and C (approximately 24 months) and for up to 36 cycles in Arm D. Subjects will be treated until disease progression, unacceptable toxicity, intercurrent illness that prevents further administration of treatment, investigator's decision to discontinue treatment, subject withdrawal of consent, pregnancy of the subject, subject completes treatment, or administrative reasons requiring cessation of treatment, at which point they will be discontinued from the study. Subjects will be treated thereafter at the discretion of the physician.

All subjects will be followed for at least 30 days after the last dose of MK-8353 or combination therapy for AE monitoring. Serious adverse events (SAE) will be collected for 90 days after discontinuation, 30 days if the subject initiates new anticancer therapy less than 30 days after study treatment discontinuation, or until the day new anticancer therapy is initiated if between 30 days and 90 days after study treatment discontinuation. Subjects with an ongoing AE of Grade >1 at the time of treatment discontinuation will be followed until

resolution of the AE to Grade 0 or 1, until considered stable by the treating physician, or until beginning a new anticancer therapy, whichever occurs first.

Subjects who discontinue treatment for reasons other than confirmed disease progression will have posttreatment follow-up for disease status (including imaging) until disease progression, initiating a new anticancer therapy, withdrawing consent for study participation, or becoming lost to follow up.

After confirmed disease progression, each subject will be contacted by telephone approximately every 12 weeks (84 ± 7 days) for survival until withdrawal of consent to participate in the trial, becoming lost to follow up, death, or end of the trial, whichever occurs first.

The trial will be conducted in conformance with Good Clinical Practices (GCP).

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 presented in Figure 1 and Figure 2.

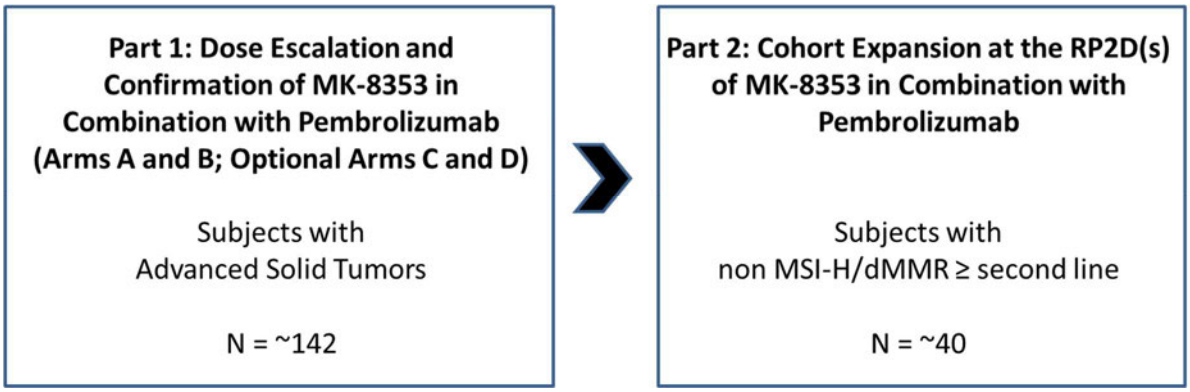

Figure 1 Phase 1b Trial of MK-8353 in Combination with Pembrolizumab: Part 1 Dose Escalation and Confirmation, and Part 2 Cohort Expansion

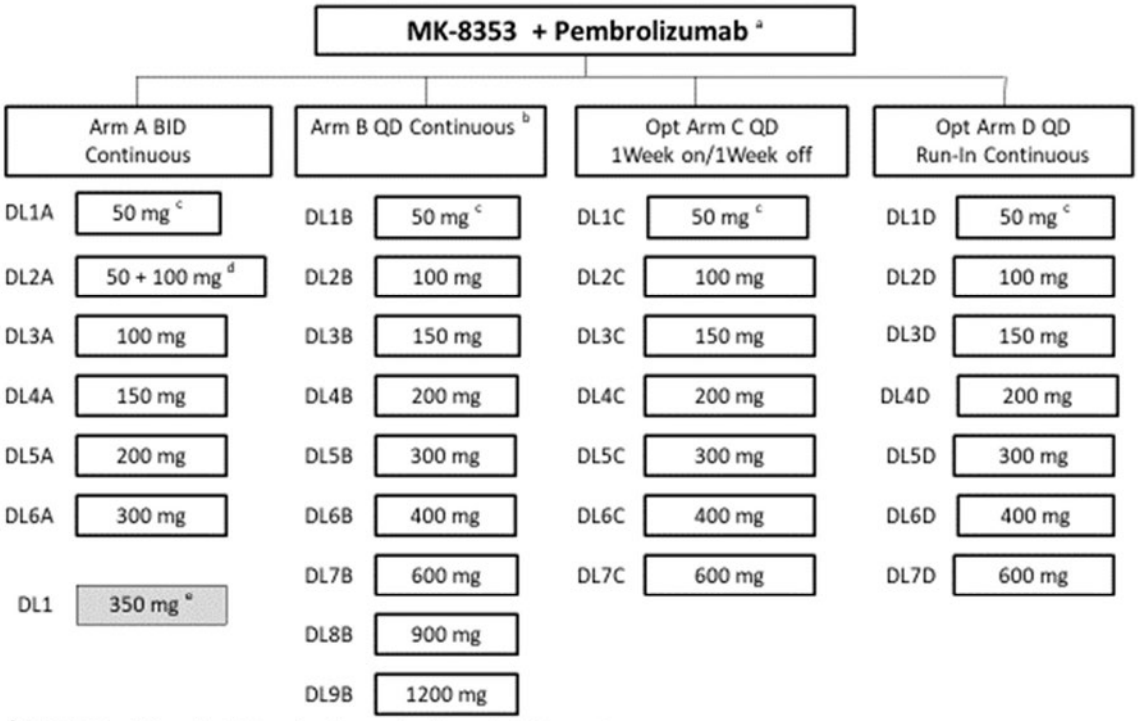

Figure 2 Part 1: Dose Escalation and Confirmation of MK-8353 in Combination with Pembrolizumab in Arm A, Arm B, and Optional Arms C and D Using the mTPI Design

3 OBJECTIVE(S) & HYPOTHESIS(ES)

3.1 Primary Objective(s) & Hypothesis(es)

(1) **Objective**: To evaluate the safety and tolerability of MK-8353 when administered in combination with pembrolizumab in subjects with advanced solid tumors and in subjects with ≥ second line advanced non-MSI-H/dMMR CRC.

3.2 Secondary Objective(s) & Hypothesis(es)

(1) **Objective**: To determine 1 or more RP2D of MK-8353 when given in combination with pembrolizumab in subjects with advanced solid tumors.

(2) **Objective**: To evaluate the antitumor activity (ORR based on RECIST 1.1 as assessed by the investigator) of MK-8353 in combination with pembrolizumab in subjects with advanced solid tumors who received MK-8353 at RP2D in Part 1 and in Part 2.

(3) **Objective**: To evaluate serum levels of protein biomarkers, such as carcinoembryonic antigen (CEA), CA-125, or CA19-9, before and after

administration of MK-8353 in combination with pembrolizumab in subjects with advanced solid tumors.

3.3 Exploratory Objectives

(1) **Objective**: To assess the PK profile of MK-8353 when given in combination with pembrolizumab in subjects with advanced solid tumors and in subjects with ≥ second line advanced non-MSI-H/dMMR CRC.

(2) **Objective**: To evaluate the DOR, DCR, and PFS based on RECIST 1.1 as assessed by the investigator, and OS, in subjects with advanced solid tumors, and in subjects with ≥ second line advanced non-MSI-H/dMMR CRC who received MK-8353 at RP2D in combination with pembrolizumab in Part 1 and in Part 2.

(3) **Objective**: To evaluate the correlation between programmed cell death-ligand 1 (PD-L1) expression levels and tumor response when MK-8353 is given in combination with pembrolizumab in subjects with advanced solid tumors or ≥ second line advanced non-MSI-H/dMMR CRC.

(4) **Objective:** To evaluate the ORR, DOR, DCR, and PFS based on RECIST 1.1 as assessed by the investigator, and OS in 1) subjects with RAS/RAF mutant versus RAS/RAF wild-type with advanced solid tumors or ≥ second line advanced non-MSI-H/dMMR CRC; 2) subjects with pMMR versus dMMR advanced solid tumors or ≥ second line advanced non-MSI-H/dMMR CRC; and 3) subjects with left versus right advanced non-MSI-H/dMMR CRC who received MK-8353 in combination with pembrolizumab.

(5) **Objective**: To identify molecular (genomic, metabolic, and/or proteomic) biomarkers that may be indicative of clinical response/resistance, safety, pharmacodynamic activity, and/or the mechanism of action of MK-8353, pembrolizumab, and/or the combination therapy.

4 BACKGROUND & RATIONALE

4.1 Background

Refer to the respective Investigator's Brochures (IBs) for detailed background information on MK-8353 and pembrolizumab.

4.1.1 Pharmaceutical and Therapeutic Background

4.1.1.1 MK-8353

MK-8353 is a highly selective, orally available, adenosine triphosphate competitive small molecule inhibitor of extracellular signal-regulated kinase (ERK). MK-8353 not only inhibits the kinase activity of ERK, but also induces a conformational change in ERK that prevents its phosphorylation and activation by mitogen-activated protein/extracellular signal-regulated kinase (MEK).

ERK1 and ERK2 are closely related serine-threonine protein kinases. They are components of the RAS/mitogen-activated protein kinase (MAPK) pathway, a critical signal transduction

pathway that is activated in response to growth factor binding and regulates cellular growth, differentiation, and survival in a variety of cell types [2]. ERK lies downstream from the small guanosine triphosphatase RAS and the protein kinases RAF and MEK in this pathway. Following its activation by RAS, RAF phosphorylates MEK1 and MEK2, which in turn phosphorylate ERK. Activated, phosphorylated ERK (pERK) phosphorylates other substrates that govern the transcriptional output of cells [2] [3]. Constitutive activation of this pathway is frequently observed in human cancers and is associated with high rates of cancer cell proliferation. Commonly, pathway activation occurs as a consequence of gain-of-function oncogenic mutations in RAS or in 1 of the RAF kinase family members (eg, BRAF).

The high frequency of RAS or BRAF mutations in many cancers makes targeting this pathway an attractive strategy for cancer therapy. Activating mutations of RAS are reported in ~25% of all cancers [4], with some, such as pancreatic cancer and CRC, harboring KRAS mutation rates of ~90% and ~50%, respectively [4]. NRAS mutations have been identified in ~10% to 25% of melanomas [4] [3] [5] and KRAS mutations have been identified in ~30% of non-small cell lung cancers (NSCLCs) [6].

BRAF somatic missense mutations have been identified in ~50% to 70% of malignant melanomas, in which all mutations are within the kinase domain and a single substitution (V600E, previously designated V599E) accounts for ~80% of mutations [7] [3] [8]. Activating BRAF mutations have also been documented in a variety of human cancers, including CRC (~10% to 12%) [9], NSCLC (2% to 3%) [9], and thyroid cancer (~50%) [5]. With very few exceptions, BRAF and RAS mutations are mutually exclusive [10].

Although the introduction of BRAF inhibitors represents a significant advance in the treatment of BRAF V600 mutation-positive metastatic melanoma subjects [11], limitations of this novel therapy have already been identified, as has been the pattern with other highly selective small molecule kinase inhibitors (eg, imatinib in bcr-abl chronic myelogenous leukemia; erlotinib and gefitinib in epidermal growth factor receptor-mutant NSCLC; and the rapid onset of drug resistance that restricts the efficacy of vemurafenib and limits the median duration of response to only 6.7 months [data from the vemurafenib Phase 3 study BRIM3]) [12]. Understanding the specific mechanisms of resistance to BRAF inhibitors is critical for the development of more effective strategies to inhibit the MAPK pathway in order to delay or prevent the onset of resistance in BRAF-mutant melanoma.

In a majority of cell models and melanoma samples, acquired resistance to BRAF inhibitors was associated with a reactivation of the MAPK pathway indicating that the ‘addiction’ to this pathway remains unchanged [13]. In these resistant BRAF-mutant melanomas, the MAPK pathway can be reactivated through secondary activating mutations of the upstream NRAS or the downstream MEK1 kinase or an overexpression of the RAF1 and COT kinase. In addition, activation of further upstream receptor tyrosine kinase most probably due to alterations in molecular feedback loops affecting in particular the insulin-like-growth factor receptor and the platelet-derived growth factor receptor have also been detected. Although all of these molecular events enable the melanoma cell to circumvent BRAF inhibition in order to reactivate the MAPK pathway, this activation renders most of the BRAF inhibitor-resistant tumors susceptible to an inhibition of the downstream MEK kinase.

Experimental data generated with a BRAF and MEK inhibitor combination therapy in BRAF-mutant melanoma cell lines in vitro and xenografts in vivo support this concept by demonstrating activity of the combination therapy in models of acquired BRAF resistance.

More importantly, superior antitumor activity of the BRAF and MEK inhibitor combination as compared with each agent as monotherapy was also observed in BRAF-sensitive models. In addition, preclinical safety data obtained with this combination therapy in a rat model indicate that the potential for proliferative skin lesions and secondary cutaneous malignancies is reduced in comparison with treatment with a BRAF inhibitor alone [14].

Data from recent clinical trials evaluating the combination of BRAF and MEK inhibitors have confirmed the efficacy of the double MAPK pathway blockade in subjects with BRAF-mutant tumors. Clinical trials combining BRAF and MEK inhibitors have demonstrated activity in subjects with tumors harboring BRAF mutations [15] [16] [17] [18] [19].

These data clearly indicate that a concomitant and more potent inhibition of the MAPK pathway at the critical level of the BRAF and MEK kinases leads to a more pronounced tumor inhibition, thus significantly delaying the onset of resistance. A similar effect might be achieved by downstream blockade of the MAPK pathway at the ERK level.

In contrast to all known ERK inhibitors, which bind to the active conformation (type I), only MK-8353 can bind to both the active as well as the inactive conformation of ERK kinases, and therefore can prevent their activating phosphorylation by MEK1 and MEK2 ("dual specificity"). This unique property of MK-8353 enables the phosphorylation status of ERK to serve as one of the target engagement biomarkers for MK-8353 action. To date, very few ERK inhibitors are in clinical development [20].

MK-8353 potently inhibits both ERK1 and ERK2 in vitro with IC_{50} values of 23.0 nM and 8.8 nM, respectively. MK-8353 caused a dose-dependent decrease in pERK1, pERK2, and phosphorylated p90 ribosomal S6 kinase levels with complete suppression of pERK1 and pERK2 at 30 nM in BRAF-mutant A2058 cells. Also, the antiproliferative effects of MK-8353 were characterized against a large panel of tumor cells. MK-8353 potently inhibited the growth of BRAF-mutant melanoma cell lines, and also inhibited growth of BRAF-mutant CRC and thyroid cancer cell lines. In addition, MK-8353 inhibited the growth of KRAS mutant colon, pancreatic, and NSCLC tumor cell lines and NRAS mutant melanoma cell lines. Inhibition of pERK by MK-8353 correlated with inhibition of cell proliferation and induction of apoptosis in vitro. The efficacy of the ERK inhibitor MK-8353 as a single agent was tested in a panel of BRAF and K/NRAS mutant mouse xenograft models. MK-8353 inhibited tumor growth and induced tumor regression in both BRAF-mutant and K/NRAS-mutant mouse xenograft models. These results further confirm the in vitro studies showing that tumor cells harboring BRAF or K- or NRAS mutations are sensitive to MK-8353. Furthermore, clinical data from PN001 confirmed that MK-8353 in monotherapy has partial clinical activity in subjects with BRAF-mutant tumors (refer to Section 4.1.2.1).

4.1.1.2 Pembrolizumab

The programmed cell death-1 (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 immunoglobulin (Ig) superfamily member related to CD28 and cytotoxic T-lymphocyte-associated antigen-4 (CTLA-4) that has been shown to negatively regulate antigen receptor signaling upon engagement of its ligands (PD-L1 and/or programmed cell death-ligand 2 [PD-L2]) [21] [22]. The structure of murine PD-1 has been resolved [23]. PD-1 and family members are type I transmembrane glycoproteins containing an Ig Variable-type domain responsible for ligand binding and a cytoplasmic tail, which is responsible for the binding of signaling molecules. The cytoplasmic tail of PD-1 contains 2 tyrosine-based signaling motifs, an immunoreceptor tyrosine-based inhibition motif and an immunoreceptor tyrosine-based switch motif (ITSM). Following T-cell stimulation, PD-1 recruits the tyrosine phosphatases SHP-1 and SHP-2 to the ITSM motif within its cytoplasmic tail, leading to the dephosphorylation of effector molecules such as CD3ζ, PKCθ, and ZAP70, which are involved in the CD3 T-cell signaling cascade [21] [24] [25] [26].

PD-1 was shown to be expressed on activated lymphocytes including peripheral $CD4^+$ and $CD8^+$ T cells, B cells, T regs, and natural killer cells [27] [28]. Expression has also been shown during thymic development on CD4-CD8- (double negative) T cells as well as subsets of macrophages and dendritic cells [29]. The ligands for PD-1 (PD-L1 and PD-L2) are constitutively expressed or can be induced in a variety of cell types, including nonhematopoietic tissues as well as in various tumors [30] [31] [32] [33]. Both ligands are type I transmembrane receptors containing both IgV- and IgC-like domains in the extracellular region and contain short cytoplasmic regions with no known signaling motifs. Binding of either PD-1 ligand to PD-1 inhibits T-cell activation triggered through the T-cell receptor. PD-L1 is expressed at low levels on various nonhematopoietic tissues, most notably on vascular endothelium, whereas PD-L2 protein is only detectable on antigen-presenting cells found in lymphoid tissue or chronic inflammatory environments. PD-L2 is thought to control immune T-cell activation in lymphoid organs, whereas PD-L1 serves to dampen unwarranted T-cell function in peripheral tissues [30]. Although healthy organs express little (if any) PD-L1, a variety of cancers were demonstrated to express abundant levels of this T-cell inhibitor. High expression of PD-L1 on tumor cells (and to a lesser extent of PD-L2) has been found to correlate with poor prognosis and survival in various cancer types.

Pembrolizumab (KEYTRUDA™) is a potent and highly selective humanized monoclonal antibody (mAb) of the IgG4/kappa isotype designed to directly block the interaction between PD-1 and its ligands, PD-L1 and PD-L2. Pembrolizumab has shown clinical activity and is indicated in multiple tumor types (refer to package circular for KEYTRUDA™).

4.1.1.3 Rationale for MK-8353 in Combination with Pembrolizumab

In preclinical studies, agents targeting the RAS/RAF/MEK/ERK pathway have been associated with checkpoint inhibitors, and demonstrated synergistic and durable tumor regression [34] [35]. MEK inhibition increased the number of effector CD8+ T-cell trafficking in tumor from animal models, and protected them from death driven by chronic T-cell receptor stimulation [35]. In biopsies from subjects with metastatic melanoma taken 10 to 14 days after treatment with BRAF or BRAF + MEK inhibitors, an increased expression of melanoma antigens and an increase in CD8+ T-cell infiltrate was observed

compared with baseline, together with a decrease in immunosuppressive cytokines [36]. Thus, preclinical data indicate a potential additive/synergistic effect between compounds targeting the MAPK-pathway and checkpoint inhibitors.

Recently, combinations of MAPK inhibitors with anti-CTLA-4, anti-PD-1 or anti-PDL-1 mAbs have been tested in the clinic in different type of tumors. In a Phase 2 clinical study, cobimetinib, a MEK1/2 small molecule inhibitor, has been evaluated in combination with atezolizumab, a PD-L1-blocking antibody, in subjects with advanced CRC and has shown clinical activity [37].

It is expected that the combination of MK-8353 and pembrolizumab may bring more benefit in tumors that are driven by MAPK pathway by inhibiting tumor growth and inducing apoptosis, as well as releasing tumor antigen and activating T-cell-based immune surveillance against tumor.

4.1.2 Preclinical and Clinical Trials

4.1.2.1 MK-8353

MK-8353 Preclinical Studies

The primary toxicological risks associated with preclinical administration of MK-8353 consisted of skin irritation/inflammation in rats, significant body weight loss in dogs with decreased food consumption, and small intestine (enterocyte necrosis) and liver (portal inflammation and necrosis) toxicity in dogs. These findings generally showed complete recovery at the end of the 1-month postdose periods. In early exploratory non-Good Laboratory Practice (GLP) rat and dog studies with an amorphous form of MK-8353, tissue mineralization was noted. In the 1-month rat and dog GLP studies using the salt form, no tissue mineralization was observed but effects of MK-8353 on serum biomarkers (ie, osteocalcin, beta-C-terminal telopeptide, parathyroid hormone, and ionized calcium) were present.

CCI

CCI

MK-8353 Phase 1 Study in Cancer Subjects (PN001)

The safety of MK-8353 as a single agent was also evaluated in a Phase 1, dose-escalation study previously completed in subjects with advanced solid tumor (refer to the MK-8353 IB). In Part 1a, MK-8353 doses were increased up to 800 mg bid in subjects with any type of advanced solid tumor. In Part 1b, subjects with BRAF- or RAS-mutant metastatic melanoma or metastatic CRC were enrolled in the dose confirmation phase.

MK-8353 400 mg bid dose was identified in Part 1a as the preliminary maximum tolerated dose (MTD), based on safety, tolerability, PK exposure, and preliminary clinical activity. The 100 mg, 200 mg, and 400 mg bid dose levels were deemed generally safe. However, at the 800 mg bid dose, 2 evaluable subjects experienced DLTs, which per protocol determined this dose as exceeding the MTD. The DLTs were Grade 3 nausea, Grade 3 vomiting, and Grade 3 diarrhea in the first subject and an event of Grade 3 fatigue in the second subject.

In Part 1b of Protocol 001, MK-8353 was administered at doses of 400 mg bid in 4 subjects. Two evaluable subjects experienced DLTs due to missed doses (due to Grade 2 diarrhea in the first subject, and an event of elevated bilirubin in the second subject). Two subsequent subjects, enrolled at a dose level of 200 mg bid (which was well tolerated), demonstrated disease progression. Four additional subjects were enrolled at a dose level of 300 mg bid, which was also well tolerated. Two of those subjects (with BRAF-mutant melanoma) exhibited some response to MK-8353 (stable disease [SD] and partial response [PR]) and stayed on therapy for 168 days and 211 days, respectively. In the next cohorts, 3 subjects received 350 mg bid with 1 PR (BRAF-mutant melanoma) and 1 SD (NRAS-mutant melanoma) reported. Three subjects were treated at 400 mg bid, with PR observed in 1 subject with BRAF-mutant melanoma previously treated with single agent vemurafenib, and concomitant administration of dabrafenib and trametinib. One subject at a dose of 400 mg bid presented a DLT of Grade 3 rash in Cycle 1. Pharmacokinetic data did not correlate with MK-8353 clinical activity. Limited PD results from skin biopsies suggest that

partial suppression of phospho-ERK protein expression may occur at doses of 300 mg bid and up.

In the overall study, the most frequently reported AEs (>20%) included diarrhea, fatigue, nausea, maculopapular rash, and vomiting, and were also the most frequent MK-8353-related AEs (>20%). The most frequent Grade 3 or 4 MK-8353-related AEs (>5%) were diarrhea, increased serum bilirubin without other liver function changes, and maculopapular rash.

In summary, although the expansion cohort did not point to a strict RP2D, partial clinical activity for MK-8353 was observed starting at a dose of 350 mg bid.

4.1.2.2 Pembrolizumab

Therapeutic studies in mouse models have shown that administration of antibodies blocking PD-1/PD-L1 interaction enhances infiltration of tumor-specific CD8+ T-cells and leads ultimately to tumor rejection, either as a monotherapy or in combination with other treatment modalities. Antimouse PD-1 or antimouse PD-L1 antibodies have demonstrated antitumor responses as a monotherapy in models of squamous cell carcinoma, pancreatic carcinoma, melanoma, and CRC. Blockade of the PD-1 pathway effectively promoted CD8+ T-cell infiltration into the tumor and the presence of interferon gamma, granzyme B, and perforin, indicating that the mechanism of action involved local infiltration and activation of effector T-cell function in vivo [38] [39] [40] [41] [42] [43]. Experiments have confirmed the in vivo efficacy of PD-1 blockade as a monotherapy as well as in combination with chemotherapy in syngeneic mouse tumor models (refer to the pembrolizumab IB).

Pembrolizumab (Humanized IgG4 Anti-PD-1 Monoclonal Antibody)

Pembrolizumab is a potent and highly selective, anti-PD-1, humanized mAb of the IgG4/kappa isotype designed to directly block the interaction between PD-1 and its ligands, PD-L1 and PD-L2. The ligands for PD-1 (PD-L1 and PD-L2) are constitutively expressed or can be induced in various tumors [44] [45] [46] [47]. High expression of PD-L1 on tumor cells (and to a lesser extent of PD-L2) has been found to correlate with poor prognosis and survival in various cancer types, including renal cell carcinoma [48], pancreatic carcinoma [49], hepatocellular carcinoma [50], ovarian carcinoma [43], and NSCLC [51]. Furthermore, PD-1 has been suggested to regulate tumor-specific T-cell expansion in subjects with malignant melanoma [27] [11].

Preclinical in vitro and in vivo experiments have shown that PD-1 and/or PD-L1 blockade using mAbs enhances tumor cell-specific T-cell activation, cytokine production, antitumor effector mechanisms, and clearance of tumor cells by the immune system [49] [52] [53] [54]. Pembrolizumab is a pure PD-1 antagonist, with higher affinity and receptor blocking activity compared with other anti PD-1 products in development. Pembrolizumab has an acceptable preclinical safety profile, and is currently in clinical development as a potential treatment for subjects with advanced malignancies in Phase 1 single agent trial.

A Phase 1 study of pembrolizumab that explored safety, PK, PD, and anti-tumor activity of pembrolizumab demonstrated that pembrolizumab is well tolerated. No DLTs were observed across the 3 dose levels tested (1, 3, and 10 mg/kg). Evaluation of the preliminary data demonstrated evidence of anti-tumor activity of pembrolizumab in subjects with NSCLC, CRC, melanoma, sarcoma, or carcinoid. Drug-related AEs included Grade 1 fatigue, nausea,

diarrhea, dysgeusia, breast pain, and pruritus. One drug-related Grade 2 AE of pruritus was also reported. No drug-related AEs ≥Grade 3 were observed.

4.1.3 Ongoing Clinical Trials

4.1.3.1 MK-8353

Current Study: Phase 1b Study of MK-8353 in Combination with Pembrolizumab in Subjects with Advanced Malignancies (PN013)

In Protocol 013-00, 4 subjects were enrolled at the original starting dose of MK-8353 at 350 mg bid in combination with a fixed dose of pembrolizumab at 200 mg q3w. Of these 4 subjects, 3 developed an acneiform rash at ~Day 10 of Cycle 1, which worsened to an extensive Grade 3 maculopapular rash at Day 11, Day 12, and Day 12, respectively. The 3 subjects stopped MK-8353, were hospitalized, and recovered with intravenous (IV) steroids and IV antibiotics in approximately 5 to 10 days. The fourth subject stopped MK-8353 on Day 9, based on the Grade 3 rashes occurring in the other subjects, and did not develop any rash or other AE in Cycle 1. These 3 DLTs triggered a de-escalation of MK-8353 as per the mTPI statistical method used in the study; however, the de-escalation dose of MK-8353 at 300 mg bid in the initial protocol was deemed too close to the starting dose of 350 mg bid, and was not used by consensus between the investigators and the Sponsor.

Amendment 1 was established to modify, in Part 1 of the study, the starting dose of MK-8353 for dose escalation in combination with pembrolizumab (Arm A: bid continuous; starting dose: 100 mg bid) with a de-escalation dose of 50 mg bid and to add 2 optional schedules: bid with a drug holiday, and qd continuous (refer to Section 5.2).

One subject with advanced CRC was enrolled at the 100 mg bid dose of MK-8353 in combination with pembrolizumab. Similar to prior observations, the subject developed a Grade 1 rash on the evening of Day 8, which became a Grade 3 maculopapular rash on Day 11. The subject was hospitalized, and recovered following administration of IV steroids and antibiotics.

Following this DLT, the consensus among investigators and the Sponsor was to de-escalate the dose to 50 mg bid of MK-8353 in combination with pembrolizumab for the next subject. The next subject (advanced CRC) completed Cycle 1 and started Cycle 2 with MK-8353 at a dose of 50 mg bid in combination with pembrolizumab. The subject did not develop any DLT during Cycle 1. Based on this information, the protocol was further amended.

In Amendment 3, the schedule of administration of MK-8353 in combination with pembrolizumab was modified in Part 1 as follows:

- Two arms, Arm A and new Arm B, are to run in parallel with alternate nonrandomized enrollment. The starting dose of MK-8353 for dose escalation in combination with pembrolizumab in these 2 arms is 50 mg bid and 50 mg qd, respectively, based on a continuous schedule (refer to Section 5.2).
- Additionally, the 2 new optional arms, Arm C and Arm D, will both have a starting dose of 50 mg qd. Arm C will follow a drug-holiday, 1 week on/1 week off schedule; whereas Arm D will include a run-in period of MK-8353 as monotherapy, from

Cycle 1 Day 1 to Day 14, prior to the continuous administration of the combination starting in Cycle 2 Day 1 (refer to Section 5.2).

4.1.3.2 Pembrolizumab

A Phase 2 clinical study has been conducted to evaluate the clinical efficacy of pembrolizumab in subjects with progressive metastatic carcinoma with or without MMR deficiency [55]. This study (KEYNOTE 016) enrolled 41 subjects: 11 subjects with dMMR CRC, 21 subjects with pMMR CRC, and 9 subjects with dMMR noncolorectal tumors (ie, 4 ampullary or cholangiocarcinomas, 2 endometrial carcinomas, 2 small bowel carcinomas, and 1 gastric carcinoma). Subjects had Stage IV disease and had failed multiple other chemotherapies. Microsatellite instability (MSI) was a significant predictor of an increased immune-related objective response rate (irORR) (40% in dMMR CRC, 71% in dMMR non-CRC, 0% in pMMR CRC) and of an improved immune-related progression-free survival (irPFS) rate (78%, 67%, and 11%, respectively). Whole-exome sequencing revealed a mean of 1,782 somatic mutations per tumor in dMMR cancers versus 73 somatic mutations per tumor in pMMR cancers. The study is ongoing, with median PFS and OS not yet reported in the cohort with dMMR CRC.

Clinical trials investigating pembrolizumab are ongoing in advanced melanoma, NSCLC, bladder cancer, hematologic malignancies, and in a number of other advanced solid tumor indications. For study details, and safety and efficacy summaries, please refer to the IB.

4.2 Rationale

4.2.1 Rationale for the Trial and Selected Subject Population

MK-8353 is a potent ERK inhibitor that has demonstrated antitumor activity in preclinical cancer cell lines and xenograft animal models, both as a single agent and in combination with other therapeutic agents. A Phase 1 study of MK-8353 was conducted in subjects with advanced solid tumors to evaluate its safety and preliminary efficacy as a single agent. The current study is a follow up to the monotherapy study to evaluate the effects of MK-8353 in combination with pembrolizumab in subjects with advanced solid tumors and in subjects with ≥ second line advanced non-MSI-H/dMMR CRC.

In Part 1 of this study, the combination of MK-8353 and pembrolizumab will be evaluated in subjects with any advanced solid tumors for which no curative therapy is available, and thus, suitable for an investigational treatment. Up to approximately 142 subjects will be enrolled in Part 1.

Part 2 will enroll until a total of 40 additional subjects are treated at the RP2D (several doses and schedules may be explored) defined in Part 1.

Colorectal tumorigenesis develops mainly via 2 pathways: chromosomal instability and MSI, which is a consequence of dMMR. Deficient MMR can result from a germline mutation in an MMR gene (MLH1, MSH2, MSH6, PMS2), which is causing the Lynch Syndrome, or is more frequently sporadic (epigenetic activation of MLH1). Sporadic dMMR tumors frequently carry the activating somatic V600E mutation in exon 15 of the BRAF

oncogene. $BRAF^{V600E}$ mutations occur downstream from and are mutually exclusive of KRAS codon 12 and 13 mutations.

This population has a high unmet medical need. Subjects with metastatic CRC whose tumors harbor $BRAF^{V600E}$ mutations generally respond poorly to standard therapies. A lower proportion of subjects with pMMR tumors with mutant BRAF or mutant KRAS survived at 5 years compared with subjects with pMMR tumors without these mutations [19] [56]. Single agent vemurafenib (BRAF inhibitor) did not show meaningful clinical activity in this population [57]. Combined BRAF and MEK inhibition with dabrafenib and trametinib in combination elicited some clinical activity in this population [19].

This contrasts with subjects with CRC tumors with dMMR (MSI-H), for which high somatic mutation loads were associated with an irORR of 40% and prolonged irPFS of 78% at 20 weeks when they received pembrolizumab in monotherapy [55]. In comparison, in subjects with tumors pMMR, the irORR was 0% and the irPFS at 20 weeks was 11%.

Therefore, in Part 2 of this study, the population of interest for the combination of MK-8353, a potent ERK inhibitor targeting the most downstream step of the MAPK pathway, and pembrolizumab, a checkpoint inhibitor, are subjects with pMMR, RAS/RAF-mutated advanced non-MSI-H/dMMR CRC.

Subjects in Part 1 or Part 2 may not need to be selected based on the presence of BRAF and KRAS/NRAS mutations in their tumors, as activating KRAS mutations have been identified in 30% to 40% of CRC, whereas BRAF mutations are found in ~5% to 15% of CRC [56] [7]. Similarly, subjects in Part 1 will not be selected based on MSI status, as MSI occurs in <5% of subjects with advanced CRC; however, subjects in Part 2 will have advanced non-MSI-H/dMMR CRC. At screening, the subject must provide a tumor sample (archival or newly obtained) evaluation of RAS and RAF mutations, pMMR and dMMR status, and PD-1, PD-L1, and PD-L2 expression, as well as left or right side location of the tumor as assessed by the investigator, for efficacy exploratory analyses.

Subjects may also agree to provide an optional on-treatment biopsy, for biomarker analysis as outlined in the Trial Flow Chart (Section 6.0).

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

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.

4.2.2 Rationale for Dose Selection/Regimen

Starting Dose and Dose Escalation of MK-8353 in Combination with Pembrolizumab

Based on data from Protocol 001 and emerging safety information from Protocol 013 (refer to Section 4.1.2.1), the doses of MK-8353 for the dose escalation in Part 1 were modified in Amendment 3 to continue Arm A at the de-escalation dose of 50 mg bid (continuous dosing),

and to start in parallel at 50 mg qd in the new Arm B (qd continuous dosing). Additionally, the 2 optional arms were modified to be new Arm C (1 week on/1week off) and new Arm D (monotherapy run-in followed by continuous dosing) (refer to Section 4.1.3.1). The drug holiday schedule in optional Arm C is to provide a release from the potential constant inhibition of ERK phosphorylation. A run-in schedule, such as the one proposed for MK-8353 in Arm D, has been used to improve the tolerability of combining 2 drugs. In Arm A, MK-8353 is administered on a continuous schedule bid, at doses based on PK data collected in earlier studies and preclinical efficacy studies in murine models (refer to the IB for MK-8353).

At a dose of 100 mg bid and 200 mg bid, MK-8353 in monotherapy was shown to be well tolerated in subjects with advanced solid tumors with no DLTs observed (PN001). At 800 mg bid, the DLTs observed in this study were nausea, vomiting, diarrhea, and fatigue (all Grade 3). The MTD was determined to be 400 mg bid. Of note, the restarting dose of MK-8353 in combination with pembrolizumab for this amendment is now more than 80% below the MTD in Protocol 001.

The dose level of MK-8353 will be escalated during this study until the RP2D(s) and schedule(s) of the combination regimen can be determined.

In Arm A, the initial dose of 50 mg bid for MK-8353 may be escalated to a daily dose of 150 mg (50 mg + 100 mg qd), 100 mg bid, 150 mg bid, 200 mg bid, and potentially 300 mg bid, based on the occurrence of DLTs during Cycle 1 and according to the mTPI method (refer to Section 5.2.1.2.).

Similarly, in Arm B, the initial dose of 50 mg qd for MK-8353 may be escalated to 100 mg qd, 150 mg qd, 200 mg qd, 300 mg qd, 400 mg qd, 600 mg qd, 900 mg qd, and potentially 1200 mg qd, based on the occurrence of DLTs during Cycle 1 and according to the mTPI method. Enrollment will alternate between arms, and will also be guided by the occurrence of toxicities.

Furthermore, additional optional arms (Arms C and D) may be implemented based on toxicities occurring at any dose level in Arm A and/or Arm B (the decision to start optional Arm C and/or Arm D will be made in conjunction with the investigators and the Sponsor). If Arm C and/or Arm D are implemented, MK-8353 will be administered qd at a starting dose of 50 mg, and this dose may be escalated to 100 mg, 150 mg, 200 mg, 300 mg, 400 mg, or 600 mg either 1 week on/1 week off (Arm C), or with a monotherapy run-in of 2 weeks followed by continuous administration (Arm D) (refer to Section 5.2.1.2).

Also, in each of these 4 arms, doses of 30 mg and 10 mg may be explored in the respective schedules, as well as additional intermediate doses, depending on the occurrence of toxicities and PK results at the higher doses, when the 10 mg capsules become available. Modifications to the dose or dosing regimen of MK-8353 may be required to achieve the scientific goals of the trial objectives and/or to ensure appropriate safety monitoring of the trial subjects. Details of allowed modifications are provided in Section 5.2.2.1.

Fixed Dose of Pembrolizumab

The planned dose of pembrolizumab for this study 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 for adults 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
- Pharmacology data showing full target saturation in both systemic circulation (inferred from PK data) and tumor (inferred from physiologically based PK [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 versus 10 mg/kg q3w (KN001 Cohort B2, KN001 Cohort D, KN002, KN010, and KN021), and 3 studies compared 10 mg/kg q3w versus 10 mg/kg q2w (KN001 Cohort B3, KN001 Cohort 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 q3w (or 200 mg fixed-dose) 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. Second, 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 participant 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.

Therefore, pembrolizumab will be evaluated in combination with MK-8353 at the fixed dose of 200 mg q3w. Modifications to the dose or dosing regimen of pembrolizumab will not be allowed in this study. Details are provided in Section 5.2.2.2.

4.2.2.1 Starting Dose for This Trial

The starting dose for MK-8353 in combination with pembrolizumab is 50 mg bid continuous in Arm A, and 50 mg qd in Arm B (continuous), optional Arm C (1 week on/1 week off),

and optional Arm D (MK-8353 monotherapy run-in) (refer to Section 4.1.2.1). Doses in Arms A and B and optional Arms C and D may be adjusted depending on PK and emerging toxicity data.

Pembrolizumab will be administered as a fixed dose of 200 mg q3w for every study subject (refer to Section 4.1.2.2).

4.2.2.2 Maximum Dose/Exposure for This Trial

The maximum dose of oral MK-8353 for this trial is as follows:

Arm A: 350 mg bid; maximum 700 mg total per day

Arm B: 1200 mg qd; maximum 1200 mg total per day

Arms C and D: 600 mg qd; maximum 600 mg total per day

The maximum dose of pembrolizumab will be 200 mg administered intravenously q3w.

The maximum dose of MK-8353 is based on the single agent doses tested in the healthy volunteer study and in Protocol 001 (refer to Section 4.1.2.1). Also, preliminary data from Protocol 013 at the 350 mg bid dose of MK-8353 in combination with pembrolizumab have suggested intolerable skin toxicity (refer to Section 4.1.3.1).

The maximum dose of pembrolizumab is based on single agent doses tested in KN-001, as well as the highest doses tested in combination in Phase 1 to 2 trials (refer to Section 4.1.2.2 and package circular for KEYTRUDA).

4.2.2.3 Rationale for Dose Interval and Trial Design

In MK-8353 Protocol 001, doses from 100 mg bid to 800 mg bid were evaluated. The highest dose level (800 mg bid) was found to be not tolerable (refer to Section 4.1.2.1 and the MK-8353 IB).

Although a dose of 350 mg bid was well tolerated in monotherapy and showed signs of clinical activity in Protocol 001, preliminary data from Protocol 013 have suggested that MK-8353 at 350 mg bid in combination with pembrolizumab leads to unacceptable toxicity (Grade 3 rash reported in 3 of the 4 subjects treated at this dose; refer to Section 4.1.3.1).

In the current amendment, dose escalation of MK-8353 (in combination with pembrolizumab) will start at 50 mg bid and 50 mg qd in Arm A and Arm B, respectively (continuous schedule). In spite of the high inter-individual variability observed in PK data from MK-8353, these doses are expected to produce meaningfully lower exposure from the previously tested 350 mg bid dose. The 2 optional Arms C and D will explore a drug holiday schedule (1 week on/1 week off; Arm C), and a 2-week run-in with MK-8353 as a single agent prior to the continuous administration of the combination (Arm D). The 2 optional arms could be triggered if unacceptable toxicities occur in Arm A and/or Arm B. In Arm B, once daily doses that achieve the same average exposure at steady state compared with bid doses (with lower trough levels, but higher C_{max}) will be explored in parallel to Arm A.

Pembrolizumab will be evaluated in the combination therapy at its full single-agent dose (200 mg intravenously q3w), and will not be escalated or de-escalated during this trial (refer

to Section 5.2.1). This dose was shown to be efficacious as a single agent and in combination, with an acceptable AE profile.

4.2.3 Rationale for Endpoints

4.2.3.1 Efficacy Endpoints

The efficacy of MK-8353 in combination with pembrolizumab will be evaluated in subjects with advanced solid tumors, and in subjects with ≥second line advanced non-MSI-H/dMMR CRC, by measuring ORR, DCR, DOR, PFS, and OS.

Overall response rate will be used as a secondary endpoint as assessed by the investigator based on RECIST 1.1, to evaluate efficacy of MK-8353 in combination with pembrolizumab in subjects with advanced solid tumors, and in subjects with ≥second line advanced non-MSI-H/dMMR CRC.

Radiological images (eg, computed tomography [CT], magnetic resonance imaging [MRI]) will be collected for possible analysis by blinded, independent central review. The Site Imaging Manual (SIM) contains specific instructions for the acquisition and submission of radiologic images to the central imaging vendor for this study.

Exploratory endpoints include OS, DCR, DOR, and PFS as assessed by the investigator based on RECIST 1.1 (refer to Appendix 12.4).

Secondary and exploratory efficacy endpoints will also be summarized according to RAS/RAF mutant status, pMMR status, and colon side of the tumors (in subjects with non-MSI-H/dMMR CRC).

Immune-related RECIST could be used by the investigator for treatment decision as outlined in Section 7.1.2.6 and Appendix 12.5.

4.2.3.2 Safety Endpoints

The primary safety objective of this study is to characterize the safety and tolerability of MK-8353 in combination with pembrolizumab in subjects with advanced solid tumors, and in subjects with ≥second line advanced non-MSI-H/dMMR CRC.

The primary safety analysis will be based on subjects who experience toxicities as defined by NCI CTCAE version 4.0 criteria for the duration of the study. Dose-limiting toxicities will be evaluated during Cycle 1 for the purpose of dose escalation and de-escalation decisions.

Safety will be assessed by quantifying the toxicities experienced by subjects who have received MK-8353 and pembrolizumab and their grades, including SAEs and events of clinical interest (ECIs).

Safety will be assessed by reported AEs using NCI 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. Safety parameters that will be analyzed include, but are not limited to, overall AEs, specific SAEs, SAEs, fatal AEs, and laboratory changes.

Other safety endpoints include laboratory safety assessments, Eastern Cooperative Oncology Group (ECOG) performance status, vital signs, and physical examinations.

4.2.3.3 Pharmacokinetic Endpoints

Serum samples will be obtained to measure PK of MK-8353 when given in combination with pembrolizumab. MK-8353 (Parts 1 and 2) and pembrolizumab (Part 1 only) serum peak and trough concentrations at planned visits and times will be summarized. Pharmacokinetic data of MK-8353 and pembrolizumab will be compared with the previously validated population PK model and potentially used to update the model.

4.2.3.4 Antidrug Antibody Assay

Formation of antidrug antibodies can potentially confound drug exposures at therapeutic doses, and prime for subsequent infusion-related toxicity. Antidrug antibody response to pembrolizumab at the beginning of each cycle will be determined to understand drug metabolism, exposure, and safety. Blood samples collected for antidrug antibody may only be stored at this time. Further analyses may be performed if required. If ongoing antidrug antibody sampling is deemed to be unnecessary by the Sponsor, it may be reduced or discontinued.

4.2.3.5 Tumor Markers

Serum samples will be obtained prior to study start and on Day 1 of each cycle to evaluate the kinetics of tumor markers such as CEA, CA-125, and CA 19-9, as appropriate. In a previous study, CEA decrease was predictive of PFS and ORR and occurred well in advance of radiographic confirmation of disease control [55]. Subjects with disease progression had rapid tumor marker elevation within 30 days after the initiation of therapy that significantly preceded radiographic changes [55].

4.2.3.6 RAS/RAF Mutations and pMMR/dMMR (MSI) Status

Testing for BRAF mutation (methodology detecting both V600E and/or V600K mutations), KRAS codon 12 and 13 mutations, and NRAS mutations (for non-CRC solid tumors) will be indicated according to tumor type as judged by the investigator, and performed by local laboratory testing.

Microsatellite instability, a form of genomic instability, occurs through the insertion or deletion of repeating nucleotides during deoxyribonucleic acid (DNA) replication and failure of the MMR system to correct errors in nucleotide repeat markers. Testing for pMMR/dMMR (MSI) status is already standardized and performed in Clinical Laboratory Improvement Amendments (CLIA)-certified laboratories without need for assay development. Mismatch repair proteins, or MSI loci testing for CRC is already clinically indicated as per National Comprehensive Cancer Network, European Society for Medical Oncology, and American Society of Clinical Oncology (ASCO) guidelines [58] [59] [60]. All means of testing for MSI status (eg, immunohistochemistry [IHC], polymerase chain reaction [PCR], next generation sequencing [NGS]) performed locally will be accepted. For other non-CRCs for which MSI testing is not currently clinically indicated, MSI status will be performed locally by CLIA-certified IHC or PCR-based tests for eligibility, or by a central laboratory if local laboratory testing is not available.

For central laboratory testing for MSI status, archived tumor samples or newly obtained biopsies will be used.

4.2.3.7 Planned Exploratory Biomarker Research

Planned Genetic Analysis

Additional biomarker research to identify factors important for MK-8353 and pembrolizumab combination therapy will be pursued.

Pretreatment and on-treatment tumor (when obtained) and blood samples collected in this study may undergo proteomic, genomic, and transcriptional analyses (both DNA and ribonucleic acid [RNA] analyses). Additional research may evaluate factors important for predicting responsiveness or resistance to MK-8353 and pembrolizumab combination therapy and other immunologic targets. Expression of candidate biomarkers in tumor tissue will be evaluated both at baseline and at least 10 to 14 days after initiation of combination therapy with MK-8353 and pembrolizumab (optional on-treatment biopsy in Cycle 2), including immune-signaling markers on the surface of tumor cells, phenotypic and functional immune cell markers on tumor-infiltrating lymphocytes (which may include PD-1, PD-L1, CD8 T cells), inhibition of ERK phosphorylation, and possible other biomarkers, as well as DNA/RNA changes. These and other additional biomarker or genomic research to identify factors important for MK-8353 and pembrolizumab combination therapy (eg, human leukocyte antigen genotype) may also be pursued.

Cancer immunotherapies represent an important and novel class of antitumor agents. However, the mechanism of action of these exciting new therapies is not completely understood and much remains to be learned regarding how best to leverage these new drugs in treating subjects. Thus, to aid future subjects, it is important to investigate the determinants of response or resistance to cancer immunotherapy as well as determinants of AEs in the course of clinical trials. These efforts will identify novel predictive/PD biomarkers and generate information that will better guide single-agent and combination therapy with immuno-oncology drugs. To identify novel biomarkers, we will collect biospecimens (eg, blood components, tumor material) 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 (eg, single nucleotide polymorphism analyses, whole exome sequencing, whole genome sequencing): this research will evaluate whether genetic variation within a clinical trial population correlates with response to the treatment(s) under evaluation. If genetic variation is found to predict efficacy or AEs, the data might inform optimal use of therapies in the subject population. Furthermore, it is important to evaluate germline DNA variation across the genome in order to interpret tumor-specific DNA mutations. Finally, MSI will be evaluated as this is an important biomarker for some cancers (ie, CRC).
- 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 (eg, mutations, methylation status, MSI). Key molecular changes of interest to immuno-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. Microsatellite instability will also be evaluated as this is an important biomarker for some cancers (ie, CRC).

- Tumor and blood RNA analyses: both genome-wide and targeted messenger RNA expression profiling and sequencing in tumor tissue and in blood may be performed to define gene signatures that correlate to clinical response to treatment with pembrolizumab or other immunotherapies. Pembrolizumab induces a response in tumors that likely reflects an inflamed/ immune phenotype. Specific immune-related gene sets (such as those capturing interferon-gamma transcriptional pathways) may be evaluated and new signatures may be identified. Individual genes related to the immune system may also be evaluated (eg, interleukin-10). MicroRNA profiling may also be pursued.
- Proteomics and IHC using blood or tumor: tumor and blood samples from this study may undergo proteomic analyses (eg, PD-L1 IHC). PD-L1 protein level in tumor sections, assessed by IHC, has been shown to correlate with response to pembrolizumab in subjects with NSCLC, and an in vitro diagnostic device has been developed for use with pembrolizumab in NSCLC. Preliminary data indicate that this association may also be true in additional cancer types (ie, triple-negative breast cancer, head and neck cancer, and gastric cancer). Additional tumor or blood-derived proteins may also correlate with response to pembrolizumab. Tumor tissue may, therefore, be subjected to proteomic analyses using a variety of platforms that could include, but are not limited to, immunoassays and liquid chromatography/mass spectrometry. This approach could identify novel protein biomarkers that could aid in subject selection for pembrolizumab therapy.
- Other blood-derived biomarkers: in addition to expression on tumor tissue, PD-L1 and other tumor-derived proteins can be shed from tumors and released into the blood. Assays such as enzyme-linked immunoassay measure these proteins in serum. Correlation of expression with response to pembrolizumab therapy may identify new approaches for predictive biomarkers in blood, representing a major advance from today's reliance on assessing tumor biomarkers. This research would serve to develop such assays for future clinical use.

4.2.3.8 Future Biomedical Research

The Sponsor will conduct Future Biomedical Research (FBR) on specimens consented for FBR 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, depending on which specimens are consented for future biomedical research.

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 FBR 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 FBR are presented in Section 12.2. Additional informational material for institutional review boards/ethics review committees (IRBs/ERCs) and investigational site staff is provided in Section 12.1.

4.3 Benefit/Risk

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

Additional details regarding specific benefits and risks for subjects participating in this clinical trial may be found in the accompanying MK-8353 and pembrolizumab IB and informed consent documents.

5 METHODOLOGY

5.1 Entry Criteria

5.1.1 Diagnosis/Condition for Entry into the Trial

Male/Female subjects with advanced or metastatic solid tumors in Part 1 and Male/Female subjects with ≥ second line advanced or metastatic non-MSI-H/dMMR CRC in Part 2 will be enrolled in this trial.

5.1.2 Subject Inclusion Criteria

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

1. Part 1: have a histologically or cytologically documented, locally advanced or metastatic solid malignancy. Each subject must have received at least 1 and up to 5 prior lines of cancer treatment regimen, excluding neo-adjuvant, adjuvant, maintenance treatment and surgery.

   Note: a repeat line of treatment does not count in the total number if the subject did not progress the first time; a 2-week or more duration of treatment counts in the total number of prior line of treatment if the subject progressed.

2. Part 2: have a histologically confirmed adenocarcinoma originating from the colon or rectum (Stage 4 American Joint Committee on Cancer 7th edition). Must be non-MSI-H/dMMR CRC. Appendiceal cancer is included.

   AND

   Experienced disease progression or was intolerant to at least 1 and up to 5 systemic chemotherapy regimen for metastatic non-MSI-H/dMMR CRC that must have included fluoropyrimidines **and** irinotecan, or oxaliplatin, ± anti-vascular endothelial growth factor or anti-epidermal growth factor receptor (if indicated by RAS mutational status); disease progression must have occurred within 3 months of the last systemic therapy administration. Subjects who were not deemed appropriate candidate for any of these agents due to medical history and/or contraindications may be eligible upon consultation with the Sponsor.

3. Provide an archival or newly obtained tumor tissue sample and blood samples for assessment of RAS/RAF mutation and pMMR/dMMR status and for biomarker analysis.
4. Have at least 1 measurable lesion as defined by RECIST 1.1 on imaging studies (CT or MRI) as assessed by the investigator/local radiology review. Cutaneous lesions and other superficial lesions that are detectable only by physical examination and subcutaneous lesions detectable by CT are not considered measurable lesions for the purposes of this protocol, but may be considered as nontarget lesions.
5. Be willing and able to provide written informed consent for the trial. The subject may also provide consent for FBR. However, the subject may participate in the main trial without participating in FBR.
6. Be ≥18 years of age on day of signing the informed consent.
7. Have a performance status of 0 or 1 on the ECOG Performance Scale.
8. Have an anticipated life expectancy of at least 3 months.
9. Be able to swallow and retain oral medication and must not have any clinically significant gastrointestinal abnormalities that may alter absorption.
10. Have adequate organ function as defined in Table 1:

Table 1 Inclusion Criteria Laboratory Parameters

System	Laboratory Value
Hematological	
ANC	≥1,500/mcL
Platelets	≥100,000/mcL
Hemoglobin	≥9 g/dL or ≥5.6 mmol/L
Renal	
Serum creatinine **OR** Measured or calculated[a] CrCl (GFR can also be used in place of creatinine or CrCl)	≤1.5 × ULN **OR** ≥60 mL/min for subject with creatinine levels >1.5 × institutional ULN
Hepatic	
Serum total bilirubin	≤1.5 × ULN **OR** Direct bilirubin ≤ULN for subjects with total bilirubin levels >1.5 × ULN
AST (SGOT) and ALT (SGPT)	≤2.5 × ULN **OR** ≤5 × ULN for subjects with liver metastases
Coagulation	
INR or PT aPTT	≤1.5 × ULN unless the subject is receiving anticoagulant therapy as long as PT or aPTT is within therapeutic range of intended use of anticoagulants

[a] Calculate CrCl using standard Cockcroft-Gault formula (Appendix 12.3).
ALT (SGOT)=alanine aminotransferase; ANC=absolute neutrophil count; aPTT=activated partial thromboplastin time; AST (SGPT)=aspartate aminotransferase; CrCl=creatinine clearance; GFR=glomerular filtration rate; INR=International Normalized Ratio; PT=prothrombin time; ULN=upper limit of normal.

11. Female subject of childbearing potential must have a negative urine or serum pregnancy test within 72 hours prior to receiving the first dose of study medication. If the urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required. The serum pregnancy test must be negative for the subject to be eligible.

12. Female subjects may be enrolled in the trial if they are:

    - Of nonchildbearing potential, which is defined as:

      - A female subject ≥45 years of age and has not had menses for greater than 1 year,
      - A female who is amenorrheic for >2 years without a hysterectomy and oophorectomy and a follicle-stimulating hormone (FSH) value in the postmenopausal range upon pretrial (screening) evaluation,

        and/or

      - A female who is status post hysterectomy, oophorectomy, or tubal ligation. Documented hysterectomy or oophorectomy must be confirmed with medical records of the actual procedure or confirmed by an ultrasound. Tubal ligation must be confirmed with medical records of the actual procedure; otherwise, the subject will be excluded. Information must be captured appropriately within the site's source documents.

    - Of childbearing potential who are willing to use either 2 adequate barrier methods, or to abstain from heterosexual activity throughout the trial, starting with the screening visit (Visit 1) through 120 days after the last dose of trial treatment. Please refer to Section 5.7.2 for a list of acceptable birth control methods.

13. Male subjects of childbearing potential must agree to use an adequate method of contraception as outlined in Section 5.7.2, starting with the first dose of study medication through 120 days after the last dose of study medication.

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

5.1.3 Subject Exclusion Criteria

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

1. Has disease that is suitable for local treatment administered with curative intent.

2. Part 1: has received prior therapy with cancer vaccines, or compounds targeting PD-1 (including pembrolizumab), PD-L1, PD-L2, CTLA-4, or MEK.

   Note: Examples of MEK inhibitors include, but are not limited to, trametinib and cobimetinib.

3. Part 2: has received prior therapy with cancer vaccines, or compounds targeting PD-1 (including pembrolizumab), PD-L1, PD-L2, CTLA-4, LAG-3, CD-137, OX-40, CD-40, GITR, BRAF, MEK or other molecules in the MAPK pathway.

   Note: Examples of BRAF inhibitors include, but are not limited to, dabrafenib and vemurafenib.

4. Is currently participating in or has participated in a study of an investigational agent or using an investigational device within 4 weeks prior to the first dose of trial treatment.

5. Has taken during the 14 days prior to enrollment, or is currently taking medication that interferes with CYP3A4 or CYP2C8 as listed in Table 8.

6. Has Gilbert's Syndrome.

7. Has a diagnosis of immunodeficiency or is receiving chronic systemic steroid therapy (in doses exceeding 10 mg daily of prednisone equivalent) or any other form of immunosuppressive therapy within 7 days prior to the first dose of trial treatment. The use of physiologic doses of corticosteroids may be approved after consultation with the Sponsor.

8. Has had a prior anticancer mAb within 4 weeks prior to study Day 1 or who has not recovered (ie, ≤Grade 1 or at baseline) from AEs due to agents administered more than 4 weeks earlier.

9. Has had prior chemotherapy, targeted small molecule therapy, or radiation therapy within 14 days prior to study Day 1 or who has not recovered (ie, ≤Grade 1 or at baseline) from AEs due to a previously administered agent.

   Note: Subjects with ≤Grade 2 neuropathy or ≤Grade 2 alopecia are an exception to this criterion and may qualify for the study upon consultation with the Sponsor.

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

10. Has received transfusion of blood products (including platelets or red blood cells) or administration of colony stimulating factors (including granulocyte-colony stimulating factor [G-CSF], granulocyte-macrophage colony-stimulating factor [GM-CSF] or recombinant erythropoietin) within 4 weeks prior to study Day 1.

11. Has a known additional malignancy that is progressing or requires active treatment. Exceptions include basal cell carcinoma of the skin, squamous cell carcinoma of the skin that has undergone potentially curative therapy, or in situ cervical cancer.

12. Has known active central nervous system metastases and/or carcinomatous meningitis.

    Note: Subjects with previously treated brain metastases may participate provided they are stable (without evidence of progression by imaging, using the identical imaging modality for each assessment, either MRI or CT scan) for at least 4 weeks prior to the first dose of trial treatment and any neurologic symptoms have returned to

baseline, have no evidence of new or enlarging brain metastases, and are not using steroids for at least 14 days prior to trial treatment. This exception does not include carcinomatous meningitis which is excluded regardless of clinical stability.

13. Active autoimmune disease that has required systemic treatment in past 2 years (ie, with use of disease modifying agents, corticosteroids, or immunosuppressive drugs). Replacement therapy (eg, thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency) is not considered a form of systemic treatment and is allowed.
14. Has a history of (noninfectious) pneumonitis that required steroids or current pneumonitis.
15. Has a history of interstitial lung disease.
16. Has an active infection requiring systemic therapy.
17. Has a history or current evidence of any condition, therapy, or laboratory abnormality that might confound the results of the trial, interfere with the subject's participation for the full duration of the trial, or is not in the best interest of the subject to participate, in the opinion of the treating investigator.
18. Has a known psychiatric or substance abuse disorder that would interfere with the subject's ability to cooperate with the requirements of the trial.
19. Is pregnant or breastfeeding, or expecting to conceive or father children within the projected duration of the trial, starting with the screening visit through 120 days after the last dose of trial treatment.
20. Has a known history of human immunodeficiency virus (HIV) (HIV 1/2 antibodies).
21. Has known active hepatitis B (eg, hepatitis B surface antigen reactive) or hepatitis C (eg, hepatitis C virus RNA [qualitative] is detected).
22. Has received a live-virus vaccination within 30 days of planned treatment start. Seasonal flu vaccines that do not contain live virus are permitted.
23. Is expected to require any other form of systemic or localized antineoplastic therapy while in study.
24. Has severe hypersensitivity (≥Grade 3) to pembrolizumab and/or any of its excipients.
25. Has had an allogeneic tissue/solid organ transplant.
26. Part 2: Have a histologically confirmed adenocarcinoma originating from the colon or rectum that is microsatellite instable (ie, MSI-H).

5.2 Trial Treatment(s)

Part 1: the treatments to be used in this trial are outlined below in Table 2. A cycle of treatment in this study is defined as 21 days (Day 1 to Day 21), except for the MK-8353 monotherapy run-in of 14 days in Arm D. In Arm A, 6 dose levels of MK-8353 are planned in Part 1 on a continuous schedule starting at 50 mg bid, (Table 2). In Arm B (continuous) and optional Arms C (1 week on/1 week off) and D (run-in), 7 dose levels of MK-8353 are planned, starting at 50 mg qd (Table 2). Concomitant administration of pembrolizumab will be at the fixed dose of 200 mg q3w in all arms.

Table 2 Part 1 Trial Treatment (21-day cycles)

Drug	Dose Potency	Dose Frequency	Route of Administration	Regimen/Treatment	Use
Arm A (bid continuous)					
MK-8353	DL1 350 mg	bid	Oral	Days 1 to 21 of each cycle	Experimental
	DL1A* 50 mg	bid			
	DL2A 50 mg + 100 mg *	bid			
	DL3A 100 mg	bid			
	DL4A 150 mg	bid			
	DL5A 200 mg	bid			
	DL6A 300 mg	bid			
Pembrolizumab	200 mg	q3w	Intravenous infusion	Day 1 of each cycle	Experimental
Arm B (qd continuous)					
MK-8353	DL1B 50 mg	qd	Oral	Days 1 to 21 of each cycle	Experimental
	DL2B 100 mg	qd			
	DL3B 150 mg	qd			
	DL4B 200 mg	qd			
	DL5B 300 mg	qd			
	DL6B 400 mg	qd			
	DL7B 600 mg	qd			
	DL8B 900 mg	qd			
	DL9B 1200 mg	qd			
Pembrolizumab	200 mg	q3w	Intravenous infusion	Day 1 of each cycle	Experimental
Optional Arm C (qd 1 week on/1 week off)					
MK-8353	DL1C 50 mg	qd	Oral	Days 1 to 7, Days 15 to 21, and Days 29 to 35 of each 42-day cycle (based on 2 cycles of 21 days)	Experimental
	DL2C 100 mg	qd			
	DL3C 150 mg	qd			
	DL4C 200 mg	qd			
	DL5C 300 mg	qd			
	DL6C 400 mg	qd			
	DL7C 600 mg	qd			

Drug	Dose Potency	Dose Frequency	Route of Administration	Regimen/Treatment	Use
Pembrolizumab	200 mg	q3w	Intravenous infusion	Days 1 and 22 of each 42-day period (based on 2 cycles of 21 days)	Experimental
Optional Arm D (MK-8353 monotherapy run-in then qd continuous)					
MK-8353	DL1D 50 mg DL2D 100 mg DL3D 150 mg DL4D 200 mg DL5D 300 mg DL6D 400 mg DL7D 600 mg	qd qd qd qd qd qd qd	Oral	Run-in from Cycle 1, Day 1 to Day 14 prior to Cycle 2, then continuous from Days 1 to 21 of each cycle	Experimental
Pembrolizumab	200 mg	q3w	Intravenous infusion	Day 1 of each cycle starting with Cycle 2	Experimental

* If 50 mg bid/qd doses are not tolerable, dose of 10 mg and 30 mg may be explored.
** DL2A (150 mg daily) will be administered as a morning dose of 50 mg and an evening dose of 100 mg MK-8353.
bid=twice daily, DL=dose level, q3w=once every 3 weeks, qd=once daily.

Part 2: MK-8353 will be administered at the RP2D(s) identified for MK-8353 in Part 1 of the study (several doses and schedules could be explored), in combination with pembrolizumab at a fixed dose of 200 mg (same fixed dose as in Part 1). The decision to bring specific schedule(s) or dose(s) into the expansion cohorts in Part 2 will be based on exposure parameters, as well as the safety profile and potential preliminary efficacy observed, and will be made jointly by the investigators and the Sponsor.

Throughout the study (Part 1 and Part 2) in Arms A and B, the first dose of MK-8353 will occur at the trial site on Day 1 of each cycle, shortly before the pembrolizumab infusion. Pembrolizumab will be then administered through an IV infusion as described in the Pharmacy Manual. For optional Arm C, administration will follow the schedule described in Table 2. For optional Arm D, after the screening visit, the subject will receive MK-8353 monotherapy unsupervised at his/her home from Cycle 1, Day 1 to Day 14, prior to Cycle 2 Day 1.

1. Arm A (bid continuous):
   - For the cohorts in Arm A (bid schedule), subsequent dosing of MK-8353 will be performed in the evening of the same day (Day 1), and then twice a day by the subject (ie, unsupervised at his/her home) at approximately the same time each day, until Day 1 of the next cycle.
2. Arm B (qd continuous):
   - In Arm B (qd schedule), subsequent dosing of MK-8353 will be performed the next day (Day 2), and then once a day by the subject (ie, unsupervised at his/her home) at approximately the same time each day, until Day 1 of the next cycle.

3. Optional Arm C (1 week on/1 week off):
    - In optional Arm C (1 week on/1 week off qd schedule), subsequent dosing of MK-8353 will be performed the next day by the subject (ie, unsupervised at his/her home) at approximately the same time each day, on Days 1 to 7, Days 15 to 21, and Days 29 to 35 of a 42-day period (corresponding to 2 cycles of 21 days) until Day 1 of Cycle 3.
4. Optional Arm D (monotherapy run-in then continuous):
    - In optional Arm D (monotherapy run-in then qd continuous), MK-8353 will be administered qd from Cycle 1, Day 1 to Day 14 (ie, unsupervised at his/her home), prior to Cycle 2 Day 1. Cycle 2 Day 1 will be performed at the clinical site. Subsequent dosing of MK-8353 will be performed the next day (Cycle 2 Day 2), and then once a day by the subject (ie, unsupervised at his/her home) at approximately the same time each day, until Day 1 of the next cycle.

Enrollment will be accomplished by nonrandom assignment to each combination treatment dose level in Part 1, using an interactive voice response system/integrated web response system (IVRS/IWRS). In Part 2, if several schedules and/or doses at RP2D are explored for the combination therapy, assignment will be randomized. Enrollment will be semi-competitive between sites.

All supplies indicated in Table 2 above will be provided centrally by the Sponsor or locally by the trial site, subsidiary or designee, depending on local country operational or regulatory requirements.

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

5.2.1 Dose Selection

5.2.1.1 Dose Selection (Preparation)

The rationale for selection of doses to be used in this trial is provided in Section 4.0 Background & Rationale. There are no specific calculations or evaluations required to be performed in order to administer the proper dose to each subject.

5.2.1.2 Dose Escalation and Confirmation

In Part 1 of the study, an mTPI design [1] with a target DLT rate of approximately 30% will be applied for dose escalation and confirmation to determine a RP2D for MK-8353 in combination with pembrolizumab.

In Arms A (bid continuous) and B (qd continuous), predetermined dose levels of MK-8353 (in combination with a fixed dose of pembrolizumab) will be explored independently. In Arm A, a de-escalation dose of 50 mg is available if the starting dose of 100 mg is deemed not tolerable. All dose escalation and de-escalation decisions will be based on the occurrence of DLTs at a given dose during the DLT evaluation period and will be made jointly by the

investigators and the Sponsor. In Arm B, additional intermediate dose levels between 600 and 1200 mgs may be explored.

Additionally, the investigators and the Sponsor can decide jointly to open the 2 optional schedules (Arm C and/or Arm D) based on safety information and PK data obtained from Arms A and B. All dose escalation and de-escalation decisions in these 2 arms will be also based on the occurrence of DLTs at a given dose during the DLT evaluation period (Cycle 1 for Arm C [21 days], and Cycles 1 and 2 for Arm D [35 days]) and will be made jointly by the investigators and the Sponsor.

Additional doses of 10 mg and 30 mg could be explored in any of the 4 arms based on safety information and exposure data obtained at the higher doses. The decision to explore these lower doses will be made jointly by the investigators and the Sponsor.

The dose of pembrolizumab will remain constant at 200 mg q3w for each dose level of MK-8353 and in each arm.

In Table 3, the number of subjects treated is indicated in the columns and the number of subjects who experienced a DLT is indicated in the rows. Dosing decisions include escalate to the next higher dose (E), stay at the current dose (S), de-escalate to the next lower dose (D), and de-escalate to a lower dose and never test this dose again (ie, unacceptably toxic dose; DU).

During dose escalation, a minimum of 3 subjects is required at each dose. At the starting dose in Arm A (DL1A), 1 subject will be enrolled, and subsequent subjects will be enrolled once the first subject has reached Cycle 1 Day 15. Additionally, previously enrolled subjects, continuing on the study, will be able to restart MK-8353 at 100 mg bid in combination with pembrolizumab once the first subject has reached Cycle 1 Day 15. In subsequent doses for each arm, staggering enrollment is optional.

Depending on accrual rate, 3, 4, 5, or 6 subjects may be enrolled at each new dose until the last of those subjects completes the DLT assessment period. For example, the dose escalation rules will proceed as follows if 3 subjects are enrolled: if 0 out of the first 3 subjects at a given dose level develops a DLT, then the dose can be escalated to the next level without further expansion. If 1 out of the first 3 subjects at a given dose level develops a DLT, no more than an additional 3 subjects should be enrolled at this dose level until additional DLT data are available since this dose would be considered unacceptably toxic if all 3 of the additional subjects experience a DLT (ie, 4 out of 6 subjects). If 2 out of the first 3 subjects at a given dose level develop a DLT, the dose will be de-escalated to the next lower level. If 3 out of the first 3 subjects at a given dose level develop a DLT, this dose will be considered unacceptably toxic (ie, the dose will be de-escalated and never re-escalated to that dose again). The same principle will be applied whether 3, 4, 5, or 6 subjects are enrolled in the same dose cohort according to Table 3.

Based on the mTPI design, the number of subjects who are enrolled at a 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 3). To determine how many more subjects can be enrolled at a dose level, one can count steps in a diagonal direction (down and to the right) from the current cell to the first cell marked DU. In total, 3 to 14 subjects may be enrolled at a given dose level.

For example, if 1/3 subjects have experienced a DLT at a given dose level, no more than an additional 3 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 3 of the additional subjects experience a DLT (ie, 4/6 subjects with DLTs as in Table 3).

This is a Phase 1b assessment of MK-8353 in humans, and the PK, PD, and safety profiles of the compound are still being elucidated. This protocol is written with some flexibility to accommodate the inherent dynamic nature of Phase 1 clinical studies. Modifications to the dose, dosing regimen and/or clinical or laboratory procedures currently outlined above may be required to achieve the scientific goals of the study objectives and/or to ensure appropriate safety monitoring of the study participants. As such, some alterations from the currently outlined dose and/or dosing regimen may be permitted based on newly available data, but the maximum daily dose may not exceed those currently outlined in the protocol, including repeat of or decrease in the dose of the study intervention administered in any given arm.

Dose escalation and confirmation will end after 14 subjects have been treated at any one of the selected doses. The pool-adjacent-violators-algorithm [1] will be used to estimate the DLT rates across doses. The dose with an estimated DLT rate closest to 30% may be treated as a preliminary MTD. The totality of the data will be considered before a dose is selected to carry forward to Part 2 and the escalation schedule may be adjusted based on PK and safety data emerging throughout the study to determine the RP2D.

Note that although 30% was the target toxicity rate used to generate the guidelines in Table 3, the observed rates of subjects with DLTs at the MTD may be slightly above or below 30%.

Table 3 Dose Escalation and Confirmation Rules Based on the Modified Toxicity Probability Interval Design

	Number of subjects treated at current dose											
Number of toxicities	3	4	5	6	7	8	9	10	11	12	13	14
0	E	E	E	E	E	E	E	E	E	E	E	E
1	S	S	S	E	E	E	E	E	E	E	E	E
2	D	S	S	S	S	S	S	S	E	E	E	E
3	DU	DU	D	S	S	S	S	S	S	S	S	S
4		DU	DU	DU	D	D	S	S	S	S	S	S
5			DU	DU	DU	DU	DU	D	S	S	S	S
6				DU	DU	DU	DU	DU	DU	D	S	S
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

Target toxicity rate = 30%

Flat non-informative prior Beta (1,1) is used as a prior and ε1=ε2=0.05[1].

D=de-escalate to the next lower dose; DU=the current dose is unacceptably toxic, E=escalate to the next higher dose, S=stay at the current dose.

5.2.1.3 Cohort Expansion

Up to approximately 40 additional subjects will be treated at the RP2D(s) identified in Part 1 for MK-8353, in combination with the fixed dose of pembrolizumab (200 mg IV q3w), to collect more safety and efficacy data at that dose. The population to be enrolled into the cohort expansion (Part 2) is defined in Inclusion Criterion #2 (Section 5.1.2). Several doses and schedules may be explored in Part 2.

5.2.1.4 Tolerability Evaluation Rules and Dose Escalation

The different dose levels of MK-8353 in Arms A and B and optional Arms C and D planned in Part 1 are presented in Table 4.

In Amendment 3 of Protocol 013, the starting dose of MK-8353 is 50 mg bid in Arm A and 50 mg qd in Arm B and optional Arms C and D. Dose escalation will continue as outlined above (Section 5.2.1.2) according to mTPI dose-finding rules. Additionally, doses of MK-8353 at 10 mg and 30 mg could be explored in each arm (Section 5.2.1.2). Concomitant administration of pembrolizumab will be at the fixed dose of 200 mg q3w in all arms and at all dose levels of MK-8353.

Table 4 Dose Levels for MK-8353 + Pembrolizumab in Part 1

Arm A	**MK-8353 bid continuous**		**Pembrolizumab (q3w)**
Dose Levels	**mg per dose**	**mg per day**	**IV Infusion**
DL1	350	700	200
DL1A*	50	100	200
DL2A**	50 @ AM + 100 @ PM	150	200
DL3A	100	200	200
DL4A	150	300	200
DL5A	200	400	200
DL6A	300	600	200
Arm B	**MK-8353 qd continuous**		**IV infusion**
DL1B	50	50	200
DL2B	100	100	200
DL3B	150	150	200
DL4B	200	200	200
DL5B	300	300	200
DL6B	400	400	200
DL7B	600	600	200
DL8B	900	900	200
DL9B	1200	1200	200
Optional Arm C	**MK-8353 qd 1 week on/1 week off**		
Dose Levels	**mg per dose**	**mg per day**	**IV Infusion**
DL1C	50	50 for Days 1 to 7, Days 15 to 21, and Days 29 to 35 of a 42-day period (corresponding to 2 cycles of 21 days)	200
DL2C	100	100 for Days 1 to 7, Days 15 to 21, and Days 29 to 35 of a 42-day period (corresponding to 2 cycles of 21 days)	200
DL3C	150	150 for Days 1 to 7, Days 15 to 21, and Days 29 to 35 of a 42-day period (corresponding to 2 cycles of 21 days)	200
DL4C	200	200 for Days 1 to 7, Days 15 to 21, and Days 29 to 35 of a 42-day period (corresponding to 2 cycles of 21 days)	200
DL5C	300	300 for Days 1 to 7, Days 15 to 21, and Days 29 to 35 of a 42-day period (corresponding to 2 cycles of 21 days)	200
DL6C	400	400 for Days 1 to 7, Days 15 to 21, and Days 29 to 35 of a 42-day period (corresponding to 2 cycles of 21 days)	200
DL7C	600	600 for Days 1 to 7, Days 15 to 21, and Days 29 to 35 of a 42-day period (corresponding to 2 cycles of 21 days)	200

Optional Arm D	MK-8353 qd monotherapy run-in then continuous		Pembrolizumab (q3w)
Dose Levels	**mg per dose**	**mg per day**	**IV Infusion**
DL1D	50	50 for Cycle 1, Day 1 to Day 14 (run-in), and Day 1 to Day 21 of subsequent cycles	200
DL2D	100	100 for Cycle 1, Day 1 to Day 14 (run-in), and Day 1 to Day 21 of subsequent cycles	200
DL3D	150	150 for Cycle 1, Day 1 to Day 14 (run-in), and Day 1 to Day 21 of subsequent cycles	200
DL4D	200	200 for Cycle 1, Day 1 to Day 14 (run-in), and Day 1 to Day 21 of subsequent cycles	200
DL5D	300	300 for Cycle 1, Day 1 to Day 14 (run-in), and Day 1 to Day 21 of subsequent cycles	200
DL6D	400	400 for Cycle 1, Day 1 to Day 14 (run-in), and Day 1 to Day 21 of subsequent cycles	200
DL7D	600	600 for Cycle 1, Day 1 to Day 14 (run-in), and Day 1 to Day 21 of subsequent cycles	200

* If 50 mg doses are not tolerable, doses of 10 mg and 30 mg may be explored.
** DL2A (150 mg daily) will be administered as a morning dose of 50 mg and an evening dose of 100 mg of MK-8353.
bid=twice daily; DL=dose level, IV=intravenous, q3w=once every 3 weeks; qd=once daily.

Each individual subject will be assigned to a single dose level of study drug. Intrasubject dose escalation is not allowed. Individual subject dose interruptions and/or dose decreases may be implemented based on toxicity as described in Section 5.2.2; however, dose adjustments should not be made during the DLT evaluation period without discussion with the Sponsor.

The decision to enroll subjects in the next dose level will be made by the Sponsor in consultation with the participating investigators after reviewing the safety and any available PK data of the previous dose level(s).

Subjects may continue on treatment until disease progression, unacceptable toxicity, investigator's decision to withdraw the subject, withdrawal of consent, development of an intercurrent condition precluding further administration of study treatment, pregnancy of the subject, failure to comply with dosing evaluations or other study requirements, or administrative reasons.

5.2.1.5 Definition of Dose-limiting Toxicities

All toxicities will be graded using NCI CTCAE Version 4.0 based on investigator assessment (Appendix 12.7).

The DLT window of observation will be during Cycle 1 for Arms A, B, and C (21 days/3 weeks), and Cycles1 and 2 for Arm D (35 days/5 weeks).

The occurrence of any of the following toxicities during the DLT window will be considered a DLT, if assessed by the investigator to be possibly, probably, or definitely related to study drug administration:

1. Grade 4 nonhematologic toxicity (not laboratory).
2. Grade 4 hematologic toxicity lasting ≥7 days, except thrombocytopenia
    a. Grade 4 thrombocytopenia of any duration
    b. Grade 3 thrombocytopenia associated with bleeding
3. Grade 3 nonhematologic toxicity (not laboratory) lasting >3 days despite optimal supportive care.
4. Any Grade 3 or Grade 4 nonhematologic laboratory value if:
    - Medical intervention is required to treat the subject, or
    - The abnormality leads to hospitalization, or
    - The abnormality persists for >1 week.
    - Exceptions:
        - Clinically nonsignificant, treatable, or reversible laboratory abnormalities (eg, liver function tests, uric acid)
5. 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 degrees C (101 degrees F) or a sustained temperature of ≥38 degrees C (100.4 degrees 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
6. Prolonged delay (>2 weeks) in initiating Cycle 2 due to treatment-related toxicity.
7. Any treatment-related toxicity that causes the subject to discontinue treatment during Cycle 1.
8. Missing >25% of MK-8353 doses as a result of drug-related AE(s) during the first cycle.
9. Grade 5 toxicity.

5.2.1.6 Replacement of Subjects in Dose-limiting Toxicity Period

In order to fully evaluate the safety of the combination therapy in this study, all subjects enrolled 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 safety evaluations due to reasons other than drug-related AEs.

- They received <90% of the total pembrolizumab infusion in Cycle 1 (eg, because the infusion had to be discontinued due to an infusion reaction) and did not experience a drug-related event.

- They received ≤75% of MK-8353 doses intended for the trial during Cycle 1 and did not experience a drug-related event.

- They must take a prohibited concomitant medication during Cycle 1, unless this medication is used to treat a study drug-related AE.

- They must undergo medical / surgical procedures or have logistical issues not related to study therapy (eg, elective surgery, unrelated medical events) during Cycle 1.

Subjects discontinuing within 21 days (or 35 days for Arm D) of the first dose due to reasons unrelated to study treatment will not be considered evaluable for DLTs and may be replaced. Subjects with a DLT within 21 days (or 35 days for Arm D) of the first dose should not be replaced.

Nonevaluable subjects will not be counted toward the (Part 1 or Part 2) total for DLT evaluation.

Subjects who experience a DLT in the DLT window should be discontinued from the trial. However, if in the opinion of the investigator, the subject is deriving clinical benefit from the study treatment, the subject may be allowed to continue on the trial after discussion with the Sponsor.

5.2.2 Dose Modification (Escalation/Titration/Other)

For individual subjects, dose delays and modifications of trial treatment will be based on treatment-related toxicity, laboratory test results prior to treatment administration, and clinical assessments during the previous cycle and on the day of treatment. Guidelines for dose delay and dose modification are described below and are applicable to the start of each cycle as well as during the cycle if treatment-related toxicities occur.

5.2.2.1 MK-8353 Dose Modifications

Criteria for Dose Delay

Except in Cycle 1 in which dosing can be delayed up to 2 weeks, dosing of MK-8353 should be delayed for up to 3 weeks, until the AE is resolved to baseline status or ≤Grade 1 in case of:

- Any treatment-related hematological or nonhematological AE ≥Grade 3

OR

- Any abnormal nonhematological laboratory value ≥Grade 3 that requires medical intervention, hospitalization, or persists for ≥1 week, except for a clinically nonsignificant, treatable, or reversible laboratory abnormalities

Any ≥Grade 3 AE of nausea and/or vomiting, or anorexia if left untreated without medical intervention will not require a dose delay.

A reoccurring Grade 2 hematological or nonhematological AE, which in the opinion of the investigator is treatment-related and significant despite medical intervention, should be discussed with the Sponsor prior to any dose delay.

Subjects should be assessed weekly until the AE has resolved to baseline status or ≤Grade 1 and dosing resumes or the subject is discontinued from the study.

If treatment is delayed by more than 3 weeks (or by more than 2 weeks in Cycle 1) because of treatment-related toxicity, study treatment should be discontinued. However, subjects with evidence of clinical benefit may be allowed to continue treatment despite a treatment delay (for any reason) of more than 3 weeks, after discussion with the Sponsor.

Criteria for Dose Modification

Once a dose delay occurs, upon resolution of any treatment-related AE to baseline status or ≤Grade 1, the dose level of MK-8353 for the subsequent doses must be reduced 1 dose level.

Any dose level reduction will be permanent (ie, dose re-escalation is NOT allowed). No more than 2 dose level reductions will be allowed. Subjects who require further dose reductions or dose reductions below DL -1 should be discontinued from the study treatment.

Dose reductions are not permitted during the DLT evaluation period.

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

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

AEs associated with pembrolizumab 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 treatment and may affect more than one body system simultaneously. Therefore, early recognition and initiation of treatment is critical to reduce complications. Based on existing clinical study data, most irAEs were reversible and could be managed with interruptions of pembrolizumab, administration of corticosteroids and/or other supportive care. For suspected irAEs, ensure adequate evaluation to confirm etiology or exclude other causes. Additional procedures or tests such as bronchoscopy, endoscopy, skin biopsy may be included as part of the evaluation. Based on the severity of irAEs, withhold or permanently discontinue pembrolizumab and administer corticosteroids.

Dose Modification and Toxicity Management Guidelines for irAEs associated with pembrolizumab 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 Pembrolizumab

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

Table 6 Pembrolizumab Infusion Reaction Dose Modification and Treatment Guidelines

NCI CTCAE Grade	Treatment	Premedication at Subsequent Dosing
Grade 1 Mild reaction; infusion interruption not indicated; intervention not indicated	Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator.	None
Grade 2 Requires therapy or infusion interruption but responds promptly to symptomatic treatment (eg, 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 (eg, from 100 mL/hr to 50 mL/hr). Otherwise dosing will be held until symptoms resolve and the subject should be premedicated for the next scheduled dose. Subjects who develop Grade 2 toxicity despite adequate premedication should be permanently discontinued from further study drug treatment.	Subject may be premedicated 1.5h (±30 minutes) prior to infusion of pembrolizumab with: Diphenhydramine 50 mg po (or equivalent dose of antihistamine). Acetaminophen 500 to 1000 mg po (or equivalent dose of analgesic).

Grades 3 or 4 Grade 3: Prolonged (ie, not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae (eg, 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 NCI CTCAE, version 4.0 at http://ctep.cancer.gov CTCAE=Common Toxicity Criteria for Adverse Events; IV=intravenous; NCI=National Cancer Institute; NSAIDs=nonsteroidal anti-inflammatory drugs; po=per os (by mouth).		

Dosing interruptions are permitted after Cycle 1 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 3 weeks of the scheduled interruption, unless otherwise discussed with the Sponsor. The reason for interruption should be documented in the subject's study record.

5.2.3 Timing of Dose Administration

All trial treatments will be administered on an outpatient basis.

Trial treatment should be administered after all procedures/assessments have been completed as detailed on the Trial Flow Chart (Section 6.0) and Table 7.

Table 7 Treatment Schedule for MK-8353 + Pembrolizumab for Each Treatment Cycle

Treatment	**Day 1**		**Days 2 – 21**	
	am	**pm**	**am**	**pm**
Arm A (bid continuous)				
MK-8353	X	X	X	X
Pembrolizumab	X			
Arm B (qd continuous)				
	Day 1		**Days 2 – 21**	
	am		**am**	
MK-8353	X		X	
Pembrolizumab	X			
Optional Arm C (qd 1 week on/ 1 week off)				
	Day 1	**Days 2 to 7, 15 to 21, and 29 to 35**	**Day 22**	**Days 8-14, 23-28, and 36-42**
	am	**am**	**am**	**am**
MK-8353	X	X		
Pembrolizumab	X		X	
Optional Arm D (monotherapy run-in then qd continuous)				
	Cycle 1, Day 1 to Day 14	**Day 1 of subsequent cycles**	**Days 2 – 21 of subsequent cycles**	
	am	**am**	**am**	
MK-8353	X	X	X	
Pembrolizumab		X		

bid=twice daily; qd=once daily.

In Arm A, starting on Day 1 of Cycle 1, MK-8353 will be administered orally approximately every 12 hours on each day (bid) of a 21-day treatment cycle. MK-8353 may be administered up to 4 hours before or after the scheduled time for MK-8353 oral intake.

In Arm B, starting on Day 1 of Cycle 1, MK-8353 will be administered orally qd approximately every 24 hours on each day of a 21-day treatment cycle. MK-8353 may be administered up to 4 hours before or after the scheduled time for MK-8353 oral intake.

In optional Arm C, starting on Day 1 of Cycle 1, MK-8353 will be administered orally qd approximately every 24 hours for Days 1 to 7, Days 15 to 21, and Days 29 to 35 of a 42-day period (corresponding to 2 cycles of 21 days) until Day 1 of Cycle 3, when this 42-day period will start again.

In optional Arm D, starting on Cycle 1, Day 1 and until Day 14 (day prior to Day 1 of Cycle 2), and then continuously starting on Day 1 of Cycle 2, MK-8353 will be administered

orally qd approximately every 24 hours on each day of a 14- or 21-day treatment cycle. MK-8353 may be administered up to 4 hours before or after the scheduled time for MK-8353 oral intake.

All capsules comprising a dose should be taken within approximately 15 minutes.

On Day 1 of each 21-day cycle, after potential MK-8353 administration in the morning (for Arms A and B, and optional Arm D), pembrolizumab will be administered at a fixed dose of 200 mg as a 30-minute IV infusion. For optional Arm C, refer to Table 7.

Sites should make every effort to target the pembrolizumab infusion timing to be as close to 30 minutes as possible. However, given the variability of infusion pumps from site to site, a window of -5 minutes and +10 minutes is permitted (ie, infusion time is 30 minutes: -5 min/+10 min).

Except for Cycle 2 of Arms A, B, and C, and Cycle 3 of Arm D (to respect the duration of evaluation for DLTs), trial treatment of pembrolizumab may be administered up to 3 days before or after the scheduled Day 1 of each cycle due to administrative reasons (up to 3 days after treatment allocation is permitted).

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

5.2.4 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

In Part 1, treatment allocation will occur centrally using IVRS/IWRS. Subjects enrolled in the trial will be allocated to treatment by nonrandom assignment using the IVRS/IWRS. In Part 2, treatment allocation will occur by random assignment using IVRS/IWRS if more than 1 schedule is being evaluated.

Enrollment will alternate between arms, and will also be guided by the occurrence of toxicities, following dose escalation and confirmation rules based on the mTPI design.

5.4 Stratification

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

5.5 Concomitant Medications/Vaccinations (Allowed & Prohibited)

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

5.5.1 Acceptable Concomitant Medications

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

All concomitant medications taken by the subject from the date of first dose of trial treatment through 30 days after the last dose of trial treatment should be recorded. Concomitant medications administered after 30 days after the last dose of trial treatment should be recorded for SAEs and ECIs as defined in Section 7.2.

Bisphosphonate or denosumab therapy is allowed as long as it is begun at least 2 weeks prior to randomization. If started after randomization, it will be determined to be consistent with symptomatic progression or disease and clinical progression will be declared at that time followed by discontinuation of study treatment.

5.5.2 Prohibited Concomitant Medications

Subjects are prohibited from receiving the following therapies during the Screening and Treatment Phase (including retreatment for post-complete response relapse) of this trial:

- Antineoplastic systemic chemotherapy or biological therapy
- Immunotherapy not specified in this protocol (with the exception of denosumab as noted above in Section 5.5.1)
- Chemotherapy not specified in this protocol
- Investigational agents other than pembrolizumab and MK-8353
- Radiation therapy
    - Note: Radiation therapy to a symptomatic solitary lesion or to the brain may be considered on an exceptional case by case basis after consultation with Sponsor. The subject must have clear measurable disease outside the radiated field. Administration of palliative radiation therapy will be considered clinical progression for the purposes of determining PFS.
- 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, Bacille Calmette-Guerin, and typhoid (oral) 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.
- Systemic glucocorticoids for any purpose other than to modulate symptoms from an AE of suspected immunologic etiology. The use of physiologic doses of corticosteroids may be approved after consultation with the Sponsor.
    - Note: Inhaled steroids are allowed for management of asthma.

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 describes other medications that are prohibited in this trial.

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

5.5.2.1 Prohibited Concomitant Medications for MK-8353

Inhibitors/inducers/substrates of the cytochrome P450 enzymes

CYP3A4 inhibitors/inducers/substrates are listed below. The subject must not take the treatments listed in Table 8 during the trial after the start of the study treatment. Because this list is not comprehensive, the investigator should use his/her medical judgment when a subject presents with a medication not on the list or call the Sponsor Clinical Director for clarification.

Subjects who, in the assessment of 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.

Table 8 Medications, Supplements, and Other Substances Prohibited During the Trial

Strong 3A4 Inducers[a,d]	Strong CYP3A4 Inhibitors[b,d]	Moderate CYP3A4 Inhibitors[b,d]	CYP3A4 or CYP2C8 Substrates With Narrow Therapeutic Range[c,d]	Other
carbamazepine phenobarbital phenytoin rifabutin rifampin troglitazone	indinavir nelfinavir ritonavir clarithromycin itraconazole ketoconazole nefazodone atazanavir saquinavir telithromycin alprazolam cannabis (oral; IV)	amprenavir aprepitant diltiazem erythromycin fluconazole fosamprenavir verapamil grapefruit juice star fruit juice	alfentanil[c] ergotamine[c] diergotamine[c] cyclosporine[c] fentanyl[c] pimozide[c] quinidine[c] sirolimus[c] tacrolimus[c] astemizole[c,e] terfenadine[c,e] cisapride[c,e] paclitaxel[c] repaglinide[c] lurasidone[c]	Any chemotherapy Any biologic therapy Any hormonal therapy Investigational drugs Radiation therapy (except palliative radiation to isolated lesions after discussion with the Sponsor)

CYP = cytochrome P450.

[a] Strong 3A4 inducers listed are those that decrease plasma AUC values of 3A4 substrates by 30% or higher.

[b] Moderate inhibitors are defined as causing a ≥2 but <5 fold increase in the AUC values or 50% to 80% decrease in clearance of sensitive CYP3A substrates when the inhibitors were given at the highest approved dose and the shortest dosing interval in clinical evaluations. Strong inhibitors are defined as causing a >5 fold increase in the plasma AUC values or more than 80% decrease in clearance.

[c] CYP3A4 and CYP2C8 substrates with narrow therapeutic range refers to drugs whose exposure response indicates that increases in their exposure levels by the concomitant use of CYP3A4 or CYP2C8 inhibitors may lead to serious safety concerns. For specific information, refer to the Classification of Substrates tables available at: http://www.fda.gov/Drugs/developmentapprovalprocess/developmentresources/druginteractionslabeling/ (then click "Drug Development and Drug Interactions: Table of Substrates, Inhibitors and Inducers")

[d] Compiled from the in vivo inhibitors and inducers, inhibitor classification, and substrate classification tables available at: http://www.fda.gov/Drugs/developmentapprovalprocess/developmentresources/druginteractionslabeling/ (then click "Drug Development and Drug Interactions: Table of Substrates, Inhibitors and Inducers") and from the CYP450 drug interaction table (accessed June 2012) available at: http://medicine.iupui.edu/clinpharm/ddis/.aspx.

[e] Not available in the United States, and limited availability in the European Union.

CYP cytochrome P450; IV intravenously.

MK-8353 is a competitive and irreversible metabolism-dependent inhibitor of cytochrome P450 (CYP) 3A4, a substrate of CYP3A4, and a direct competitive inhibitor of CYP2C8. As such, concomitant use of other drugs that are identified in Table 8 as strong inducers, strong or moderate inhibitors, or substrates (characterized with a narrow therapeutic range) of CYP3A4 or CYP2C8, is **prohibited** while the subject is enrolled in this study.

If the use of a CYP3A4 or CYP2C8 medication listed in Table 8 is medically necessary, and an alternate therapeutic agent is not available, then the subject must discontinue treatment with MK-8353.

MK-8353 may potentially inhibit the activity of other CYP3A4 or CYP2C8 substrates that are not identified as prohibited in Table 8. Caution and close drug monitoring is strongly advised when MK-8353 is administered concomitantly with other CYP3A4 or CYP2C8

substrates. Refer to Table 8 for more detailed information regarding adverse effects of CYP3A4 substrates with a narrow therapeutic range.

Investigators should check an actively updated list of drugs that are clinically relevant substrates, inducers or inhibitors of cytochrome P450, including CYP3A4 (http://medicine.iupui.edu/clinpharm/ddis/table.asp) as well as the product labeling of these compounds for reference.

5.5.2.2 Prohibited Concomitant Medications for Pembrolizumab

Glucocorticoids (inhaled steroids as part of a stable regimen for the treatment of asthma/chronic obstructive pulmonary disease) are permitted for any purpose other than to modulate symptoms from an AE. The use of physiologic doses of corticosteroids may be approved after consultation with the Sponsor. Additionally, a short limited course of steroids may be used to treat medical conditions and/or AEs during the study after Sponsor notification and consultation.

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

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

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

5.6 Rescue Medications & Supportive Care

5.6.1 Supportive Care Guidelines

5.6.1.1 Supportive Care Guidelines for MK-8353

Medications required to treat AEs or concurrent illnesses other than those prohibited in Table 8 are allowed during the study. These include antiemetics, growth factors, and other supportive care medications. Contraceptive medications as described in Section 5.1 are allowed.

Bisphosphonates are allowed for subjects with lytic bone metastases. Antiemetics, including serotonin-receptor antagonists, metoclopramide, prochlorperazine, or thiethylperazine are allowed. Aprepitant is a CYP3A4 inhibitor and should not be used in the study.

Skin rash has been observed in subjects treated with inhibitors of the MAPK pathway and is expected in the current study. It may be representative of an on-target effect of the study medication. Appropriate clinical management of skin rash may be utilized as clinically indicated. An algorithm based on dermatology best practices for other contemporary targeted agents that cause skin toxicity is offered below as guidance to manage skin toxicities seen in subjects being treated on this protocol. The algorithm suggests a step-wise approach to rash management.

- If the rash is NCI CTCAE Grade 1, consider starting with topical steroids (eg, betamethasone), topical antibiotics such as clindamycin gel, or no treatment if the subject is asymptomatic. Use of topical steroid cream with higher potency may be considered early in subjects with moderate rash on the face.

- If the rash is NCI CTCAE Grade 2, continue topical steroid or pimecrolimus cream and consider adding an oral tetracycline or a similar agent.
- If the rash reaches NCI CTCAE Grade 3 or above, dose interruption and/or dose reduction, coupled with the addition of topical steroids is recommended.
- Pruritus of any grade may be treated with an antihistamine, such as diphenhydramine or hydroxyzine hydrochloride.
- Xerosis can be treated with classical emollients.
- Secondary infection may complicate or worsen skin toxicity. To reduce the likelihood of nasal infection, intranasal mupirocin may be considered. Infected rash may be treated with a short course of an oral tetracycline, such as doxycycline. Sun exposure should be avoided in subjects receiving doxycycline or other tetracycline antibiotics.
- If there is a clinical diagnosis of impetigo, or an infection with Staphylococcus aureus is confirmed, topical mupirocin may be used. Infected lesions suspected to be treatment-resistant should be cultured. If there is no improvement after 2 weeks of treatment, therapy for the rash should be considered ineffective and discontinued.
- Additionally, oral antihistamines (nonsedative) may also be considered for the treatment of Grade 1 to 3 rashes. Oral steroids may be considered for Grade 3 rash.

Every medication taken by the subject during the trial and the reason for use must be recorded in the electronic case report form (eCRF). Note that the use of any concomitant medication must relate to the documented medical history, prophylaxis, or an AE of the subject.

Subjects will be permitted to receive appropriate supportive care measures as deemed necessary by the treating physician including but not limited to the items outlined below:

- **Diarrhea**: diarrhea should be treated promptly with appropriate supportive care, including loperamide. Subjects should be instructed to begin taking loperamide at the first sign of: 1) poorly formed or loose stool, 2) occurrence of more bowel movements than usual in one day, or 3) unusually high volume of stool. Loperamide should be taken in the following manner: 4 mg at first onset of diarrhea, then 2 mg after each unformed stool. The daily dose of loperamide should not exceed 16 mg/day. Loperamide should be deferred if blood or mucus is present in the stool or if diarrhea is accompanied by fever. In this setting, appropriate diagnostic microbiologic specimens should be obtained to exclude an infectious etiology. Subjects should be also advised to drink liberal quantities of clear fluids to help prevent dehydration. Supportive care with steroids (as described in Section 5.6.2) or other CYP3A4 inhibitor/inducer /substrate according to institutional guidelines in the context of standard of care for diarrhea are permitted.

- **Nausea/vomiting:** nausea and vomiting should be treated aggressively. After an initial occurrence of Grade 2 or higher nausea or vomiting, strong consideration should be given to the administration of prophylactic antiemetic therapy according to

standard institutional practice. Subjects should be strongly encouraged to maintain liberal oral fluid intake.

- **Anemia:** transfusions and/or erythropoietin may be utilized as clinically indicated per ASCO/American Society of Hematology (ASH) guidelines after the first cycle of combination therapy for the treatment of anemia, but should be clearly noted as concurrent medications.

- **Neutropenia:** colony stimulating factors including G-CSF, pegylated G-CSF or GM-CSF according to ASCO/ASH guidelines after the first cycle of combination therapy. Colony stimulating factors can be administered for the management of neutropenia toxicities after Cycle 1.

- **Thrombocytopenia:** transfusion of platelets may be used per ASCO/ASH guidelines if clinically indicated.

- **Anti-infectives**: subjects with a documented infectious complication should receive oral or IV antibiotics or other anti-infective agents as considered appropriate by the treating investigator for a given infectious condition, according to standard institutional practice.

5.6.2 Supportive Care Guidelines for Pembrolizumab

Subjects should receive appropriate supportive care measures as deemed necessary by the treating investigator. Suggested supportive care measures for the management of adverse events with potential immunologic etiology are outlined along with the dose modification guidelines in Section 5.2.2.2, Table 5. Where appropriate, these guidelines include the use of oral or IV treatment with corticosteroids, as well as additional anti-inflammatory agents if symptoms do not improve with administration of corticosteroids. Note that several courses of steroid tapering may be necessary as symptoms may worsen when the steroid dose is decreased. For each disorder, attempts should be made to rule out other causes such as metastatic disease or bacterial or viral infection, which might require additional supportive care. The treatment guidelines are intended to be applied when the investigator determines the events to be related to pembrolizumab.

Note: If after the evaluation of the event, it is determined not to be related to pembrolizumab, the investigator does not need to follow the treatment guidance. Refer to Table 5 in Section 5.2.2.2 for guidelines regarding dose modification and supportive care.

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

5.7 Diet/Activity/Other Considerations

5.7.1 Diet

Foods that are CYP3A inhibitors must not be consumed during the study. Grapefruit and star fruit are known to be CYP3A inhibitors, and should not be consumed for 2 weeks before the first dose of MK-8353 and for the entire duration of the study. Consumption of CYP3A4

inhibitors, such as grapefruit juice, may significantly increase the levels of MK-8353 and cause increased toxicity. St. John's Wort is a CYP3A inducer, and the consumption of St. John's Wort or products containing St. John's Wort may reduce the levels of MK-8353. A partial list of CYP3A inhibitors is provided in Section 5.5.2.1.

5.7.2 Contraception

MK-8353 and/or pembrolizumab may have adverse effects on a fetus in utero. Furthermore, it is not known if MK-8353 and/or pembrolizumab have transient adverse effects on the composition of sperm.

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

Female subjects will be considered of nonreproductive potential if they are either:

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

OR

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

OR

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

Female and male subjects of reproductive potential must agree to avoid becoming pregnant or impregnating a partner, respectively, while receiving MK-8353 and/or pembrolizumab and for 120 days after the last dose. Subjects must comply with one of the following:

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

OR

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

Acceptable methods of contraception are[‡]:

Single method (one of the following is acceptable):

- Intrauterine device
- Vasectomy of a female subject's male partner
- Contraceptive rod implanted into the skin

Combination method (requires use of 2 of the following):

- Diaphragm with spermicide (cannot be used in conjunction with cervical cap/spermicide)

- Cervical cap with spermicide (nulliparous women only)
- Contraceptive sponge (nulliparous women only)
- Male condom or female condom (cannot be used together)
- Hormonal contraceptive: oral contraceptive pill (estrogen/progestin pill or progestin-only pill), contraceptive skin patch, vaginal contraceptive ring, or subcutaneous contraceptive injection

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

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

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

5.7.3 Use in Pregnancy

If a subject inadvertently becomes pregnant while on treatment with MK-8353 and/or pembrolizumab, the subject will be immediately discontinued from treatment. The site will contact the subject at least monthly and document the subject's status until the pregnancy has been completed or terminated. The outcome of the pregnancy will be reported to the Sponsor without delay and within 24 hours if the outcome is a serious adverse experience (eg, death, abortion, congenital anomaly, or other disabling or life-threatening complication to the mother or newborn). The study investigator will make every effort to obtain permission to follow the outcome of the pregnancy and report the condition of the fetus or newborn to the Sponsor. If a male subject impregnates his female partner, the study personnel at the site must be informed immediately and the pregnancy must be reported to the Sponsor and followed as described in Section 7.2.

5.7.4 Use in Nursing Women

It is unknown whether MK-8353 and/or pembrolizumab are 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

5.8.1 Discontinuation of Treatment

Discontinuation of treatment does not represent withdrawal from the trial.

As certain data on clinical events beyond treatment discontinuation may be important to the study, they must be collected through the subject's last scheduled follow-up, even if the subject has discontinued treatment. Therefore, all subjects who discontinue trial treatment prior to completion of the treatment will still continue to participate in the trial as specified in Section 6.0 and Section 7.1.5.4.

Subjects may discontinue treatment at any time for any reason or be dropped from treatment at the discretion of the investigator should any untoward effect occur. In addition, a subject may be discontinued from treatment by the investigator or the Sponsor if treatment is inappropriate, the trial plan is violated, or for administrative and/or other safety reasons. Specific details regarding procedures to be performed at treatment discontinuation are provided in Section 7.1.4 Other Procedures.

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

- The subject or subject's legally acceptable representative requests to discontinue treatment.
- The subject interrupts trial medication administration due to treatment-related toxicity for more than 14 consecutive days in Cycle 1, or 21 days in ≥Cycle 2.
- The subject has a medical condition or personal circumstance that, in the opinion of the investigator and/or Sponsor, places the subject at unnecessary risk from continued administration of study drug.
- The subject has a confirmed positive serum pregnancy test.
- The subject presents clinical progression or has confirmed radiological disease progression per RECIST 1.1 criteria as assessed by the investigator (exception if the Sponsor approves treatment continuation).
- The subjects present unacceptable adverse experiences as described in Section 5.2.1.5.
- The subject is noncompliant with trial treatment or procedure requirements.
- The investigator decides to withdraw the subject from treatment.
- The subject has completed 35 treatments (approximately 2 years) with pembrolizumab.

After treatment discontinuation, each subject will be followed for 30 days for AE monitoring. Subjects will be monitored for SAEs for 90 days after treatment discontinuation, 30 days if the subject initiates new anticancer therapy less than 30 days after study treatment discontinuation, or the day new anticancer therapy is initiated if between 30 days and 90 days after study treatment discontinuation. Subjects with an ongoing AE of Grade >1 at the time of treatment discontinuation will be followed until resolution of the AE to Grade 0 to 1, until considered stable by the treating physician, or until beginning a new anticancer therapy, whichever occurs first.

Subjects who discontinue treatment for reasons other than confirmed disease progression will have posttreatment follow up for disease status until disease progression, initiating a new anticancer therapy, withdrawing consent for study participation, or becoming lost to follow up.

After confirmed disease progression each subject will be contacted by telephone approximately every 12 weeks (84 ±7 days) for survival until withdrawal of consent to participate in the study, becoming lost to follow up, death, or end of the study, whichever occurs first.

5.8.1.1 Discontinuation of Trial Treatment After Disease Response

Subjects who attain an investigator-determined confirmed disease response of complete response (CR) may discontinue study treatment (MK-8353 and pembrolizumab) after receiving at least 2 additional cycles of MK-8353 and pembrolizumab, as applicable, beyond the date when the initial response was declared and after a total of at least 8 cycles of MK-8353 and pembrolizumab, as applicable. The decision to continue or discontinue study treatment after confirmed disease response is at the investigator's discretion.

After treatment discontinuation, each subject will be followed for 30 days for AE monitoring. Subjects will be monitored for SAEs for 90 days after treatment discontinuation, 30 days if the subject initiates new anticancer therapy less than 30 days after study treatment discontinuation, or the day new anticancer therapy is initiated if between 30 days and 90 days after study treatment discontinuation. Subjects with an ongoing AE of Grade >1 at the time of treatment discontinuation will be followed until resolution of the AE to Grade 0 to 1, until considered stable by the treating physician, or until beginning a new anticancer therapy, whichever occurs first.

Subjects will have posttreatment follow up for disease status until disease progression, initiating a new anticancer therapy, withdrawing consent for study participation, or becoming lost to follow up.

After confirmed disease progression each subject will be contacted by telephone approximately every 12 weeks (84 ±7 days) for survival until withdrawal of consent to participate in the study, becoming lost to follow up, death, or end of the study, whichever occurs first.

Subjects who discontinue study treatment after confirmed CR may be eligible to be re-treated with study treatment at the discretion of the investigator, if all of the following conditions are met:

- The subject experiences investigator-determined confirmed disease progression;
- No other anticancer therapy was administered since the last dose of study treatment;
- The subject meets the safety parameters listed in the Inclusion/Exclusion criteria; and
- The study is ongoing.

Subjects will resume study treatment in the same Part of the study and at the same dose of MK-8353 to which they were initially allocated and at the 200 mg fixed dose of pembrolizumab. The criteria for withdrawal and discontinuation after re-treatment are as

outlined in Section 5.8. Response or progression after re-treatment will not be counted toward the secondary and exploratory efficacy endpoints, ORR, or PFS of this study.

For subjects who are discontinued from treatment but continue to be monitored in the trial, see Section 6.0 and Section 7.1.5.4 for those procedures to be completed at each specified visit.

5.8.2 Withdrawal from the Trial

A subject must be withdrawn from the trial if the subject or subject's legally acceptable representative withdraws consent from the trial.

If a subject withdraws from the trial, they will no longer receive treatment or be followed at scheduled protocol visits.

Specific details regarding procedures to be performed at the time of withdrawal from the trial including the procedures to be performed should a subject repeatedly fail to return for scheduled visits and/or if the study site is unable to contact the subject, as well as specific details regarding withdrawal from Future Biomedical Research are outlined in Section 7.1.4 Other Procedures.

5.9 Subject Replacement Strategy

A subject who discontinues from trial treatment or withdraws from the trial during or after Cycle 2 (refer to Section 5.2.1.6 for subject replacement during Cycle 1) will not be replaced.

5.10 Beginning and End of the Trial

The overall trial begins when the first subject signs the informed consent form. The overall trial ends when the last subject completes the last study-related phone-call or visit, withdraws from the trial or is lost to follow-up (ie, the subject is unable to be contacted by the investigator).

5.11 Clinical Criteria for Early Trial Termination

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

1. Quality or quantity of data recording is inaccurate or incomplete
2. Poor adherence to protocol and regulatory requirements
3. Incidence or severity of adverse drug reaction in this or other studies indicates a potential health hazard to subjects
4. Plans to modify or discontinue the development of the study drug

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

6 TRIAL FLOW CHART

MK-8353 + Pembrolizumab in Part 1 (Arms A and B and optional Arm C) and Part 2												
	Screening	**Treatment Phase**						**Tumor Assessment**	**End of Treatment**	**Posttreatment Follow-up Phase [9]**		
		Cycle 1			Cycle 2 4		Cycle 5 and all Subsequent Cycles	Every 9 weeks	Discontinuation	Safety Follow Up Phase		Survival Follow Up Phase[12]
	Up to 28 days prior to Day 1 Cycle 1	Day 1	Day 8	Day 15	Day 1[1]	Day 15	Day 1		At Treatment Discontinuation	30 days after the last dose	90 days after the last dose	Approximately every 12 weeks post discontinuation
Scheduling Window (Days) [1]	28 to 1		±3	±3	±3[1]	±3	±3	±7		±7	±7	±7
Administrative Procedures												
Informed Consent [2]	X											
Informed Consent for Optional On treatment Tumor Biopsy [2, 24]	X											
Informed Consent for Optional Future Biomedical Research [2, 24]	X											
Inclusion/Exclusion Criteria [2]	X											
Subject Identification Card [3]	X											
Medical History [2]	X											
Prior Oncology Treatment History [2]	X											
Prior Medications [2, 4]	X											
Concomitant Medications [2, 4]	X	X	X	X	X	X	X		X	X		
Clinic Procedures/Assessments												
Physical Examination [5]	X[5]	X			X		X		X[5]	X		
12 Lead Electrocardiogram [5, 6]	X											
Vital Signs [5, 7]	X	X [5]		X	X		X		X	X		

MK-8353 + Pembrolizumab in Part 1 (Arms A and B and optional Arm C) and Part 2												
	Screening	**Treatment Phase**						**Tumor Assessment**	**End of Treatment**	**Posttreatment Follow-up Phase [9]**		
		Cycle 1			Cycle 2 4		Cycle 5 and all Subsequent Cycles	Every 9 weeks	Discontinuation	Safety Follow Up Phase		Survival Follow Up Phase[12]
	Up to 28 days prior to Day 1 Cycle 1	Day 1	Day 8	Day 15	Day 1[1]	Day 15	Day 1		At Treatment Discontinuation	30 days after the last dose	90 days after the last dose	Approximately every 12 weeks post discontinuation
Scheduling Window (Days) [1]	28 to 1		±3	±3	±3[1]	±3	±3	±7		±7	±7	±7
ECOG Performance Status [5]	X	X [5]			X		X		X	X		
Dispense MK 8353 [8]		X			X		X					
Pembrolizumab Infusion [9]		X			X		X					
Adverse Events Reporting [10]	X	X	X	X	X	X	X		X	X	X	
Tumor Imaging and RECIST 1.1 Response Assessment [11]	X							X	X			
Survival Status [12]		←									→	X
Laboratory Procedures/Assessments												
Archival or Newly Obtained Tumor Tissue Collection for Mutation Analysis and Molecular Profiling [13]	X											
Blood for Genetic Analyses [1, 14]		X										
Blood for RNA Analyses [15]		X			X		X		X			
Blood for Plasma Biomarker Analyses [15]		X			X		X		X			
Blood for Serum Biomarkers [15]		X			X		X		X			
Hematology [5, 16]	X	X	X	X	X	X	X		X	X		
Urinalysis [5, 17]	X											

MK-8353 + Pembrolizumab in Part 1 (Arms A and B and optional Arm C) and Part 2												
	Screening	**Treatment Phase**						**Tumor Assessment**	**End of Treatment**	**Posttreatment Follow-up Phase [9]**		
		Cycle 1			Cycle 2 4		Cycle 5 and all Subsequent Cycles	Every 9 weeks	Discontinuation	Safety Follow Up Phase		Survival Follow Up Phase[12]
	Up to 28 days prior to Day 1 Cycle 1	Day 1	Day 8	Day 15	Day 1[1]	Day 15	Day 1		At Treatment Discontinuation	30 days after the last dose	90 days after the last dose	Approximately every 12 weeks post discontinuation
Scheduling Window (Days) [1]	28 to 1		±3	±3	±3[1]	±3	±3	±7		±7	±7	±7
Chemistry [5, 18]	X	X	X	X	X	X	X		X	X		
Prothrombin Time (PT)/International Normalized Ratio (INR) and Activated Partial Thromboplastin Time (aPTT) [19]	X											
Tumor Markers (CEA, CA 125 and CA 19 9, as appropriate)	X	X			X		X		X	X		
Serum or Urine Pregnancy Test if applicable [20]	X	X										
HIV/Hepatitis Screen [21]	X											
Thyroid Function (T3 or FT3, T4 or FT4 and TSH) [22]	X	X			X		X			X		
Anti pembrolizumab Antibodies (Part 1 only) [23]		X			X		X			X		
Optional On treatment Tumor Biopsy [2, 24]						X						
Pharmacokinetics Evaluations												
Blood for MK 8353 PK assay (Arms A and B)[25]		X	X	X	X		X					
Blood for MK 8353 PK assay (Arm C) [25]		X	X	X								

MK-8353 + Pembrolizumab in Part 1 (Arms A and B and optional Arm C) and Part 2												
	Screening	**Treatment Phase**						**Tumor Assessment**	**End of Treatment**	**Posttreatment Follow-up Phase [9]**		
		Cycle 1			Cycle 2 4		Cycle 5 and all Subsequent Cycles	Every 9 weeks	Discontinuation	Safety Follow Up Phase		Survival Follow Up Phase[12]
	Up to 28 days prior to Day 1 Cycle 1	Day 1	Day 8	Day 15	Day 1[1]	Day 15	Day 1		At Treatment Discontinuation	30 days after the last dose	90 days after the last dose	Approximately every 12 weeks post discontinuation
Scheduling Window (Days) [1]	28 to 1		±3	±3	±3[1]	±3	±3	±7		±7	±7	±7
Blood for Pembrolizumab PK assay (Part 1 only) [26]		X			X		X			X		

1. Visits should occur within the prespecified days window (eg, +/ 3 days), except Cycle 2 Day 1, which should occur with a window of +3 days.
2. Screening procedures to be performed within 28 days prior C1D1, unless otherwise noted. Informed consent may be obtained more than 28 days prior to C1D1 to allow for tumor tissue collection.
3. Subject Identification Card must be given to subject at the start of study and must be collected when the subject is no longer participating in any portion of the study.
4. Record medications taken 4 weeks prior to C1D1 and all medications taken up to and including 30 days after the last dose of study drug or the End of Treatment (whichever is later). Refer to inclusion/exclusion criteria for prohibited medications and washout periods.
5. Must be performed within 3 days prior to Day 1 of each cycle. Physical examination, ECOG Performance Status, ECG, vital signs, and screening laboratory tests must be performed within 3 days prior to C1D1. It is not necessary to repeat C1D1 testing if the Screening testing was performed within 7 days prior to C1D1. Full physical examination will be performed at the Screening Visit and at the Treatment Discontinuation Visit. Directed physical examination will be done as indicated at all other visits.
6. Perform standard 12 lead ECG reporting ventricular rate, PR and QRS duration, and QT/QTcF intervals prior to any blood collections or other study procedures.
7. Vital signs include blood pressure, pulse rate, and respiratory rate while sitting; temperature, height (at screening only), and weight.
8. After Cycle 1, MK 8353 may be dispensed up to 3 days prior to the cycle start to coincide with the physical exam. In Arm A, MK 8353 will be administered continuously, twice a day. In Arm B, MK 8353 will be administered continuously, once a day. In optional Arm C, MK 8353 will be administered 1 week on/1 week off, orally, qd, on Days 1 to 7, Days 15 to 21, and Days 29 to 35 of a 42 day period (corresponding to 2 cycles of 21 days) until Day 1 of Cycle 3, when this 42 day period will start again. Study drug may only be dispensed after the treating physician has confirmed the subject will continue on to the next cycle. Each cycle is 21 days. Subjects may receive treatment for up to 35 cycles.
9. Pembrolizumab will be administered via IV infusion on Day 1 of each cycle (except for Cycle 1 [MK 8353 monotherapy run in] of optional Arm D). Refer to Figure 2 for dosing instructions. Each cycle is 21 days (except for Cycle 1 [MK 8353 monotherapy run in] of optional Arm D). Subjects may receive treatment for up to 35 cycles.
10. AEs and SAEs will be recorded from the time of treatment allocation. All AEs and SAEs that occur after the consent form is signed but before treatment allocation must be reported by the investigator if they cause the subject to be excluded from the trial, or are the result of a protocol specified intervention, including but not limited to washout or discontinuation of usual therapy or a study procedure. After treatment discontinuation, each subject will be followed for 30 days for AE monitoring. Subjects will be monitored for SAEs for 90 days after treatment discontinuation, 30 days if the subject initiates new anticancer therapy less than 30 days after study treatment discontinuation, or until the day new anticancer therapy is initiated if between 30 days and 90 days after study treatment discontinuation. Subjects with an ongoing AE of

Grade >1 at the time of treatment discontinuation will be followed until resolution of the AE to Grade 0 to 1, until considered stable by the treating physician, or until beginning a new anticancer therapy, whichever occurs first.

11. Baseline radiology scans of chest, abdomen, and pelvis, and all known tumor sites (if evaluable by imaging) must be obtained within 28 days prior to C1D1 and must be repeated every 9 weeks (±7 days) from C1D1. Confirmatory scans to confirm progressive disease should be obtained at least 4 to 5 weeks after the documented response. Imaging must be obtained at the End of Treatment Visit at discontinuation unless done within the previous 4 weeks. Imaging is to be continued if subject discontinues study for reason other than progressive disease.
12. After confirmed disease progression, subjects will be contacted by telephone approximately every 12 weeks for survival until withdrawal of consent to participate in the study, becoming lost to follow up, death, or end of the study, whichever occurs first. 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 participants that have a death event previously recorded).
13. Tumor tissue (archival or newly obtained biopsy) will be required at Screening upon signing the informed consent for the study. This sample will be assessed to collect information on the RAS/RAF and pMMR/dMMR (MSI) tumor mutation status and exploratory biomarkers for all subjects enrolled in the study. Sample can be evaluated for mutation by local laboratory testing, or sent to central laboratory for analysis (if cannot be performed by local laboratory). Tissue will be also sent to central laboratory for biomarker analysis and leftover tissue may be saved for FBR if the subject signs the FBR consent.
14. This sample should be drawn for planned analysis of the association between genetic variants in DNA and drug response. This sample will not be collected at that site if there is either a local law or regulation prohibiting collection, or if the IRB/IEC does not approve the collection of the sample for these purposes. If the sample is collected, leftover extracted DNA will be stored for FBR if the subject signs the FBR consent. If the planned genetic analyses are not approved, but FBR is approved and consent is given, this sample will be collected for the purpose of FBR.
15. Whole blood samples should be collected predose at Cycle 1, Cycle 2, Cycle 5, and again at discontinuation. Leftover specimens will be stored for FBR if the subject consents to FBR.
16. Hematology tests include complete blood count with 5 part differential and platelets. Hematology does not need to be repeated on C1D1 if Screening samples were obtained within 3 days of C1D1.
17. Urine dipstick or microscopic urinalysis may be performed according to site SOP. Urine dipstick includes pH, protein, glucose, leukocyte, esterase, ketones, and nitrite. Mandatory microscopic urinalysis will be performed if the dipstick results are abnormal. Microscopic analysis includes white blood cell count, red blood cell count, epithelial cells and casts.
18. Serum Chemistry tests include sodium, potassium, calcium, phosphate, chloride, bicarbonate/CO_2 (if performed in region), BUN, creatinine (cystatin C could be evaluated if creatinine is abnormal), SGOT (AST), SGPT (ALT), total proteins, total bilirubin (direct bilirubin if abnormal), albumin, alkaline phosphatase, glucose, uric acid, amylase, lipase, lactate dehydrogenase (LDH), and γ glutamyltransferase (GGT). Serum chemistry does not need to be repeated on C1D1 if screening samples were obtained within 3 days of C1D1. Cystatin C may be conducted by central vendor only if analysis was not available from local study site laboratory.
19. Coagulation factors (PT/INR and aPTT) should be tested as part of the screening procedures for all subjects. Furthermore, any subject receiving anticoagulant therapy should have coagulation factors monitored closely throughout the trial.
20. For women of reproductive potential, a urine pregnancy test will be performed at Screening and within 72 hours prior to the first dose of study treatment. If a urine pregnancy test cannot be confirmed as negative, a serum pregnancy test is required and must be negative. Monthly pregnancy testing should be conducted as per local regulations where applicable.
21. HIV testing should include HIV Type 1 and Type 2 (eg, HIV 1/ 2 antibody screening test and evaluation of HIV viral load as needed). Hepatitis testing should include HCV, RNA (qualitative), or Hepatitis C antibody, and HBsAg.
22. Samples for thyroid function testing should be collected on Day 1 of Cycle 1 and on Day 1 of Cycle 2. Following Cycle 2, testing will be performed every other cycle (ie, Cycles 1, 2, 4, 6, etc., with a window of +/ 3 days) and at the Posttreatment Safety Follow up Visit. Analysis of T3 or FT3, T4 or FT4, and TSH will be performed by the local study site laboratory (conducted by central vendor only if analysis was not available from local study site laboratory).
23. In Part 1 only, blood for pembrolizumab antidrug antibodies should be collected prior to dosing on Day 1 of Cycles 1, 2, 4, and 8, and every 4 cycles thereafter, and at the 30 day Posttreatment Safety Follow up Visit. Please refer to the procedure manual for detailed sampling time points.
24. Optional on treatment tumor biopsy will be performed on Day 15 of Cycle 2 if the informed consent for optional on treatment biopsy sample has been obtained. Leftover tissue may also be saved for FBR if the subject signs the FBR consent.

25. Procedures for collection of PK samples and precise time points are described in the Procedures Manual. Cycle 1 Day 1 (Arms A, B, and C) and Cycle 2 Day 1 (Arms A and B only) samples for MK 8353 PK testing should be collected prior to dosing, and 1 hour, 2 hours, 4 hours, and 8 hours after drug administration of MK 8353 (+/ 10 minutes); prior to dosing on Cycle 1 Day 8 (Arms A, B and C); prior to dosing on Cycle 1 Day 15 (Arms A, B, and C); prior to dosing on Cycle 4 Day 1 (Arms A and B); and prior to dosing on Cycle 8 Day 1 (Arms A and B). If the sample day falls on a weekend or a holiday, please consult the Sponsor for alternate sample collection times.
26. Procedures for collection of PK samples and precise time points are described in the Procedures Manual. Predose (trough) PK samples for pembrolizumab will be collected within 24 hours before infusion in Cycles 1, 2, 4, and 8 and every 4 cycles thereafter, 30 days after discontinuation of study drug (or until the subject starts new anticancer therapy). Postdose (peak) PK samples will be drawn within 30 minutes after end of pembrolizumab infusion in Cycles 1 and 8.

AE adverse event; ALT alanine aminotransferase; AST aspartate aminotransferase; BUN blood urea nitrogen; C1D1 Cycle 1 Day 1; CR complete response; CT computed tomography; ECG electrocardiogram; ECOG Eastern Cooperative Oncology Group; FBR future biomedical research; min minute; PD progressive disease; pERK phosphorylated extracellular regulated kinase; PGt pharmacogenetic; PK pharmacokinetic; PR interval between the P wave and the QRS wave; QRS interval from onset of the Q wave to end of the S wave; QT interval from onset of the QRS complex to end of the T wave; QTcF QT interval corrected for heart rate; SAE serious adverse event; SGOT serum glutamic oxaloacetic transaminase; SGPT serum glutamic pyruvic transaminase.

MK-8353 + Pembrolizumab in Part 1 (optional Arm D) and Part 2 (optional Arm D)													
	Screening	**Treatment Phase**						**Tumor Assessment**	**End of Treatment**	**Post-treatment Follow-Up Phase [9]**		
		Mono therapy Run In Cycle 1	Cycle 2			Cycle 3 4		Cycle 5 and all Subsequent Cycles	Every 9 weeks	Discontinuation	Safety Follow Up Phase		Survival Follow Up Phase[12]
	Up to 28 days Prior to Cycle 1 Day 1	Days 1 to 14	Day 1	Day 8	Day 15	Day 1[1]	Day 15	Day 1		At Treatment Discontinuation	30 days after the last dose	90 days after the last dose	Approximately every 12 weeks post discontinuation
Scheduling Window (Days) [1]	28 to 15		±3	±3	±3	±3[1]	±3	±3	±7		±7	±7	±7
Administrative Procedures													
Informed Consent [2]	X												
Informed Consent for Optional On treatment Tumor Biopsy [2, 24]	X												
Informed Consent for Optional Future Biomedical Research [2, 24]	X												
Inclusion/Exclusion Criteria[2]	X												
Subject Identification Card [3]	X												
Medical History [2]	X												
Prior Oncology Treatment History [2]	X												
Prior Medications [2, 4]	X												
Concomitant Medications [2, 4]	X		X	X	X	X	X	X		X	X		
Clinic Procedures/Assessments													
Physical Examination[5]	X[5]		X			X		X		X[5]	X		
12 Lead Electrocardiogram [5, 6]	X												

MK-8353 + Pembrolizumab in Part 1 (optional Arm D) and Part 2 (optional Arm D)													
	Screening	**Treatment Phase**							**Tumor Assessment**	**End of Treatment**	**Post-treatment Follow-Up Phase [9]**		
		Mono therapy Run In Cycle 1	Cycle 2			Cycle 3 4		Cycle 5 and all Subsequent Cycles	Every 9 weeks	Discontinuation	Safety Follow Up Phase		Survival Follow Up Phase[12]
	Up to 28 days Prior to Cycle 1 Day 1	Days 1 to 14	Day 1	Day 8	Day 15	Day 1[1]	Day 15	Day 1		At Treatment Discontinuation	30 days after the last dose	90 days after the last dose	Approximately every 12 weeks post discontinuation
Scheduling Window (Days) [1]	28 to 15		±3	±3	±3	±3[1]	±3	±3	±7		±7	±7	±7
Vital Signs [5, 7]	X		X [5]		X	X		X		X	X		
ECOG Performance Status [5]	X		X [5]			X		X		X	X		
Dispense MK 8353 [8]		X	X			X		X					
Pembrolizumab Infusion [9]			X			X		X					
Adverse Events Reporting [10]	X		X	X	X	X	X	X		X	X	X	
Tumor Imaging and RECIST 1.1 Response Assessment [11]	X								X	X			
Survival Status [12]		←										→	X
Laboratory Procedures/Assessments													
Archival or Newly Obtained Tumor Tissue Collection for Mutation Analysis and Molecular Profiling [13]	X												
Blood for Genetic Analyses [1, 14]			X										
Blood for RNA Analyses [15]			X			X		X		X			
Blood for Plasma Biomarker Analyses [15]			X			X		X		X			
Blood for Serum Biomarkers [15]			X			X		X		X			
Hematology [5, 16]	X		X	X	X	X	X	X		X	X		
Urinalysis [5, 17]	X												
Chemistry [5, 18]	X		X	X	X	X	X	X		X	X		

MK-8353 + Pembrolizumab in Part 1 (optional Arm D) and Part 2 (optional Arm D)													
	Screening	**Treatment Phase**						**Tumor Assessment**	**End of Treatment**	**Post-treatment Follow-Up Phase [9]**		
		Mono therapy Run In Cycle 1	Cycle 2			Cycle 3 4		Cycle 5 and all Subsequent Cycles	Every 9 weeks	Discontinuation	Safety Follow Up Phase		Survival Follow Up Phase[12]
	Up to 28 days Prior to Cycle 1 Day 1	Days 1 to 14	Day 1	Day 8	Day 15	Day 1[1]	Day 15	Day 1		At Treatment Discontinuation	30 days after the last dose	90 days after the last dose	Approximately every 12 weeks post discontinuation
Scheduling Window (Days) [1]	28 to 15		±3	±3	±3	±3[1]	±3	±3	±7		±7	±7	±7
Prothrombin Time (PT)/International Normalized Ratio (INR) and Activated Partial Thromboplastin Time (aPTT)[19]	X												
Tumor Markers (CEA, CA 125, and CA 19 9, as appropriate)	X		X			X		X		X	X		
Serum or Urine Pregnancy Test if applicable [20]	X		X										
HIV/Hepatitis Screen [21]	X												
Thyroid Function (T3 or FT3, T4 or FT4, and TSH) [22]	X		X			X		X			X		
Anti pembrolizumab Antibodies (Part 1 only) [23]			X			X		X			X		
Optional On treatment Tumor Biopsy [2, 24]							X						
Pharmacokinetics Evaluations													
Blood for MK 8353 PK assay [25]			X	X	X	X		X					
Blood for Pembrolizumab PK assay (Part 1 only)[26]			X			X		X			X		

1. Visits should occur within the prespecified days window (eg, +/ 3 days), except Cycle 3 Day 1, which should occur with a window of +3 days.
2. Screening procedures to be performed within 28 days prior C1D1, unless otherwise noted. Informed consent may be obtained more than 28 days prior to C1D1 to allow for tumor tissue collection.
3. Subject Identification Card must be given to subject at the start of study and must be collected when the subject is no longer participating in any portion of the study.
4. Record medications taken 4 weeks prior to C1D1 and all medications taken up to and including 30 days after the last dose of study drug or the End of Treatment (whichever is later). Refer to inclusion/exclusion criteria for prohibited medications and washout periods.
5. Must be performed within 3 days prior to Day 1 of each cycle. Physical examination, ECOG Performance Status, ECG, vital signs must be performed within 3 days prior to C1D1. It is not necessary to repeat C1D1 testing if the Screening testing was performed within 7 days prior to C1D1. Full physical examination will be performed at the Screening Visit and at the Treatment Discontinuation Visit. Directed physical examination will be done as indicated at all other visits.
6. Perform standard 12 lead ECG reporting ventricular rate, PR and QRS duration, and QT/QTcF intervals prior to any blood collections or other study procedures.
7. Vital signs include blood pressure, pulse rate, and respiratory rate while sitting; temperature, height (at screening only), and weight.
8. After Cycle 2, MK 8353 may be dispensed up to 3 days prior to the cycle start to coincide with the physical exam. In Arm D, MK 8353 will be administered continuously, once a day starting on Cycle 1 Day 1 to Day 14, prior to Cycle 2 Day 1. Study drug may only be dispensed after the treating physician has confirmed the subject will continue on to the next cycle. Each subsequent cycle is 21 days. Subjects may receive treatment for up to 36 cycles in optional Arm D.
9. Pembrolizumab will be administered via IV infusion beginning with Cycle 2 Day 1. Refer to Figure 2 for dosing instructions. Each cycle is 21 days (except for Cycle 1 of optional Arm D, which is a 14 day MK 8353 monotherapy run in cycle). Subjects may receive treatment for up to 36 cycles in optional Arm D.
10. AEs and SAEs will be recorded from the time of treatment allocation. All AEs and SAEs that occur after the consent form is signed but before treatment allocation must be reported by the investigator if they cause the subject to be excluded from the trial, or are the result of a protocol specified intervention, including but not limited to washout or discontinuation of usual therapy or a study procedure. After treatment discontinuation, each subject will be followed for 30 days for AE monitoring. Subjects will be monitored for SAEs for 90 days after treatment discontinuation, 30 days if the subject initiates new anticancer therapy less than 30 days after study treatment discontinuation, or until the day new anticancer therapy is initiated if between 30 days and 90 days after study treatment discontinuation. Subjects with an ongoing AE of Grade >1 at the time of treatment discontinuation will be followed until resolution of the AE to Grade 0 to 1, until considered stable by the treating physician, or until beginning a new anticancer therapy, whichever occurs first.
11. Baseline radiology scans of chest, abdomen, and pelvis, and all known tumor sites (if evaluable by imaging) must be obtained within 28 days prior to C1D1 and must be repeated every 9 weeks (±7 days) from C1D1. Confirmatory scans to confirm PD should be obtained at least 4 to 5 weeks after the documented response. Imaging must be obtained at the End of Treatment visit at discontinuation unless done within the previous 4 weeks. Imaging is to be continued if subject discontinues study for reason other than PD.
12. After confirmed disease progression each subject will be contacted by telephone approximately every 12 weeks for survival until withdrawal of consent to participate in the study, becoming lost to follow up, death, or end of the study, whichever occurs first. 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 participants that have a death event previously recorded).
13. Tumor tissue (archival or newly obtained biopsy) will be required at Screening upon signing the informed consent for the study. This sample will be assessed to collect information on the RAS/RAF and pMMR/dMMR (MSI) tumor mutation status and exploratory biomarkers for all subjects enrolled in the study. Sample can be evaluated for mutation by local laboratory testing, or sent to central laboratory for analysis (if cannot be performed by local laboratory). Tissue will be also sent to central laboratory for biomarker analysis and leftover tissue may be saved for FBR if the subject signs the FBR consent.
14. This sample should be drawn for planned analysis of the association between genetic variants in DNA and drug response. This sample will not be collected at that site if there is either a local law or regulation prohibiting collection, or if the IRB/IEC does not approve the collection of the sample for these purposes. If the sample is collected, leftover extracted DNA will be stored for future biomedical research if the subject signs the FBR consent. If the planned genetic analyses are not approved, but FBR is approved and consent is given, this sample will be collected for the purpose of FBR.
15. Whole blood samples should be collected predose at Cycle 2, Cycle 3, Cycle 5, and again at discontinuation. Leftover specimens will be stored for FBR if the subject consents to FBR.
16. Hematology tests include complete blood count with 5 part differential and platelets.

17. Urine dipstick or microscopic urinalysis may be performed according to site SOP. Urine dipstick includes pH, protein, glucose, leukocyte, esterase, ketones, and nitrite. Mandatory microscopic urinalysis will be performed if the dipstick results are abnormal. Microscopic analysis includes white blood cell count, red blood cell count, epithelial cells and casts.
18. Serum Chemistry tests include sodium, potassium, calcium, phosphate, chloride, bicarbonate/CO_2 (if performed in region), BUN, creatinine (cystatin C could be evaluated if creatinine is abnormal), SGOT (AST), SGPT (ALT), total proteins, total bilirubin (direct bilirubin if abnormal), albumin, alkaline phosphatase, glucose, uric acid, amylase, lipase, lactate dehydrogenase (LDH), and γ glutamyltransferase (GGT). . Cystatin C may be conducted by central vendor only if analysis was not available from local study site laboratory.
19. Coagulation factors (PT/INR and aPTT) should be tested as part of the screening procedures for all subjects. Furthermore, any subject receiving anticoagulant therapy should have coagulation factors monitored closely throughout the trial.
20. For women of reproductive potential, a urine pregnancy test will be performed at Screening and within 72 hours prior to the first dose of study treatment. If a urine pregnancy test cannot be confirmed as negative, a serum pregnancy test is required and must be negative. Monthly pregnancy testing should be conducted as per local regulations where applicable.
21. HIV testing should include HIV Type 1 and Type 2 (eg, HIV 1/ 2 antibody screening test and evaluation of HIV viral load as needed). Hepatitis testing should include HCV, RNA (qualitative), or Hepatitis C antibody, and HBsAg.
22. Samples for thyroid function testing should be collected on Day 1 of Cycle 2 and on Day 1 of Cycle 3. Following Cycle 3, testing will be performed every other cycle (ie, Cycles 2, 3, 5, 7, etc., +/ 3 day window) and at the Posttreatment Safety Follow up Visit. Analysis of T3 or FT3, T4 or FT4, and TSH will be performed by the local study site laboratory (conducted by central vendor only if analysis was not available from local study site laboratory).
23. In Part 1 only, blood for pembrolizumab antidrug antibodies should be collected prior to dosing on Day 1 of Cycles 2, 4, and 8, and every 4 cycles thereafter, and at the 30 day Post treatment Safety Follow up Visit. Please refer to the procedure manual for detailed sampling time points.
24. Optional on treatment tumor biopsy will be performed on Day 15 of Cycle 3 if the informed consent for optional on treatment biopsy sample has been obtained. Leftover tissue may also be saved for future biomedical research if the subject signs the FBR consent.
25. Procedures for collection of PK samples and precise time points are described in the Procedures Manual. Cycle 2 Day 1 and Cycle 3 Day 1 samples for MK 8353 PK testing should be collected prior to dosing, and 1 hour, 2 hours, 4 hours, and 8 hours after drug administration of MK 8353 (+/ 10 minutes); prior to dosing on Cycle 2 Day 8; prior to dosing on Cycle 2 Day 15; prior to dosing on Cycle 5 Day 1; and prior to dosing on Cycle 9 Day 1. If the sample day falls on a weekend or a holiday, please consult the Sponsor for alternate sample collection times.
26. Procedures for collection of PK samples and precise time points are described in the Procedures Manual. For Part 1 only, predose (trough) PK samples for pembrolizumab will be collected within 24 hours before infusion in Cycles 2, 5, and 9 and every 4 cycles thereafter, 30 days after discontinuation of study drug (or until the subject starts new anticancer therapy). Postdose (peak) PK samples will be drawn within 30 minutes after end of pembrolizumab infusion in Cycles 2 and 9.

AE adverse event; ALT alanine aminotransferase; AST aspartate aminotransferase; BUN blood urea nitrogen; C1D1 Cycle 1 Day 1; C complete response; CT computed tomography; ECG electrocardiogram; ECOG Eastern Cooperative Oncology Group; FBR future biomedical research; min minute; PD progressive disease; pERK phosphorylated extracellular regulated kinase; PGt pharmacogenetic; PK pharmacokinetic; PR interval between the P wave and the QRS wave; QRS interval from onset of the Q wave to end of the S wave; QT interval from onset of the QRS complex to end of the T wave; QTcF QT interval corrected for heart rate; SAE serious adverse event; SGOT serum glutamic oxaloacetic transaminase; SGPT serum glutamic pyruvic transaminase.

7 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 (eg, HIV, Hepatitis C, etc.), and thus local regulations may require that additional informed consent be obtained from the subject. In these cases, such evaluations/testing will be performed in accordance with those regulations.

7.1.1 Administrative Procedures

7.1.1.1 Informed Consent

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

7.1.1.1.1 General Informed Consent

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

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

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

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

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

7.1.1.1.2 Consent and Collection of Specimens for Future Biomedical Research

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

7.1.1.2 Inclusion/Exclusion Criteria

All inclusion and exclusion criteria will be reviewed by the investigator or qualified designee to ensure that the subject qualifies for the trial as per Sections 5.1.2 and 5.1.3.

7.1.1.3 Subject Identification Card

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

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

7.1.1.4 Medical History

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 previous 10 years that are considered to be clinically significant by the Investigator. Details regarding the disease for which the subject has 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 4 weeks days before Day 1, Cycle 1 of the study.

7.1.1.5.2 Concomitant Medications

The investigator or qualified designee will record medications, if any, taken by the subject during the trial from start of study treatment through the Safety Follow-up Visit, 30 days after the last dose of study drug. After the Safety Follow-up Visit, record all medications related to reportable SAEs and ECIs as defined in Section 7.2.

7.1.1.6 Disease Details and Treatments

7.1.1.6.1 Oncology Disease Details

Prior and current details regarding the disease for which the subject has been enrolled in the trial will be obtained by the investigator or qualified designee.

7.1.1.6.2 Prior Oncology Treatment History

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

7.1.1.7 Assignment of Screening Number

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

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

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

7.1.1.8 Assignment of Treatment/Randomization Number

All 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. Although subjects are being allocated, and not randomized, to treatment in Part 1, this unique number is termed a randomization number throughout the protocol for operational purposes. Allocation of subjects will be managed by the Sponsor through an IVRS/IWRS. If more than 1 schedule is to be evaluated in Part 2, treatment allocation will occur by random assignment using 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.

7.1.1.9 Trial Compliance

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.

7.1.2 Clinical Procedures/Assessments

7.1.2.1 Full Physical Examination

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

Height will be measured at Screening only.

Weight will be measured at the time of full physical examination as outlined in the Trial Flow Chart (Section 6.0).

Full physical examination will be performed at the Screening Visit and at the Treatment Discontinuation Visit. Directed physical examination will be done as indicated at all other visits as outlined in the Trial Flow Chart (Section 6.0).

After the first dose of study treatment, new clinically significant abnormal findings should be recorded as AEs.

7.1.2.2 Vital Signs

The investigator or qualified designee will measure vital signs at the time points outlined in the Trial Flow Chart (Section 6.0). Vital signs should include body temperature, pulse, respiratory rate, and blood pressure.

7.1.2.3 Eastern Cooperative Oncology Group Performance Status

The investigator or qualified designee will assess the ECOG performance status of the subject (Appendix 12.6) at the time points outlined in the Trial Flow Chart (Section 6.0).

7.1.2.4 Electrocardiogram

A 12-lead electrocardiogram (ECG) will be performed by the investigator or qualified designee at screening as outlined in the Trial Flow Chart (Section 6.0).

7.1.2.5 Administration of MK-8353 and Pembrolizumab

MK-8353 will be taken orally by the subject at the dose and schedule allocated through an IVRS/IWRS for the currently enrolling cohort(s).

Pembrolizumab will be administered at the fixed dose of 200 mg by IV infusion on Day 1 of each 21-day cycle (beginning with Cycle 2 for optional Arm D). The Pharmacy Manual contains specific instructions for the preparation and administration of the infusion solution.

Designated site personnel will be responsible for preparing and administering pembrolizumab. They will also 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, etc.). Refer to Pharmacy Manual for further details.

Subjects may receive study treatment (MK-8353 and pembrolizumab) for up to 35 cycles in Arms A, B, and C, and up to 36 cycles in Arm D.

7.1.2.6 Disease Assessments

Response will be based on RECIST 1.1 (Appendix 12.4) as assessed by investigator/local radiology review. Images used for tumor measurements will be sent to a central imaging vendor for potential blinded, central review. The process for image collection and transmission to the central imaging vendor can be found in the SIM.

Immunotherapeutic agents, such as pembrolizumab, may produce antitumor effects by potentiating an endogenous cancer-specific immune response. The response patterns seen with such an approach may extend beyond the usual 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. Subjects could, at the discretion of the investigator, continue in the trial until the initial assessment of progressive disease is confirmed at least 4 weeks later (refer to Section 4.2.3.1). The details on the irRECIST assessment can be found in Appendix 12.5.

Initial imaging (eg, CT scan, MRI, positron emission tomography) should be performed within 28 days prior to the first dose of study treatment, and should be repeated 9 weeks after the first dose and every 9 weeks until confirmed progressive disease, initiating a new anticancer therapy, withdrawing consent for study participation, or becoming lost to follow up, whichever occurs first.

The same imaging technique should be used at each time point and the schedule of disease assessment should not be adjusted for delays, if any, in cycle starts.

7.1.2.7 Adverse Event Monitoring

The investigator or qualified designee will assess each subject to evaluate for potential new or worsening AEs as outlined in the Trial Flow Chart (Section 6.0), and more frequently, if clinically indicated. Adverse events will be graded according to the NCI CTCAE, version 4.0 or later (Appendix 12.7). Toxicities will be characterized in terms of seriousness, causality, toxicity grade, and action taken with regard to study treatment(s).

Because this is a dose escalation trial to establish the RP2D of MK-8353 when used in combination with pembrolizumab, each dose escalation will be based on the safety and tolerability experienced by subjects at each dose level. The safety and tolerability for the DLT evaluation period in each cohort will be reviewed prior to the start of the next cohort in each treatment arm. The Sponsor and the Principal Investigators will review the safety and tolerability in each treatment arm independently and the appropriateness of dose escalation, when each cohort is completed and the next cohort is opened for enrollment. The frequency of these communications will depend on enrollment at each dose level, as well as any potential new information regarding a safety concern in this trial or other relevant trials.

As this is 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 applicable Principal Investigator and the Sponsor.

7.1.3 Laboratory Procedures/Assessments

Details regarding specific laboratory procedures/assessments to be performed in this trial are provided below in Table 9. The total amount of blood/tissue to be drawn/collected over the course of the trial (from pretrial and posttrial cycles), including approximate blood/tissue volumes drawn/collected by cycle and by sample type per subject can be found in the Procedures Manual and for the FBR samples, in Section 12.2.

7.1.3.1 Laboratory Safety Evaluations (Hematology, Chemistry and Urinalysis)

Laboratory tests for hematology, chemistry and urinalysis are specified in Table 9.

Table 9 Laboratory Tests

Hematology	Chemistry	Urinalysis	Other
Red blood cell (RBC) count	Total protein	Blood	Prothrombin time (PT)/International normalized ratio (INR)[4]
Hemoglobin	Albumin	Glucose	Activated partial thromboplastin time (aPTT)[4]
Hematocrit	Alanine aminotransferase (ALT)	Protein	Thyroid function testing (T4, T3, TSH)[5]
White blood cell (WBC) count (total and differential)	Aspartate aminotransferase (AST)	Specific gravity	Serum β-human chorionic gonadotropin (β-hCG)[3]
Absolute neutrophil count (ANC)	Alkaline phosphatase	Microscopic exam, if abnormal results are noted	Follicle stimulating hormone (FSH)[6]
Platelet count	Lactate dehydrogenase (LDH)	Urine pregnancy test[3]	Human immunodeficiency virus (HIV; HIV Type 1 and Type 2)
	Gamma glutamyl transferase (GGT)		Hepatitis (HCV, RNA [qualitative], or Hepatitis C antibody, and HBsAg)
	Total bilirubin		
	Direct bilirubin, if total bilirubin is above the upper limit of normal		
	Bicarbonate/Carbon dioxide (CO_2)[1]		
	Calcium		
	Chloride		
	Phosphorus		
	Potassium		
	Sodium		
	Glucose		
	Creatinine		
	Cystatin C		
	Blood urea nitrogen (BUN)/Urea[2]		
	Uric acid		

Hematology	Chemistry	Urinalysis	Other
	Amylase		
	Lipase		

1. If bicarbonate/CO_2 testing is not done as part of standard of care in your region then these tests do not need to be performed.
2. Blood urea nitrogen is preferred; if not available urea may be tested.
3. 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 is required.
4. Coagulation factors (PT/INR and aPTT) should be tested as part of the screening procedures for all subjects. Any subject receiving anticoagulant therapy should have coagulation factors monitored closely throughout the trial.
5. Total T3 is preferred; if not available free T3 may be tested. Total T4 is preferred; if not available free T4 may be tested.
6. In women <45 years of age, a high FSH level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormone replacement therapy. In the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.

ALT alanine aminotransferase; ANC absolute neutrophil count; aPTT activated partial thromboplastin time; AST aspartate aminotransferase; β hCG serum β human chorionic gonadotropin; BUN blood urea nitrogen; CO_2 carbon dioxide; FSH follicle stimulating hormone; GGT gamma glutamyl transferase; HBsAg hepatitis B surface antigen; HCV hepatitis C virus; HIV human immunodeficiency virus; INR International Normalized Ratio; LDH lactate dehydrogenase; PD progressive disease; pERK phosphorylated extracellular regulated kinase; PGt pharmacogenetic; PT prothrombin time; RBC red blood cell; RNA ribonucleic acid; T3 triiodothyronine; T4 thyroxine; TSH thyroid stimulating hormone.

Laboratory tests will be performed at the time points outlined in the Trial Flow Chart (Section 6.0). Results must be reviewed by the investigator or qualified designee and found to be acceptable prior to each dose of MK-8353.

7.1.3.2 Other Laboratory Evaluations

Samples for antidrug antibody testing (pembrolizumab) and blood for biomarker analyses will be collected at the time points outlined in the Trial Flow Chart (Section 6.0). Collection, storage and shipment instructions will be provided in the Procedures Manual. Blood samples collected for antidrug antibody may only be stored at this time. Further analyses may be performed if required. If ongoing antidrug antibody sampling is deemed to be unnecessary by the Sponsor, it may be reduced or discontinued.

7.1.3.3 Pharmacokinetic/Pharmacodynamic Evaluations

7.1.3.3.1 Blood Collection for PK Assessment for MK-8353

Samples for PK evaluations for MK-8353 will be collected at the time points outlined in Section 6.0 Trial Flow Chart. Sample collection, storage and shipment instructions for blood samples will be provided in the Procedures Manual. Blood samples collected for PK may only be stored at this time. Further analyses may be performed if required. If ongoing PK sampling is deemed to be unnecessary by the Sponsor, it may be reduced or discontinued.

7.1.3.3.2 Blood Collection for PK Assessment for Pembrolizumab

Samples for PK evaluations for pembrolizumab will be collected in Part 1 only at the timepoints outlined in Section 6.0 Trial Flow Chart. Sample collection, storage and shipment instructions for blood samples will be provided in the Procedures Manual. Blood

samples collected for PK may only be stored at this time. Further analyses may be performed if required. If ongoing PK sampling is deemed to be unnecessary by the Sponsor, it may be reduced or discontinued.

7.1.3.3.3 Blood Collection for RNA, Plasma, and Serum

Blood samples will be collected at the time points outlined in Section 6.0 Trial Flow Chart. Sample collection, storage, and shipment instructions for blood samples will be provided in the Procedures Manual. Any leftover samples will be stored for FBR if the subject signs the FBR consent.

7.1.3.4 Tumor Tissue Collection

At screening subjects must provide a tumor sample (archival or newly obtained) for biomarker analysis. Analysis will include tumor's RAS/RAF mutation and pMMR status.

Subjects may also agree to provide an optional on-treatment biopsy, for biomarker analysis as outlined in the Trial Flow Chart (Section 6.0).

Sample collection, storage, and shipment instructions for tumor samples will be provided in the Procedures Manual. Archival samples are not required to be submitted within the screening period but must be obtained by the site at the earliest convenient time.

Any leftover samples will be stored for FBR if the subject signs the FBR consent.

7.1.3.5 Planned Genetic Analysis Sample Collection

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

7.1.3.6 Future Biomedical Research Samples

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

- DNA for future research
- Leftover RNA from blood for RNA analysis
- Leftover plasma from blood for plasma biomarker analysis
- Leftover serum from blood for serum biomarker analysis
- Leftover main study tumor

See Appendix 12.2 regarding collection and management of specimens.

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. Subjects may withdraw consent at any time by contacting the principal investigator for the main trial. If medical records for the main trial are still available, the investigator will contact the Sponsor using the designated mailbox (clinical.specimen.management@merck.com). Subsequently, the subject's consent for Future Biomedical Research will be withdrawn. A letter will be sent from the Sponsor to the investigator confirming the withdrawal. It is the responsibility of the investigator to inform the subject of completion of withdrawal. Any analyses in progress at the time of request for withdrawal 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 (eg, 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 withdrawal cannot be processed.

7.1.4.1.2 Lost to Follow up

If a subject fails to return to the clinic for a required study visit and/or if the site is unable to contact the subject, the following procedures are to be performed:

- The site must attempt to contact the subject and reschedule the missed visit. If the subject is contacted, the subject should be counseled on the importance of maintaining the protocol-specified visit schedule.
- The investigator or designee must make every effort to regain contact with the subject at each missed visit (eg, phone calls and/or a certified letter to the subject's last known mailing address or locally equivalent methods). These contact attempts should be documented in the subject's medical record.

  Note: A subject is not considered lost to follow up until the last scheduled visit for the individual subject. The amount of missing data for the subject will be managed via the prespecified data handling and analysis guidelines.

7.1.4.2 Subject Blinding/Unblinding

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

7.1.4.3 Domiciling

Subjects will report to the clinical research unit prior to dosing on Day 1 of each 21-day cycle to allow for completion of all pretreatment procedures as outlined in the Trial Flow Chart (Section 6.0). On Day 1 of Cycles 1 and 2 (for Arm D, on Day 1 of Cycles 2 and 3),

the subject will remain in the unit for at least 8 hours after the start of the MK-8353 administration and pembrolizumab infusion for PK blood sampling.

7.1.4.4 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 study 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 study 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 Period

During the screening period, potential subjects will be evaluated to determine whether or not they fulfill the entry requirements as detailed in Section 5.1.

Written informed consent must be obtained prior to performing any protocol-specific procedures. Results of 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.

Screening procedures, including tumor imaging, are to be completed within 28 days prior to the first dose of study treatment except for screening laboratory tests which are to be performed within 3 days prior to the first dose of study treatment.

Screening procedures may be repeated after consultation with the Sponsor.

7.1.5.2 Treatment Period Visits

Subjects who are eligible for study participation will be allocated by nonrandom assignment to a dose cohort and assigned to receive a specified dose of MK-8353 on a specific schedule by the Sponsor. Subjects will receive a 200 mg fixed dose of pembrolizumab in addition to their assigned dose of MK-8353. MK-8353 and pembrolizumab treatment will be administered on Day 1 of each 21-day cycle (except in optional Arm C and Cycle 1 of optional Arm D), as outlined in Section 5.2.

During Cycle 1 (Cycle 2 for optional Arm D), study visits will occur on Days 1, 8, and 15. From Cycles 2 to 4 inclusively (Cycles 3 to 5 inclusively for optional Arm D), study visits will occur on Days 1 and 15. Starting at Cycle 5 (Cycle 6ˆfor optional Arm D), subjects will be required to attend study visits on Day 1. The investigator may require more frequent visits from subjects, if clinically indicated. Tumor imaging and response assessment will occur every 9 weeks after the first dose of study treatment (first dose of pembrolizumab in optional Arm D).

Study treatment (MK-8353 and pembrolizumab) may be administered for up to 35 cycles (up to 36 cycles for optional Arm D).

7.1.5.3 Discontinued Subjects Continuing to be Monitored in the Trial

When a subject discontinues trial treatment in treatment period and/or retreatment period, procedures for discontinuation will be conducted.

7.1.5.4 Posttreatment Period

When subjects discontinue study treatment, the assessments at the End-of-Treatment Visit should be completed.

Furthermore, subjects will be required to return to the clinic approximately 30 days after the last dose of study treatment for the Posttreatment Safety Follow-up Visit. If a subject initiates a new anticancer therapy within 30 days after the last dose of study treatment, the Posttreatment Safety Follow-up Visit should occur before the first dose of the new therapy.

After treatment discontinuation, each subject will be followed for 30 days for AE monitoring. Subjects will be monitored for SAEs for 90 days after treatment discontinuation, 30 days if the subject initiates new anticancer therapy less than 30 days after study treatment discontinuation, or until the day new anticancer therapy is initiated if between 30 days and 90 days after study treatment discontinuation. Subjects with an ongoing AE of Grade >1 at the time of treatment discontinuation will be followed until resolution of the AE to Grade 0 to 1, until considered stable by the treating physician, or until beginning a new anticancer therapy, whichever occurs first.

Subjects who discontinue treatment for reasons other than confirmed disease progression will have posttreatment follow up for disease status until disease progression, initiating a new anticancer therapy, withdrawing consent for study participation, or becoming lost to follow up.

After confirmed disease progression, each subject will be contacted by telephone approximately every 12 weeks (84 ±7 days) for survival until withdrawal of consent to participate in the study, becoming lost to follow up, death, or end of the study, whichever occurs first as shown in Section 6.0 Trial Flow Chart.

7.1.5.5 Survival Status

To ensure current and complete survival data are available, updated survival status may be requested during the course of the study by the Sponsor. 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 who have a previously recorded death event in the collection tool).

7.2 Assessing and Recording Adverse Events

An adverse event is defined as any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment. An adverse event can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product or protocol-specified procedure, whether or not considered related to the medicinal product or protocol-specified procedure. Any worsening (ie, any clinically significant adverse change in

frequency and/or intensity) of a preexisting condition that is temporally associated with the use of the Sponsor's product, is also an adverse event.

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

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

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

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

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

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

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 this trial, an overdose of MK-8353 will be defined as any dose above what is indicated for the specific treatment arms:

Arm A: 350 mg twice a day

Arm B: 1200 mg once a day

Optional Arms C and D: 600 mg once a day

An 800 mg bid dose has been administered every day in MK-8353 Protocol 001 in 6 subjects as a single agent (refer to Section 4.1.2.1).

An overdose of pembrolizumab will be defined as any dose of 1000 mg or greater (≥5 times the indicated dose).

No specific information is available on the treatment of overdose of MK-8353 or pembrolizumab. In the event of overdose, the subject should be observed closely for signs of toxicity. Appropriate supportive treatment should be provided if clinically indicated.

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

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

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

7.2.2 Reporting of Pregnancy and Lactation to the Sponsor

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

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

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

7.2.3 Immediate Reporting of Adverse Events to the Sponsor

7.2.3.1 Serious Adverse Events

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

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

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

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

Refer to Table 10 for additional details regarding each of the above criteria.

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

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

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

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

7.2.3.2 Events of Clinical Interest

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

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

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

Events of clinical interest for this trial include:

1. an overdose of Sponsor's product, as defined in Section 7.2.1 - Definition of an Overdose for This Protocol and Reporting of Overdose to the Sponsor, that is not associated with clinical symptoms or abnormal laboratory results.
2. an elevated AST or ALT lab value that is greater than or equal to 3X the upper limit of normal and an elevated total bilirubin lab value that is greater than or equal to 2X the upper limit of normal and, at the same time, an alkaline phosphatase lab value that is less than 2X the upper limit of normal, as determined by way of protocol-specified laboratory testing or unscheduled laboratory testing.*

   *Note: These criteria are based upon available regulatory guidance documents. The purpose of the criteria is to specify a threshold of abnormal hepatic tests that may require an additional evaluation for an underlying etiology. The trial site guidance for assessment and follow up of these criteria can be found in the Investigator Trial File Binder (or equivalent).

7.2.3.3 Protocol-Specific Exceptions to Serious Adverse Event Reporting

Efficacy endpoints as outlined in this section will not be reported to the Sponsor as described in Section 7.2.3 to the Sponsor, unless there is evidence suggesting a causal relationship between the drug and the event. Any such event will be submitted to the Sponsor within 24 hours either by electronic or paper media. Specifically, the suspected/actual events covered in this exception include any event that is disease progression of the cancer under study.

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

7.2.4 Evaluating Adverse Events

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

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

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 (ie, to all agents in the regimen). However, causality attribution may be assigned to a single agent if in the investigator's opinion, there is sufficient data to support full attribution of the adverse experience to the single agent.

Table 10 Evaluating Adverse Events

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

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

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

7.2.5 Sponsor Responsibility for Reporting Adverse Events

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

8 STATISTICAL ANALYSIS PLAN

This section outlines the statistical analysis strategies and procedures for the primary and key secondary analyses of the study. Exploratory and other nonconfirmatory analyses will be outlined in a separate supplemental Statistical Analysis Plan (sSAP).

If, after the study has begun, changes are made to primary and/or key secondary objectives, or the statistical methods related to those objectives, then the protocol will be amended (consistent with ICH Guideline E9). Changes to exploratory or other nonconfirmatory analyses made after the protocol has been finalized, but prior to the conduct of any analyses, 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 details are in the Statistical Analysis Plan, Section 8.2 to Section 8.12.

Study Design Overview	Phase 1b Study of MK-8353 + Pembrolizumab in Subjects with Advanced Malignancies. The study applies an mTPI design for dose escalation and confirmation of the MTD, followed by a cohort expansion.
Analysis Populations	Safety: All-Subjects-as-Treated (ASaT) Efficacy: Full Analysis Set (FAS)
Primary Endpoint(s)	Proportion of subjects experiencing at least one DLT in Cycle 1 (Day 1 to 21) for Arms A, B, and C, or Cycles 1 and 2 (35 days) for optional Arm D
Key Secondary Endpoints	ORR based on RECIST 1.1 as assessed by the investigator
Statistical Methods for Key Efficacy/Immunogenicity/ Pharmacokinetic Analyses	ORR will be estimated using an exact method based on the binomial distribution (Clopper-Pearson interval).
Treatment Assignment	Subjects will be allocated by nonrandom assignment to different dose levels of MK-8353 coadministered with pembrolizumab centrally through IVRS/IWRS; the study is open-label.
Statistical Methods for Key Safety Analyses	Summary statistics (counts, percentages, means, standard deviations, etc.) will be provided for the safety endpoints as appropriate. The pool-adjacent-violators-algorithm [61] will be used to estimate the DLT rates across doses. The estimates of the DLT rates among subjects treated at the MTD of MK-8353 and the 80% Bayesian credible intervals for the estimates will be provided.
Interim Analyses	There is no formal hypothesis testing at the interim analyses. An interim futility check will be performed for Part 2.
Multiplicity	No multiplicity adjustment is planned in this Phase 1b trial.

Sample Size and Power	The study is designed to assess the safety and tolerability of MK-8353 when administered in combination with pembrolizumab in subjects with advanced solid tumors with an expansion to subjects with ≥ second line advanced non-MSI-H/dMMR CRC. The study is not powered to address a statistical hypothesis. For Part 1, up to approximately 142 evaluable subjects (up to 14 per dose level) will be included. The final sample size for Part 1 will depend on the number of subjects experiencing DLTs at each dose level and may be increased if the RP2D is not reached and additional dose levels are required. For Part 2, the planned sample size is up to approximately 40 subjects.

8.2 Responsibility for Analyses/In-House Blinding

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

The trial is open-label (ie, subjects, investigators, and Sponsor personnel will be aware of subject treatment assignment after each subject is enrolled and treatment is assigned). Allocation to treatment will not be randomized.

8.3 Hypotheses/Estimation

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

8.4 Analysis Endpoints

8.4.1 Efficacy/Immunogenicity/Pharmacokinetic Endpoints

Efficacy endpoints are secondary and exploratory endpoints in this study (refer to Sections 3.2 and 3.3).

The following efficacy endpoints are derived from the RECIST 1.1 criteria:

Objective Response Rate: defined as the proportion of subjects who have achieved confirmed CR or PR.

Duration of Response: defined for subjects who achieved a tumor response (CR or PR) as the time between the date of the first documented tumor response and the subsequent date of the objectively documented disease progression or death, whichever occurs first. Response duration for subjects who have not progressed or died at the time of analysis will be censored at the date of their last tumor assessment.

Disease Control Rate: defined as the proportion of subjects who have achieved CR, PR, or SD.

Progression-free Survival: defined as the time from the first dose of study medication to the first objective documentation of tumor progression or death due to any cause. Detailed censoring rules will be described in the sSAP.

Overall survival: defined as the time from the first dose of study medication to death due to any cause. Subjects who did not die will be censored on the date of their last study assessment or contact.

PK endpoints include serum concentrations of MK-8353 and pembrolizumab and derived PK parameters.

8.4.2 Safety Endpoints

The primary safety endpoint is the rate of DLTs. Safety will be monitored by cumulative data reviews throughout the trial. The toxicities experienced by subjects who have received study treatment, including AEs and SAEs and their grades will be summarized. Other safety measures evaluated in all parts of the study include laboratory safety assessments, ECGs, vital signs, and physical examinations.

A description of safety measures is provided in Section 7.

8.5 Analysis Populations

8.5.1 Safety Analysis Population

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 35 days for subjects in optional Arm D) or experienced a DLT prior to 21 days after the first dose of assigned treatment (or prior to 35 days for subjects in optional Arm D) will be included. The replacement subjects will also be considered evaluable if the above specified criteria are met.

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 Efficacy Analysis Populations

The FAS population will be used for the analysis of efficacy data in this study. It consists of all subjects with a baseline scan with measurable disease by investigator assessment who were administered a dose of the study medicine.

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.

PK will be analyzed and reported separately.

8.6.1 Statistical Methods for Efficacy Analyses

Objective response rate will be estimated using an exact method based on the binomial distribution (Clopper-Pearson interval).

8.6.2 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.

Adverse events will be summarized as counts and frequencies for each dose level. Laboratory tests, vital signs, and other safety endpoints will be summarized as appropriate.

Dose-limiting toxicities will be listed, and further summarized by dose level. The pool adjacent-violators-algorithm [1], which forces the DLT rate estimates to be non-decreasing with increasing dose levels and pools adjacent violators for weighted estimates by sample size, will be used to estimate the DLT rates across doses. The estimates of the DLT rates among subjects treated at the MTD and the 80% Bayesian credible intervals based on a prior distribution of Beta (1,1) for the estimates will be provided.

8.6.3 Summaries of Baseline Characteristics, Demographics, and Other Analyses

Demographic variables, baseline characteristics, primary and secondary diagnoses, and prior and concomitant therapies will be summarized.

8.7 Interim Analyses

In this study there will be no formal hypothesis testing, although an interim analysis may be conducted to enable future trial planning at the Sponsor's discretion and data will be examined on a continuous basis to allow for dose escalation and confirmation decisions.

An interim futility check will be performed for Part 2. If there are no responders among approximately the first 18 evaluable subjects that have at least 1 postbaseline scan assessment, the trial may be stopped early for futility. If the true response rate is 10%, there is an 85% chance to observe at least one responder among 18 subjects.

8.8 Multiplicity

There will be no multiplicity control in this study.

8.9 Sample Size and Power Calculations

Part 1 dose escalation and confirmation is expected to enroll up to approximately 142 subjects (up to 14 subjects per dose level). The final sample size for Part 1 will depend on the number of subjects experiencing DLTs at each dose level, and may be increased if the RP2D is not reached and additional dose levels are required.

For Part 2, the planned sample size is up to approximately 40 subjects. The primary efficacy endpoint will be the ORR based on the investigator assessment per RECIST 1.1. Table 11 shows the ORR estimate and 95% CI under various scenarios. Of note, any ≥second line advanced non-MSI-H/dMMR CRC subjects enrolled in Part 1 and treated at the dose level that is selected for Part 2 will also be included for this efficacy analysis.

Table 11 Estimate and 95% CI of ORR Under Various Scenarios

Sample Size	Number of Responses (PR/CR)	Observed ORR	95% Confidence Interval of ORR
40	4	10%	(2.8%, 23.7%)
	5	12.5%	(4.2%, 26.8%)
	6	15%	(5.7%, 29.8%)
	7	17.5%	(7.3%, 32.8%)
	8	20%	(9.1%, 35.7%)
	9	22.5%	(10.8%, 38.4%)
	10	25%	(12.7%, 41.2%)
54	4	7.4%	(2.1%, 17.9%)
	5	9.3%	(3.1%, 20.3%)
	6	11.1%	(4.2%, 22.6%)
	7	13.0%	(5.4%, 24.9%)
	8	14.8%	(6.6%, 27.1%)
	9	16.7%	(7.9%, 29.3%)
	10	18.5%	(9.3%, 31.4%)

It is assumed that: 1) 40 $\geq$ second line advanced non-MSI-H/dMMR CRC subjects are enrolled in Part 2 (expansion) and are also evaluable for efficacy analysis; 2) the number of $\geq$ second line advanced non-MSI-H/dMMR CRC subjects enrolled in Part 1 and treated at the dose level that is selected for Part 2 could be between 0 and 14.

CR=complete response; CRC=colorectal; ORR=overall response rate; PR=partial response.

8.10 Subgroup Analyses and Effect of Baseline Factors

Subgroup analyses of efficacy endpoints will be conducted as needed (eg, RAS/RAF mutation status [mutant versus wild-type], Mismatch Repair status [pMMR versus dMMR] and tumor location [left versus right]).

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

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

9 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 12. 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 12 Product Descriptions

Product Name & Potency	Dosage Form	Source/Additional Information
Pembrolizumab (100 mg/4 mL)	Injection	Provided centrally by the Sponsor
MK-8353 CCI [redacted]	Capsules	Provided centrally by the Sponsor

All supplies indicated in Table 12 will be provided centrally by the Sponsor.

Any commercially available product not included in Table 12 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.

Sites will receive open-label bottles of MK-8353 and open-label kits of pembrolizumab.

9.3 Clinical Supplies Disclosure

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

9.4 Storage and Handling Requirements

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

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

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

9.5 Discard/Destruction/Returns and Reconciliation

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

9.6 Standard Policies

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

10 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 (eg, International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use Good Clinical Practice: Consolidated Guideline and other generally accepted standards of good clinical practice); and all applicable federal, state and local laws, rules and regulations relating to the conduct of the clinical trial.

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

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

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

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

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

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

when documents may be destroyed. The Sponsor will determine the minimum retention period and upon request, will provide guidance to the investigator when documents no longer need to be retained. The sponsor also recognizes that documents may need to be retained for a longer period if required by local regulatory requirements. All trial documents shall be made available if required by relevant regulatory authorities. The investigator must consult with and obtain written approval by the Sponsor prior to destroying trial and/or subject files.

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

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

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

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

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

10.4 Compliance with Trial Registration and Results Posting Requirements

Under the terms of the Food and Drug Administration Amendments Act (FDAAA) of 2007 and the European Medicines Agency (EMA) clinical trial Directive 2001/20/EC, the Sponsor of the trial is solely responsible for determining whether the trial and its results are subject to the requirements for submission to http://www.clinicaltrials.gov, www.clinicaltrialsregister.eu or other local registries. Merck, as Sponsor of this trial, will review this protocol and submit the information necessary to fulfill these requirements. Merck entries are not limited to FDAAA or the EMA clinical trial directive mandated trials. Information posted will allow subjects to identify potentially appropriate trials for their disease conditions and pursue participation by calling a central contact number for further information on appropriate trial locations and trial site contact information.

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

10.5 Quality Management System

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

10.6 Data Management

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

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

10.7 Publications

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

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

and hypotheses, the subject inclusion and exclusion criteria, the trial design and procedures, the efficacy and safety measures, the statistical analysis plan, and any amendments relating to those sections. The Sponsor reserves the right to redact proprietary information.

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

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

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

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12 APPENDICES

12.1 Merck Code of Conduct for Clinical Trials

Merck*
Code of Conduct for Clinical Trials

I. Introduction

A. Purpose

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

B. Scope

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

II. Scientific Issues

A. Trial Conduct

1. Trial Design

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

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

2. Site Selection

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

3. Site Monitoring/Scientific Integrity

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

B. Publication and Authorship

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

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

III. Subject Protection

A. IRB/ERC review

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

B. Safety

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

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

C. Confidentiality

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

D. Genomic Research

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

IV. Financial Considerations

A. Payments to Investigators

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

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

B. Clinical Research Funding

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

C. Funding for Travel and Other Requests

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

V. Investigator Commitment

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

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

12.2 Collection and Management of Specimens for Future Biomedical Research

1. Definitions

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

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

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

d. DNA: Deoxyribonucleic acid.

e. RNA: Ribonucleic acid.

2. Scope of Future Biomedical Research

The specimens consented and/or collected in this trial as outlined in Section 7.1.3.3 Future Biomedical Research Samples will be used in various experiments to understand:

- The biology of how drugs/vaccines work
- Biomarkers responsible for how a drug/vaccine enters and is removed by the body
- Other pathways drugs/vaccines may interact with
- The biology of disease

The specimen(s) may be used for future assay development and/or drug/vaccine development.

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

3. Summary of Procedures for Future Biomedical Research

a. Subjects for Enrollment

All subjects enrolled in the clinical trial will be considered for enrollment in the future biomedical research.

b. Informed Consent

Informed consent for specimens (ie, 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 the visit designated in the trial flow chart. If delayed, present consent at next possible Subject Visit. 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.

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(s)

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. This 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 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 Sponsor 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 (eg, 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 ask that their biospecimens not be used for Future Biomedical Research. Subjects may withdraw consent at any time by contacting the principal investigator for the main trial. If medical records for the main trial are still available, the investigator will contact the Sponsor using the designated mailbox (clinical.specimen.management@merck.com).

Subsequently, the subject's specimens will be flagged in the biorepository and restricted to main study use only. If specimens were collected from study participants specifically for Future Biomedical Research, these specimens will be removed from the biorepository and destroyed. Documentation will be sent to the investigator confirming withdrawal and/or destruction, if applicable. It is the responsibility of the investigator to inform the subject of completion of the withdrawal and/or destruction, if applicable. Any analyses in progress at the time of request for withdrawal/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 (eg, 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 withdrawal of consent and/or destruction cannot 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 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 important research findings are discovered, the Sponsor may publish results, present results in national meetings, and make results accessible on a public website in order to rapidly report this information to doctors and subjects. 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@merck.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
3. Industry Pharmacogenomics Working Group. Understanding the Intent, Scope and Public Health Benefits of Exploratory Biomarker Research: A Guide for IRBs/IECs and Investigational Site Staff. Available at http://i-pwg.org/
4. Industry Pharmacogenomics Working Group. Pharmacogenomics Informational Brochure for IRBs/IECs and Investigational Site Staff. Available at http://i-pwg.org/

12.3 Cockcroft-Gault Formula

Calculated Creatinine Clearance Sex × ((140 - Age) / (Serum Creatinine))
× (Weight / 72), where male 1 and female 0.85

12.4 Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 Criteria for Evaluating Response in Solid Tumors

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

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

12.5 irRECIST

irRECIST is RECIST 1.1 adapted as described below to account for the unique tumor response seen with immunotherapeutic drugs. irRECIST will be used by site investigator/local radiology review to assess tumor response and progression, and make treatment decisions while subjects are receiving pembrolizumab (MK-3475). Treatment efficacy based on irRECIST as assessed by central imaging vendor review will be evaluated retrospectively and is an exploratory objective for this study. Refer to Table 13 for management of subjects per irRECIST.

This clinical judgment decision by the site 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, cord compression) requiring urgent alternative medical intervention

In determining whether or not the tumor burden has increased or decreased per irRECIST, the local site investigator should consider all target and non-target lesions as well as any incremental new lesion(s). Confirmation of progressive disease at repeat imaging is defined by occurrence of ANY of the following conditions:

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

ALL of the following conditions must be met in order for progressive disease NOT to be confirmed at repeat imaging:

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

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

When feasible, subjects should not be discontinued until progression is confirmed by the local site investigator/radiology assessment.

Table 13 Imaging and Treatment after First Radiologic Evidence of Progressive Disease for Subjects Receiving Pembrolizumab (MK-3475) (management per irRECIST)

	Clinically Stable		**Clinically Unstable**	
	Imaging	**Treatment**	**Imaging**	**Treatment**
1st radiologic evidence of PD by RECIST 1.1[(1)]	Repeat imaging at ≥ 4 weeks at site to confirm PD	May continue study treatment at the investigator's discretion while awaiting confirmatory tumor imaging.	Repeat imaging at ≥ 4 weeks to confirm PD per physician discretion only	Discontinue treatment
Repeat tumor imaging confirms PD by irRECIST at the local site	No additional imaging required	Discontinue treatment [(2)]	No additional imaging required	N/A
Repeat tumor imaging shows SD, PR or CR by irRECIST by the local site	Continue regularly scheduled imaging assessments	Continue study treatment at the local site investigator's discretion	Continue regularly scheduled imaging assessments	May restart study treatment if condition has improved and/or clinically stable per investigator's discretion. Next tumor image should occur according to the regular imaging schedule outlined in the protocol

1) Disease progression will be assessed by the local site/investigator for subjects participating in the study. All images will be submitted to a central imaging vendor for potential analysis at the end of the study.

2) If a subject has confirmed radiographic progression (ie, 2 scans at least 4 weeks apart demonstrating progressive disease) per irRECIST, but the subject is achieving a clinically meaningful benefit, an exception to continue treatment may be considered following consultation with the Sponsor. Follow up scans will then be performed Q9W (63 ± 7 days) or earlier as clinically indicated.

12.6 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 (eg, 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.
Source: 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.	

12.7 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.html).

12.8 List of Abbreviations

Abbreviation/Term	Definition
AE	adverse event
ALT	alanine aminotransferase
ANC	absolute neutrophil count
aPTT	activated partial thromboplastin time
ASaT	All Subjects as Treated
ASCO	American Society of Clinical Oncology
ASH	American Society of Hematology
AST	aspartate aminotransferase
$AUC_{0-\infty}$	area under the curve from time 0 extrapolated to infinite time
bid	twice daily
BUN	blood urea nitrogen
CEA	carcinoembryonic antigen
CFR	Code of Federal Regulations
CI	Coordinating Investigator
CLIA	Clinical Laboratory Improvement Amendments
C_{max}	maximum concentration in blood
CR	complete response
CRC	colorectal cancer
CrCl	creatinine clearance
CRF	case report form
CSR	clinical study report
CT	computed tomography
CTCAE	Common Toxicity Criteria for Adverse Events
CTLA-4	cytotoxic t-lymphocyte-associated antigen-4
DCR	drug control rate
DL	dose level
DLT	dose-limiting toxicity
dMMR	deficient mismatch repair
DNA	deoxyribonucleic acid
DOR	duration of response
ECG	electrocardiogram
ECI	events of clinical interest
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EDC	electronic data capture
EMA	European Medicines Agency
ERC	Ethics Review Committee
ERK	extracellular signal-regulated kinase
FAS	Full Analysis Set
FBR	Future Biomedical Research
FDAAA	Food and Drug Administration Amendments Act
FSH	follicle-stimulating hormone
FT3	free triiodothyronine
FT4	free thyroxine
GCP	Good Clinical Practice
GFR	glomerular filtration rate
GGT	gamma glutamyl transferase
GLP	Good Laboratory Practice
G-CSF	granulocyte-colony stimulating factor
GM-CSF	granulocyte-macrophage colony-stimulating factor

Abbreviation/Term	Definition
HBsAg	hepatitis B surface antigen
HIV	human immunodeficiency virus
IB	Investigator's Brochure
IC_{50}	half-maximal inhibitory concentration
ICH	International Conference on Harmonization
Ig	immunoglobulin
IHC	immunohistochemistry
INR	international normalized ratio
irAE	immune-related adverse event
IRB	Institutional Review Board
irORR	immune-related overall response rate
irPFS	immune-related progression-free survival
irRECIST	Immune-related Response Evaluation Criteria in Solid Tumors
ITSM	immunoreceptor tyrosine-based switch motif
IV	intravenous
IVRS	interactive voice response system
IWRS	integrated web response system
LDH	lactate dehydrogenase
mAB	monoclonal antibody
MAPK	mitogen-activated protein kinase
MEK	mitogen-activated protein/extracellular signal-regulated kinase
MMR	mismatch repair
MRI	magnetic resonance imaging
MSI	microsatellite instability
MTD	maximum tolerated dose
mTPI	modified toxicity probability interval
NCI	National Cancer Institute
non-MSI-H/dMMR	Non-microsatellite instability-high/deficient mismatch repair
NSCLC	non-small cell lung cancer
ORR	overall response rate
OS	overall survival
OTC	over-the-counter
PD-1	programmed cell death-1
PD-L1	programmed cell death-ligand 1
PD-L2	programmed cell death-ligand 2
PD	pharmacodynamic
pERK	phosphorylated extracellular signal-regulated kinase
PFS	progression-free survival
PK	pharmacokinetic
pMMR	proficient mismatch repair
PR	partial response
PT	prothrombin time
q2w	once every 2 weeks
q3w	once every 3 weeks
qd	once daily
RECIST	Response Evaluation Criteria in Solid Tumors
RAF	rapidly accelerated fibrosarcoma
RAS	rat sarcoma
RNA	ribonucleic acid
RP2D	Recommended Phase 2 Dose
SAE	serious adverse event
SD	stable disease

Abbreviation/Term	Definition
SGOT	serum glutamic oxaloacetic transaminase
SGPT	serum glutamic-pyruvic transaminase
SIM	Site Imaging Manual
sSAP	supplemental Statistical Analysis Plan
T3	triiodothyronine
T_{max}	time to maximum concentration
T4	thyroxine
TSH	thyroid stimulating hormone
ULN	upper limit of normal
WBC	white blood cells
β-hCG	β-human chorionic gonadotropin

13 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	