Official Protocol Title:	A Phase 1 Trial of MK-7684 as Monotherapy and in Combination with Pembrolizumab in Subjects with Advanced Solid Tumors
NCT number:	NCT02964013
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SPONSOR:
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Protocol-specific Sponsor Contact information can be found in the Investigator Trial File Binder (or equivalent).

TITLE:

A Phase 1 Trial of MK-7684 as Monotherapy and in Combination with Pembrolizumab in Subjects with Advanced Solid Tumors

IND NUMBER: 131789
EudraCT NUMBER: Not Applicable

TABLE OF CONTENTS

LIST OF TABLES

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SUMMARY OF CHANGES

PRIMARY REASON(S) FOR THIS AMENDMENT:

Section Number (s)	Section Title(s)	Description of Change (s)	Rationale
Title Page Section 12.1 Throughout	Code of Conduct for Clinical Trials Throughout	Sponsor entity name and address change.	Merck Sharp & Dohme Corp. underwent an entity name and address change to Merck Sharp & Dohme LLC, Rahway, NJ, USA. This conversion resulted only in an entity name change and update to the address.

ADDITIONAL CHANGE(S) FOR THIS AMENDMENT:

No additional changes.

1.0 TRIAL SUMMARY

Abbreviated Title	Phase 1 Trial of MK-7684 as Monotherapy and in Combination with Pembrolizumab in Subjects with Advanced Solid Tumors
Sponsor Product Identifiers	MK-7684 (N/A) MK-3475 (Pembrolizumab) MK-7684A (N/A)
Trial Phase	Phase 1/1b
Clinical Indication	Part A (dose escalation and confirmation phase): The treatment of subjects with advanced solid tumors Part B (expansion phase): The treatment of subjects with non-small cell lung cancer (NSCLC), CCI [redacted]
Trial Type	Interventional
Type of control	None
Route of administration	Intravenous
Trial Blinding	Unblinded Open-label
Treatment Groups	There are 5 treatment arms in this trial: Arm 1: MK-7684 Arm 2: MK-7684 + pembrolizumab CCI [redacted] During Part A (dose escalation and confirmation phase): • Subjects with advanced solid tumors will be allocated to either Arm 1 or Arm 2. CCI [redacted] During Part B (expansion phase): • Subjects with NSCLC will be allocated to either Arm 1 or Arm 2. CCI [redacted]
Number of trial subjects	Approximately up to 492 subjects will be enrolled.

Estimated duration of trial	The Sponsor estimates that the trial will require approximately 9 years from the time the first subject (or the subject's legally acceptable representative) provides documented informed consent until the last subject's last study-related contact.
Duration of Participation	Each subject will participate in the trial from the time the subject (or the subject's legally acceptable representative) provides documented informed consent through the final protocol-specified contact. During Part A (dose escalation and confirmation phase) and Part B (expansion phase), after a screening period of up to 28 days, each subject will be allocated to a treatment arm (MK-7684 monotherapy [Arm 1], MK-7684 in combination with pembrolizumab [Arm 2], CCI [redacted] Study treatment in all arms will be given on Day 1 of each 3-week cycle, CCI [redacted] In Arms 1 and 2, subjects may receive up to 35 cycles of study treatment with MK-7684 and/or pembrolizumab. CCI [redacted] Study treatment will continue until disease progression, unacceptable adverse event(s) (AEs), intercurrent illness that prevents further administration of treatment, investigator's decision to withdraw treatment, subject withdrawal of consent, pregnancy of the subject, noncompliance with trial treatment or procedure requirements, subject completes treatment, or administrative reasons requiring cessation of treatment. Subjects who discontinue MK-7684 in the monotherapy arm due to disease progression may, at the investigator's discretion and after consultation with the Sponsor, switch to combination treatment (Arm 2). After treatment discontinuation, subjects will be monitored for AEs and serious adverse events (SAEs) for 90 days. Subjects who initiate new anticancer therapy less than 30 days after study treatment discontinuation will be monitored for AEs/SAEs for 30 days. Subjects who initiate new anticancer therapy between 30 days and 90 days after study treatment discontinuation will be monitored for AEs/SAEs until the day new anticancer therapy is initiated. Subjects who discontinue treatment for reasons other than confirmed disease progression will have post-treatment follow-up for disease status until disease progression, initiating a new anticancer therapy, withdrawing consent for trial participation, or becoming lost to follow-up, whichever occurs first. After confirmed disease progression, each subject will be contacted by telephone every 12 weeks for survival until withdrawal of consent to participate in the trial, becoming lost to follow-up, death, or the end of the trial, whichever occurs first.
Randomization Ratio	All subjects in Part A, and all subjects in Part B CCI [redacted], will be allocated to treatment without randomization. CCI [redacted]

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

2.0 TRIAL DESIGN

2.1 Trial Design

This is a first-in-human, multi-site, open-label trial of MK-7684 as monotherapy, in combination with pembrolizumab, or in combination with pembrolizumab and standard of care (SOC) chemotherapy in subjects with a histologically or cytologically confirmed diagnosis of a solid tumor. The trial will include 2 parts: Part A will be a dose escalation and confirmation phase to examine safety, tolerability, and identify a preliminary recommended Phase 2 dose (RPTD; [Section 5.2.1.2]) and Part B will be an expansion phase to further examine safety and exploratory efficacy in specific tumor types/populations (Section 5.2.1.3). Part A will test MK-7684 as monotherapy (Arm 1) and combination therapy with pembrolizumab (Arm 2) in subjects with advanced solid tumors, CCI [redacted] Part B will assess the safety and antitumor efficacy of MK-7684 monotherapy (Arm 1) in subjects with NSCLC, the safety and antitumor efficacy of MK-7684 in combination with pembrolizumab (Arm 2) in subjects with NSCLC, CCI [redacted]

2.1.1 Part A (Dose Escalation and Confirmation)

Advanced Solid Tumors (Part A, Arms 1 and 2)

Subjects with advanced solid tumors of all types will be allocated by non-random assignment to receive escalating doses of MK-7684 as monotherapy (Arm 1) or in combination with pembrolizumab (Arm 2) centrally using an interactive voice response system/integrated web response system (IVRS/IWRS). Details of the enrollment process are described in Section 5.3. A modified toxicity probability interval (mTPI) design [1] with a target dose-limiting toxicity (DLT) rate of approximately 30% will be applied to identify a preliminary RPTD of MK-7684 in Arm 1 and Arm 2. Five pre-determined dose levels of MK-7684 will be explored independently in each arm: 2.1 mg, 7 mg, 21 mg, 70 mg, and 210 mg. A single additional dose level of 700 mg may be added after the completion of the DLT period for 210 mg and provided that the DLT rate at 210 mg based on Table 5 grants the decision to “escalate”. Intermediate doses may be explored if one of the pre-planned doses is deemed unacceptably toxic and the immediate lower dose is deemed too low.

During dose escalation, a minimum of 3 subjects are required at each dose, and up to 6 subjects may be enrolled in the same cycle at each new dose. As outlined in Table 5, 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. Dose escalation and confirmation in Arms 1 and 2 will end after 14 subjects have been treated at any of the selected doses (including intermediate doses) as long as the decision based on Table 5 is to "stay" or "escalate". The pool-adjacent-violators algorithm [1] will be used to estimate the DLT rates across doses in each treatment arm under the assumption of monotonicity between DLT rates and dose levels. The dose with an estimated DLT rate closest to 30% may be treated as a preliminary RPTD. The totality of the data will be considered before deciding on the dose(s) to carry forward to Part B. The preliminary RPTD in Arm 2 will not exceed, but may equal, the preliminary RPTD in Arm 1.

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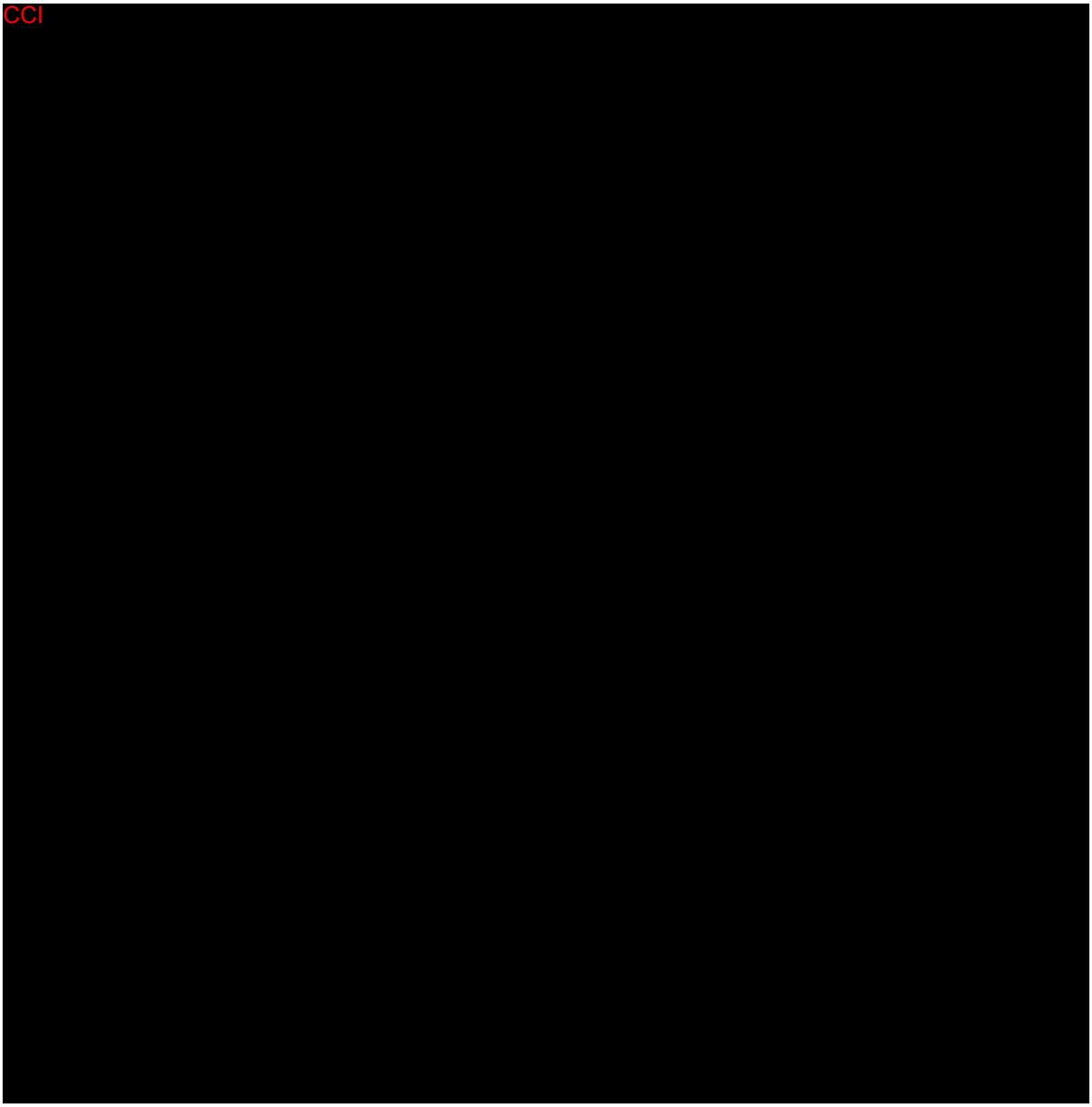

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2.1.2 Part B (Dose Expansion)

Part B, Arms 1 and 2 will use the preliminary RPTDs identified for MK-7684 using the mTPI design in Part A. CCI [redacted]

PD-1/PD-L1 inhibitor treatment-refractory NSCLC (Part B, Arms 1 and 2)

Subjects with PD-1/PD-L1 inhibitor treatment-refractory NSCLC will be allocated by non-random assignment to receive MK-7684 at the preliminary RPTD as monotherapy (Arm 1) or in combination with pembrolizumab (Arm 2) centrally using IVRS/IWRS; IVRS/IWRS will alternate assignment of subjects between Arm 1 and Arm 2 starting with Arm 1 until a maximum of 40 subjects are enrolled in each arm.

PD-1/PD-L1 inhibitor treatment-naïve NSCLC, CCI [redacted]

Subjects with PD-1/PD-L1 inhibitor treatment-naïve NSCLC (n=14-40), CCI [redacted] will be allocated to receive MK-7684 at the preliminary RPTD in combination with pembrolizumab (Arm 2). Enrollment of subjects with NSCLC CCI [redacted] will use an adaptive design. In the adaptive design, if 3 or more objective responses are observed out of the first 14 subjects in a cohort based on Response Evaluation Criteria in Solid Tumors (RECIST), version 1.1, the corresponding cohort may continue enrolling up to a maximum of 40 subjects. If 3 objective responses are not observed in the first 14 subjects of these cohorts, the Sponsor will evaluate all available data to determine whether or not to expand enrollment.

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Each treatment arm will begin Part B once a preliminary RPTD for that arm is identified in Part A. To maximize enrollment efficiency, once a possible preliminary RPTD is reached, Part A enrollment of subjects with advanced solid tumors of all types will be restricted to the tumor indications specified in Inclusion Criterion 1 for Part B (Section 5.1.2), CCI [redacted]. Part A subjects eligible for the Part B tumor cohorts who receive the preliminary RPTD may be used toward enrollment caps in Part B. Data from subjects treated at the preliminary RPTDs in Part A will be included in the analysis of Part B if they meet the specifications described in Inclusion Criterion 1 (Section 5.1.2). Final RPTDs for MK-7684, both when used as monotherapy and in combination with pembrolizumab, will be determined using PK and pharmacodynamic (PD) endpoints, as well as all available safety data from subjects in Part A and Part B, including DLT rates and the cumulative incidence of late toxicities (i.e., toxicities that occur after the 21-day DLT observation period).

The Sponsor may prematurely terminate enrollment into a cohort for administrative reasons; in such cases, the sites will be notified via an administrative letter. All subjects already enrolled or in the screening period will be allowed to continue in the study.

All study treatments in Parts A and B will be administered by intravenous (IV) infusion on Day 1 of each 21-day cycle with the exception of etoposide which will be given on Days 1, 2 and 3 of each 21-day cycle. The dose of pembrolizumab in Arms 2, 3 and 5 will remain fixed at 200 mg.

Subjects in both parts of the trial may receive up to 35 cycles of treatment with MK-7684 (Arms 1-5) and pembrolizumab (Arms 2-5), CCI [redacted]

Study treatment will continue until disease progression, unacceptable AE(s), intercurrent illness that prevents further administration of treatment, investigator's decision to withdraw treatment, subject withdrawal of consent, pregnancy of the subject, noncompliance with trial treatment or procedure requirements, subject completes treatment, or administrative reasons requiring cessation of treatment. Arm 1 subjects with disease progression following treatment with MK-7684 monotherapy may be eligible to cross over to combination treatment. Subjects eligible for cross-over must have received at least 2 cycles of MK-7684 monotherapy and must have radiographic imaging to document disease progression by RECIST, version 1.1 and to establish a new imaging baseline prior to cross-over. Subjects who permanently discontinue MK-7684 monotherapy for any reason other than radiologic disease progression are not eligible for cross-over.

After treatment discontinuation, subjects will be monitored for AEs and SAEs for 90 days. Subjects who initiate new anticancer therapy less than 30 days after study treatment discontinuation will be monitored for AEs/SAEs for 30 days. Subjects who initiate new anticancer therapy between 30 days and 90 days after study treatment discontinuation will be monitored for AEs/SAEs until the day new anticancer therapy is initiated.

Subjects who discontinue treatment for reasons other than confirmed disease progression will have post-treatment follow-up for disease status until disease progression, initiating a new anticancer therapy, withdrawing consent for trial participation, or becoming lost to follow-up, whichever occurs first.

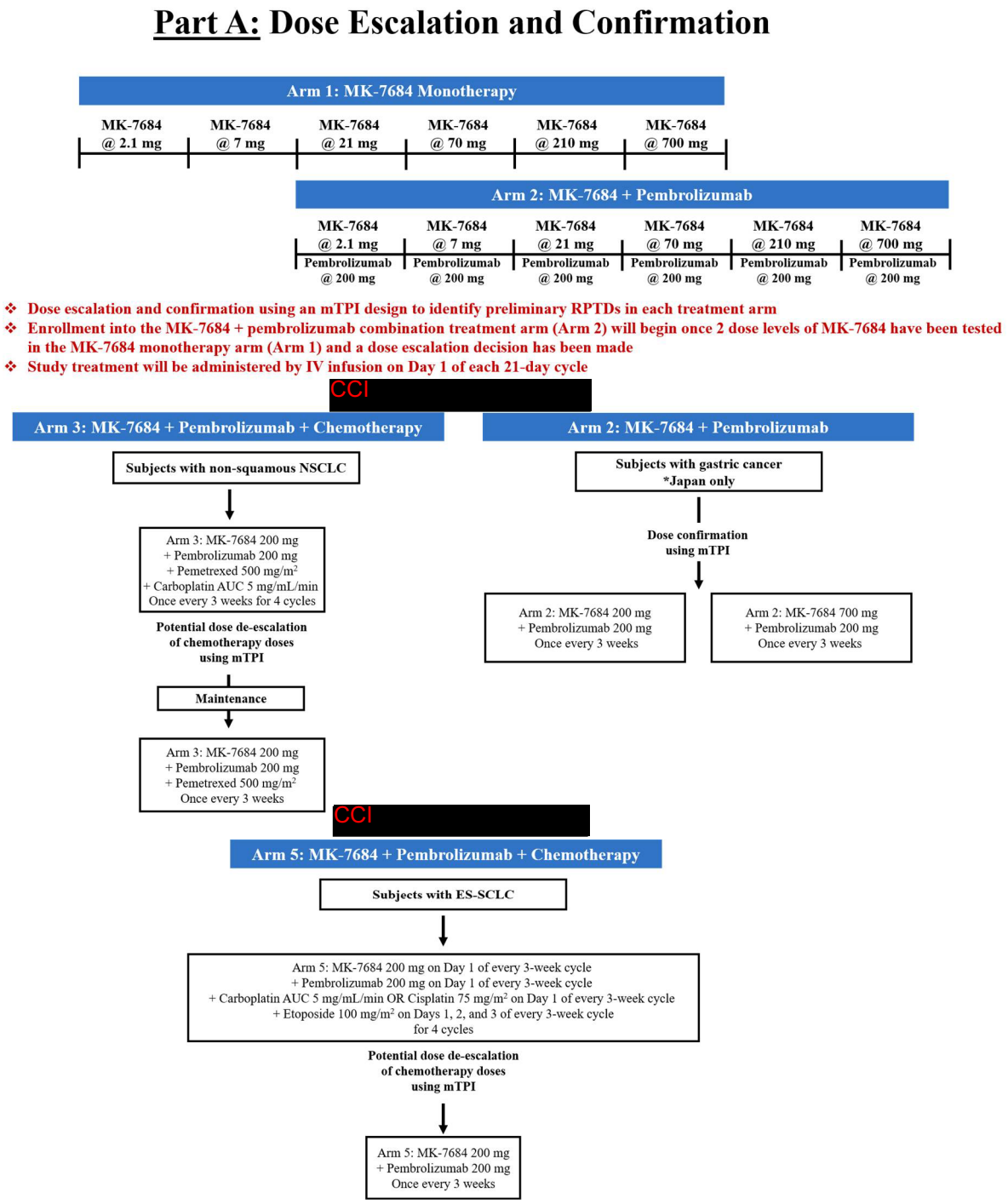
After confirmed disease progression, each subject will be contacted by telephone every 12 weeks for survival until withdrawal of consent to participate in the trial, becoming lost to follow-up, death, or the end of the trial, whichever occurs first.

The trial will be conducted in conformance with Good Clinical Practice (GCP). Adverse events will be evaluated according to criteria outlined in the National Cancer Institute's (NCI) Common Terminology Criteria for Adverse Events (CTCAE), version 4.0.

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

2.2 Trial Diagram

The trial design is depicted in Figure 1.



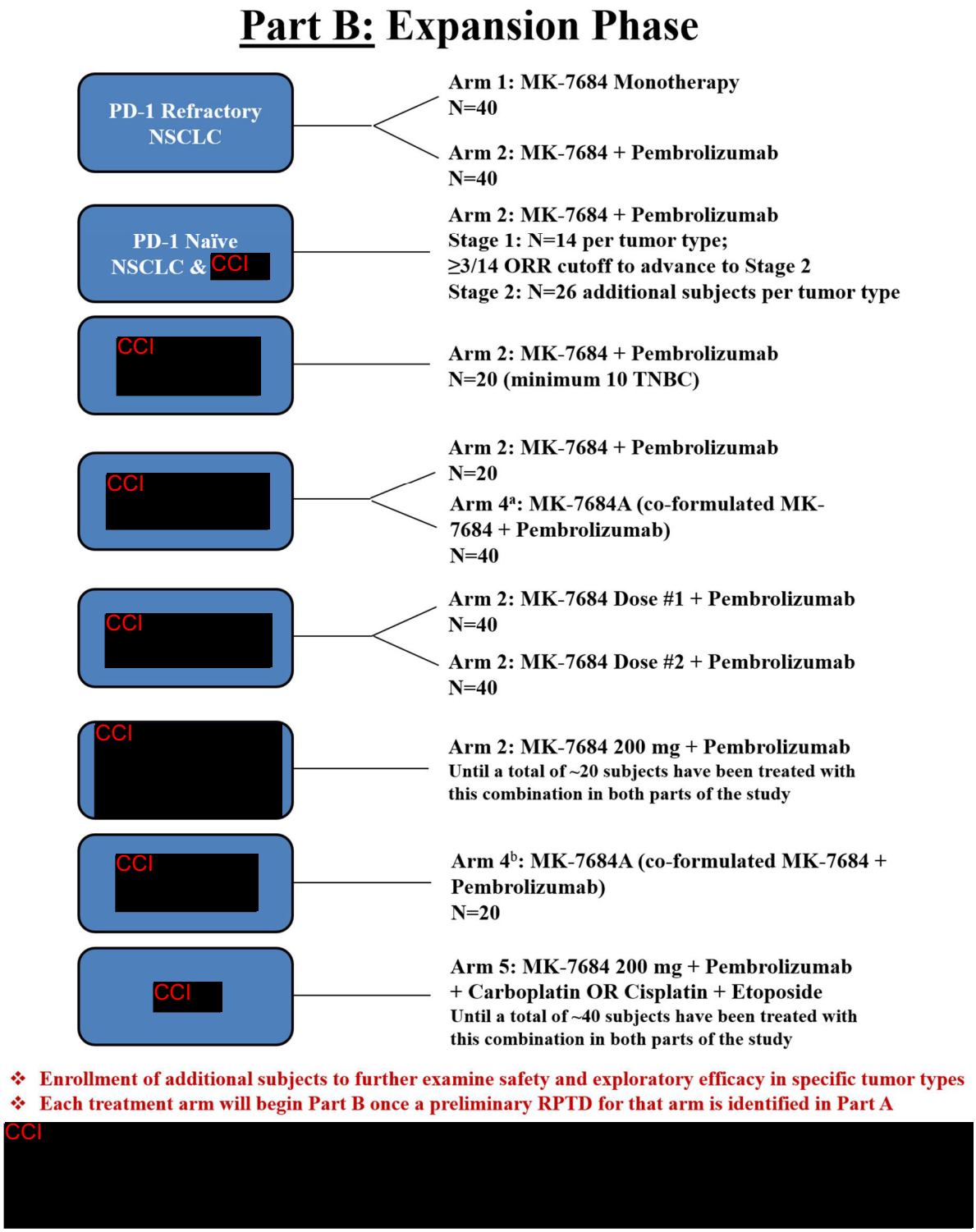


Figure 1 Trial Design

AUC = area under the curve; CCI ; IV = intravenous; mTPI = modified toxicity probability interval; NSCLC = non-small cell lung cancer; ORR = overall response rate; PD-1 = programmed death 1; RPTD = recommended Phase 2 dose; CCI
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3.0 OBJECTIVE(S) & HYPOTHESIS(ES)

In male and female subjects with advanced solid tumors who are at least 18 years of age:

3.1 Primary Objective(s) & Hypothesis(es)

1) **Objective:** To determine the safety and tolerability of MK-7684 monotherapy and to establish an RPTD
2) **Objective:** To determine the safety and tolerability of MK-7684 in combination with pembrolizumab and to establish an RPTD for MK-7684 when used in combination with pembrolizumab
3) CCI [redacted]

3.2 Secondary Objective(s) & Hypothesis(es)

1) **Objective:** To characterize the pharmacokinetic (PK) profile of MK-7684 when used as monotherapy in Arm 1, in combination with pembrolizumab in Arm 2, CCI [redacted]
2) **Objective:** To characterize the PK profile of pembrolizumab when used in combination with MK-7684 in Arm 2, CCI [redacted]
3) **Objective:** To evaluate the antitumor activity of MK-7684 when used as monotherapy in Arm 1, in combination with pembrolizumab in Arm 2, CCI [redacted] using Response Evaluation Criteria in Solid Tumors (RECIST), version 1.1 as assessed by investigator review and measured by overall response rate (ORR)

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3.3 Exploratory Objectives

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4.0 BACKGROUND & RATIONALE

4.1 Background

Refer to the MK-7684 Investigator's Brochure (IB) and the pembrolizumab IB for detailed background information on MK-7684, MK-7684A, and pembrolizumab.

4.1.1 Pharmaceutical and Therapeutic Background

The importance of intact immune surveillance function in controlling outgrowth of neoplastic transformation has been known for decades [2]. Accumulating evidence shows a correlation between tumor-infiltrating lymphocytes (TILs) in cancer tissue and favorable prognosis in various malignancies [3] [4] [5] [6] [7] [8] [9]. In particular, the presence of CD8+ T cells and the ratio of CD8+ effector T cells (T_{effs})/FoxP3+ regulatory T cells (T_{regs}) seems to correlate with improved prognosis and long-term survival in solid malignancies such as ovarian, colorectal, and pancreatic cancers, hepatocellular carcinoma, malignant melanoma, and renal cell carcinoma (RCC). Tumor-infiltrating lymphocytes can be expanded ex vivo and re-infused, inducing durable objective tumor responses in cancers such as melanoma [10] [11].

4.1.1.1 MK-7684 Background

MK-7684 is a humanized, antagonist monoclonal antibody (mAb) that binds to the immune checkpoint receptor, TIGIT, and blocks the interaction between TIGIT and its ligands. This human immunoglobulin G1 (IgG1) antibody is being developed as a cancer immunotherapeutic with the potential to be used as monotherapy or to be combined with pembrolizumab (a humanized anti-PD-1 receptor antibody) to increase benefit to patients with various tumor types.

TIGIT is an immunomodulatory receptor expressed primarily on activated CD4+ and CD8+ T cells, natural killer (NK) cells, and natural killer T (NKT) cells. Its structure reveals a single extracellular immunoglobulin domain, a transmembrane region, an immunoglobulin tail tyrosine (ITT)-like phosphorylation motif, and an immunoreceptor tyrosine-based inhibitory motif (ITIM).

TIGIT forms part of a co-stimulatory network that consists of a positive (CD226) and negative (TIGIT) immunomodulatory receptor on T cells, and ligands (CD155 and CD112) expressed on tumor cells and antigen presenting cells [12]. Whereas CD226 is widely expressed on most immune cells, TIGIT is highly expressed on memory T cells, T_{regs}, NK cells, and NKT cells [13] [14]. CD155/PVR (poliovirus receptor) and CD112/PVRL-2

(poliovirus receptor-related 2) are two nectin family members that are widely expressed both on cells of the hematopoietic system and on fibroblasts and endothelial cells. Functionally, these receptor ligands are involved in cell adhesion and motility. CD155 is reported to be overexpressed in several tumor types, and has been found to be induced by Ras activation and genotoxic stress [15] [16] [17] [18] [19].

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In addition, TIGIT is highly co-expressed with PD-1 on both CD4+ and CD8+ TILs including T_{regs}, in mouse and human tumors, and has been reported to be co-expressed with PD-1 and T-cell immunoglobulin and mucin domain containing-3 (Tim-3) on the TILs with the most exhausted phenotype [20] [21]. CCI [redacted] We hypothesize, therefore, that combining MK-7684 with pembrolizumab will offer substantially augmented antitumor efficacy.

4.1.1.2 Pembrolizumab (MK-3475) Background

Pembrolizumab is a potent humanized IgG4 mAb with high specificity of binding to the PD-1 receptor, thus inhibiting its interaction with PD-L1 and programmed cell death ligand 2 (PD-L2). Based on preclinical in vitro data, pembrolizumab has high affinity and potent receptor blocking activity for PD-1.

The PD-1 receptor-ligand interaction is a major pathway hijacked by tumors to suppress immune control. The normal function of PD-1, expressed on the cell surface of activated T cells under healthy conditions, is to down-modulate unwanted or excessive immune responses, including autoimmune reactions. PD-1 (encoded by the gene Pdcd1) is an Ig superfamily member related to CD28 and cytotoxic T-lymphocyte-associated antigen-4 (CTLA-4), which has been shown to negatively regulate antigen receptor signaling upon engagement of its ligands (PD-L1 and/or PD-L2) [22] [23].

The structure of murine PD-1 has been resolved [24]. PD-1 and family members are type I transmembrane glycoproteins containing an Ig variable-type (IgV-type) domain responsible for ligand binding and a cytoplasmic tail responsible for the binding of signaling molecules. The cytoplasmic tail of PD-1 contains 2 tyrosine-based signaling motifs, an ITIM, and an immunoreceptor tyrosine-based switch motif. After T-cell stimulation, PD-1 recruits the tyrosine phosphatases, SHP-1 and SHP-2, to the immunoreceptor tyrosine-based switch motif within its cytoplasmic tail, leading to the dephosphorylation of effector molecules such as CD3 zeta (CD3ζ), protein kinase C-theta (PKCθ), and zeta-chain-associated protein kinase (ZAP70), which are involved in the CD3 T-cell signaling cascade [25] [26] [27] [28]. The mechanism by which PD-1 down modulates T-cell responses is similar to, but distinct from that of CTLA-4 as both molecules regulate an overlapping set of signaling proteins [29] [30]. As a consequence, the PD-1/PD-L1 pathway is an attractive target for therapeutic intervention in a variety of cancers.

4.1.1.3 Lung Cancer: Epidemiology and Current Therapeutic Options

The global incidence of lung cancer was 1.8 million in 2012, resulting in an estimated 1.6 million deaths [31]. In the United States (US), the 2018 estimated incidence of new diagnoses was 234,030, and the estimated number of deaths was 154,050 [32].

4.1.1.3.1 NSCLC

NSCLC represents approximately 80% to 85% of all lung cancers. Of the patients with NSCLC, tumor histology is approximately 40% to 60% adenocarcinoma, 10% to 15% squamous, 5% neuroendocrine, and the rest, "not otherwise specified" [33].

Approximately 70% of patients with NSCLC have advanced disease not amenable to surgical resection at the time of diagnosis. From 2006 to 2012, the overall 5-year relative survival rate for lung cancer in the US was 17.7%. Five-year relative survival rates were 55% for localized, 28% for regional, 4.3% for distant, and 7.4% for unstaged [34].

In the open-label Phase 3 study KEYNOTE-024, treatment with pembrolizumab resulted in statistically significant increases in overall survival (OS) and PFS in treatment-naïve participants with metastatic NSCLC whose tumors expressed high levels of PD-L1 (tumor proportion score [TPS] ≥50%) with no epidermal growth factor receptor (EGFR) or anaplastic lymphoma kinase (ALK) genomic tumor aberrations compared to treatment with SOC platinum-based chemotherapy [35]. Furthermore, in the pembrolizumab treatment arm, treatment-related AEs of any grade were less frequent (occurring in 73.4% vs 90.0% of patients), as were Grades 3, 4, or 5 treatment-related AEs (26.6% vs 53.3%). Data from this study led to regulatory approval of pembrolizumab for this indication in the US and other countries around the world.

In the randomized Phase 2 cohort, Cohort G, of the open-label study, KEYNOTE-021, pembrolizumab plus pemetrexed and carboplatin showed statistically significant increases in objective response rate ([ORR]; 55% vs 29%) and PFS (8.9 vs 13.0 months, HR 0.53 [95% confidence interval [CI] 0.31 to 0.91]) compared to pemetrexed and carboplatin alone in participants with advanced non-squamous NSCLC, regardless of PD-L1 status [36]. The incidence of Grades ≥3 treatment-related AEs was similar between groups. Moreover, a recent update of data from KEYNOTE-021 showed that an OS benefit has also been seen when pembrolizumab is added to chemotherapy (hazard ratio [HR] 0.59; 95% CI 0.34 to 1.05; p=0.03) [37]. These findings were confirmed in a randomized Phase 3, double-blinded study, KEYNOTE-189, that showed that treatment with pembrolizumab plus pemetrexed and either carboplatin or cisplatin significantly prolonged OS (HR 0.49; 95% CI 0.38 to 0.64; p<0.001) and PFS (HR 0.52; 95% CI 0.43 to 0.64; p<0.001) compared with SOC chemotherapy as first-line treatment of metastatic, non-squamous NSCLC [38]. Adverse events of Grades ≥3 occurred in 67.2% of the patients in the pembrolizumab-containing arm and in 65.8% of patients in the placebo treatment arm. These results established pembrolizumab plus chemotherapy as an efficacious option for first-line treatment in patients with non-squamous NSCLC.

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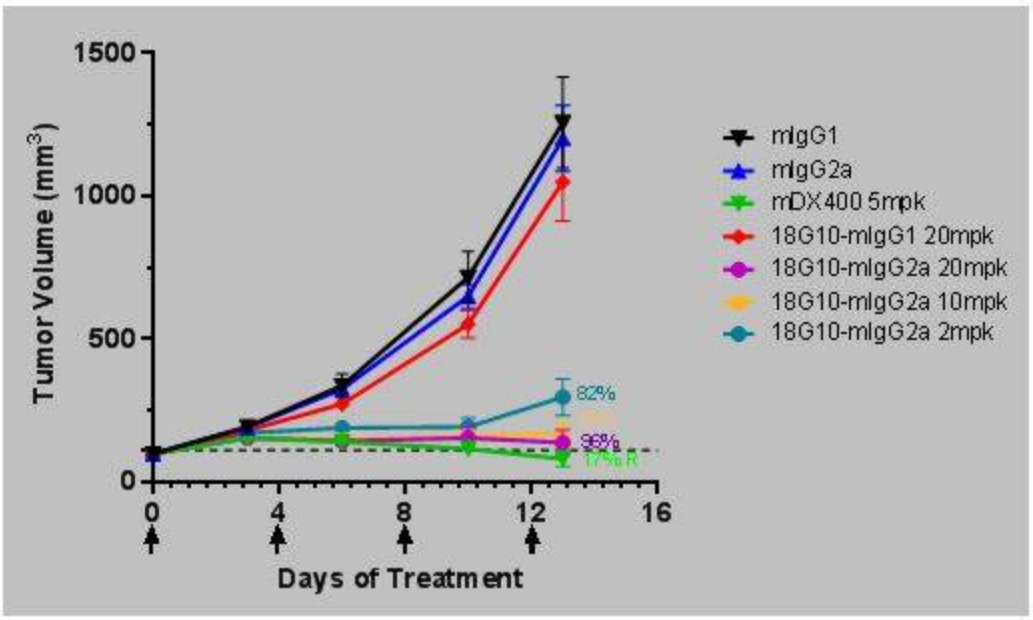
1500
1000
500
0
Tumor Volume (mm3)
0
4
8
12
16
Days of Treatment
mIgG1
mIgG2a
mDX400 5mpk
18G10-mIgG1 20mpk
18G10-mIgG2a 20mpk
18G10-mIgG2a 10mpk
18G10-mIgG2a 2mpk
82%
96%

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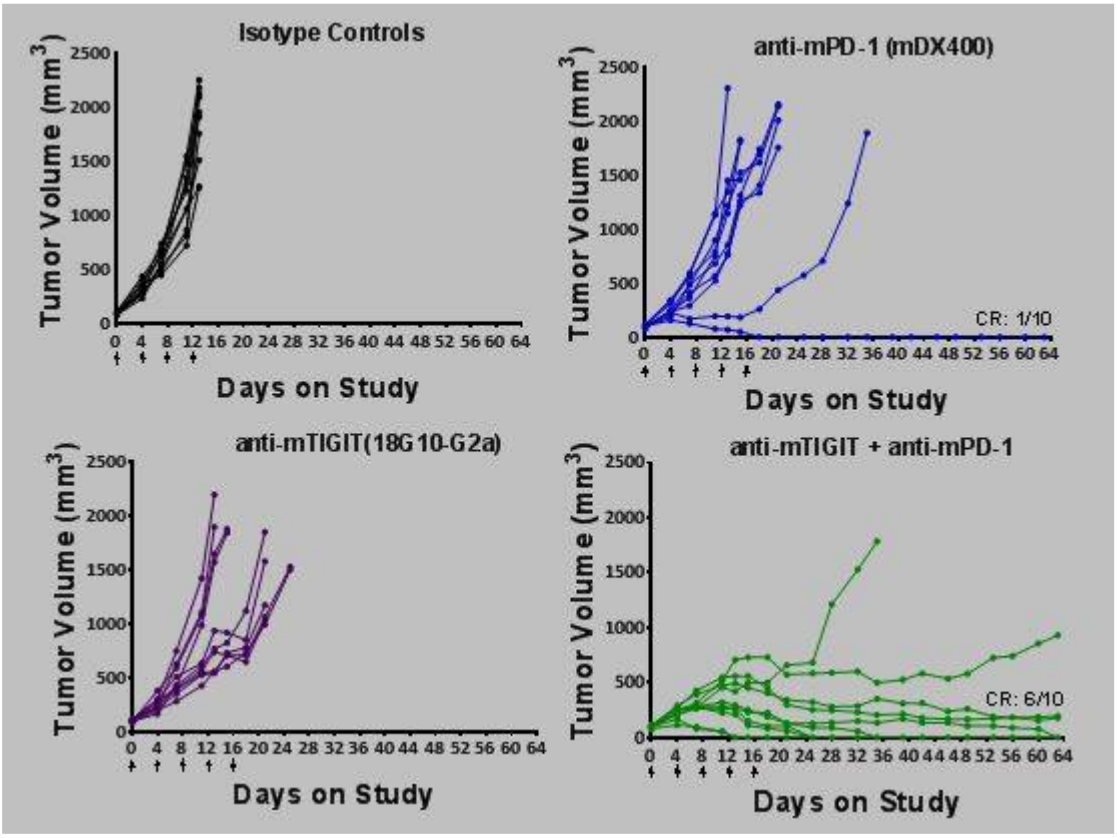
Isotype Controls
anti-mPD-1 (mDX400)
CR: 1/10
anti-mTIGIT(18G10-G2a)
anti-mTIGIT + anti-mPD-1
CR: 6/10
Tumor Volume (mm3)
Days on Study

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4.1.2.2 Pembrolizumab (MK-3475) Preclinical and Clinical Trials

Anti-mouse PD-1 or anti-mouse PD-L1 antibodies have demonstrated antitumor responses as a monotherapy in models of squamous cell carcinoma, pancreatic carcinoma, melanoma, and colorectal carcinoma. 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 T_{eff} function in vivo [54] [55] [56] [57] [25] [58]. In-house 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.

Pembrolizumab has an acceptable preclinical safety profile and is in clinical development as an IV immunotherapy for advanced malignancies. KEYTRUDA™ (pembrolizumab) is indicated for the treatment of patients across a number of indications.

No hematology changes have been observed in non-human primate safety studies of pembrolizumab; however, slight focal mononuclear cell infiltrates in multiple tissues that were considered an exacerbation of spontaneously occurring background mononuclear changes were detected in individual animals. Based on clinical experience with pembrolizumab, immune-mediated adverse effects may occur in patients. In clinical trials, the main immune-mediated adverse effects associated with pembrolizumab included low grade and low incidence of immune-mediated endocrinopathies, pneumonitis, colitis, hepatitis, and nephritis. Most immune-mediated adverse effects were reversible and managed with interruptions of pembrolizumab and administration of corticosteroids and/or supportive care. Immune-mediated adverse effects affecting more than one body system can occur simultaneously. While these immune-mediated adverse effects are not unexpected based on the mechanism of action of anti-PD-1 activity, they are fundamentally different in nature from phenotypes developed in PD-1 KO mice. In those models, PD-1 deficiency is associated with the onset of progressive autoimmune diseases. An immune-mediated dilated cardiomyopathy can be detected as early as 5 weeks of age in PD-1-/-mice on a BALB/c background [59] while lupus-like proliferative arthritis and glomerulonephritis developed in aging PD-1-/-C57BL/6 mice [60]. Also, earlier onset of diabetes and inflammatory insulitis

were observed in PD-L1/PD-L2-/-non-obese diabetic mice, which indicates that the loss of the PD-1 pathway leads to an accelerated disease course [61].

4.1.3 Ongoing Clinical Trials

4.1.3.1 MK-7684 Ongoing Clinical Trials

This trial represents the first-in-human use of MK-7684.

4.1.3.2 Pembrolizumab Ongoing Clinical Trials

Over 300 interventional clinical studies involving pembrolizumab are currently ongoing in a number of advanced solid tumor indications, as well as in hematological malignancies.

For further details, please refer to the IB.

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4.2 Rationale

4.2.1 Rationale for the Trial and Selected Subject Population

MK-7684 is being developed for treatment of solid tumors. This is the first-in-human trial of MK-7684 and is designed to assess the safety, tolerability, PK, and PD of escalating doses of MK-7684 when used as monotherapy and in combination with pembrolizumab in subjects with advanced solid tumors that have not responded to conventional therapy. The effect of MK-7684 on tumor size will also be explored.

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Overall, the Part B tumor types were selected based on expression of TIGIT and its receptors CD155 and CD112, known susceptibility of tumor types to immune checkpoint therapies, unmet medical need, and/or preliminary signs of clinical activity in the Part A portion of the study.

The NSCLC cohort was chosen based on its high expression of TIGIT and known responsiveness to PD-1 blockade. Both PD-1/PD-L1 inhibitor treatment-refractory and treatment-naïve populations are being assessed.

PD-1/PD-L1 inhibitor treatment-refractory NSCLC is an indication with a high unmet medical need, with reported objective response rates of ~10% for second-line chemotherapies [65]. There is scientific evidence that the expression of alternate immune checkpoints including TIGIT may increase after PD-1 blockade, suggesting that TIGIT could function as an escape mechanism to PD-1 therapy. TIGIT blockade may, therefore, reverse PD-1 resistance in some cases [20]. Since further PD-1/PD-L1 inhibitor monotherapy is not expected to benefit patients who have radiographic progression on a PD-1/PD-L1 inhibitor agent, both Arm 1 (MK-7684 monotherapy) and Arm 2 (MK-7684 and pembrolizumab combination therapy) will be tested. The intention is to assess preliminary efficacy in this population, and to compare the clinical efficacy of MK-7684 monotherapy to MK-7684 and pembrolizumab combination therapy in a uniform population.

The PD-1/PD-L1 inhibitor treatment-naïve Arm 2 cohort will assess activity of MK-7684 in combination with pembrolizumab. The intention is to determine whether adding MK-7684 to pembrolizumab provides added efficacy benefit to pembrolizumab alone, since a chemotherapy-free treatment option is preferable for some patients including those that are elderly, frail, or those with significant co-morbidities.

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

4.2.2 Rationale for Dose Selection/Regimen/Modification

4.2.2.1 CCI [redacted]

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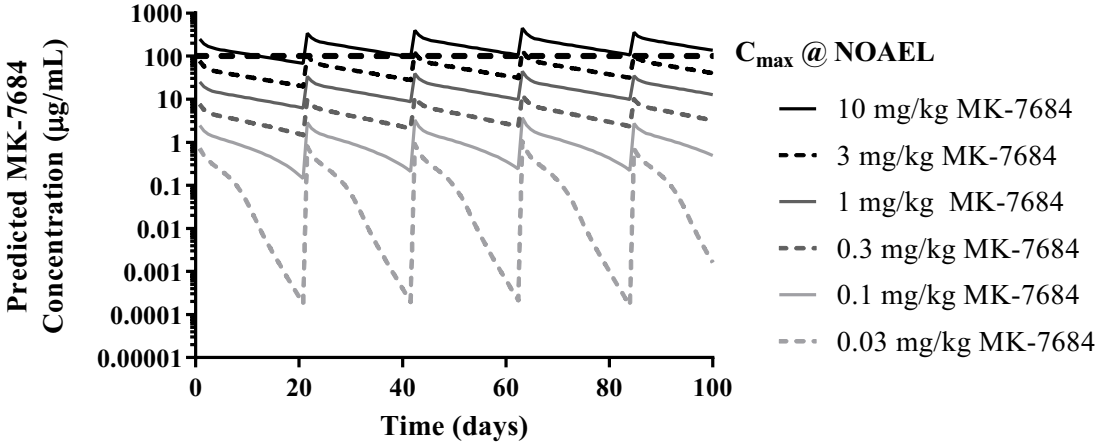
[redacted]


Predicted MK-7684 Concentration (µg/mL)
1000
100
10
1
0.1
0.01
0.001
0.0001
0.00001
0
20
40
60
80
100
Time (days)
C_{max} @ NOAEL
10 mg/kg MK-7684
3 mg/kg MK-7684
1 mg/kg MK-7684
0.3 mg/kg MK-7684
0.1 mg/kg MK-7684
0.03 mg/kg MK-7684

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4.2.2.2 Rationale for Preliminary MK-7684 RPTD (200 mg)

Based on the totality of available data, a preliminary MK-7684 RPTD of 200 mg was defined for Part B in select tumor types. The dosing recommendation was based on preliminary PK, safety, and efficacy data.

Preliminary PK profiles of MK-7684 suggested that target-mediated drug disposition of MK-7684 was saturated at the 200-mg dose. Saturation of target-mediated drug disposition reflects saturation of the target (TIGIT).

Available clinical safety data indicate that MK-7684 was well tolerated at doses up to and including 700 mg, both when used as monotherapy and in combination with pembrolizumab. No DLTs were observed at any of the MK-7684 doses tested either as monotherapy or in combination with pembrolizumab during dose escalation and confirmation, and the MTD was not reached. Reported AEs were consistent with those observed in subjects treated with pembrolizumab monotherapy in previous studies [71] and with those expected for patients with advanced cancers. No obvious dose-dependency of AE severity or frequency was observed.

Clinical efficacy was observed at the 200-mg dose level both during dose escalation and confirmation in subjects with advanced solid tumors of all types and during dose expansion in subjects with specific tumor types. Responses observed in PD-1/PD-L1 inhibitor treatment-refractory NSCLC, especially in subjects treated with MK-7684 monotherapy, demonstrate clinical antitumor activity at the 200-mg dose.

4.2.2.3 Rationale for Pembrolizumab Dose

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

- Clinical data from 8 randomized studies demonstrating flat dose-efficacy and exposure-efficacy relationships from doses of 2 mg/kg given once every 3 weeks to 10 mg/kg given once every 2 weeks;
- Clinical data showing meaningful improvement in benefit-risk including overall survival at 200 mg given once every 3 weeks across multiple indications; and
- Pharmacology data showing full target saturation in both systemic circulation (inferred from PK data) and tumor (inferred from physiologically-based PK analysis) at 200 mg given once every 3 weeks.

Among the 8 randomized dose-comparison studies, a total of 2262 subjects with either melanoma or NSCLC were enrolled, covering different disease settings (i.e., treatment-naïve, previously treated, PD-L1-enriched, and all-comers) and different treatment settings (i.e., monotherapy and in combination with chemotherapy). Five studies compared 2 mg/kg given once every 3 weeks with 10 mg/kg given once every 3 weeks (KN001 B2, KN001 D, KN002, KN010, and KN021), and 3 studies compared 10 mg/kg given once every 3 weeks with 10 mg/kg given once every 2 weeks (KN001 B3, KN001 F2, and KN006). All of these studies demonstrated flat dose-response and exposure-response relationships across the doses studied representing an approximate 5-fold to 7.5-fold difference in exposure. The 2-mg/kg (or 200-mg fixed dose) given once every 3 weeks provided similar responses to the highest doses studied. Subsequently, flat dose-response and exposure-response relationships were also observed in other tumor types including head and neck cancer, bladder cancer, gastric cancer, and classical Hodgkin's lymphoma, confirming 200 mg given once every 3 weeks 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 by direct binding to cancer cells.

Additionally, pharmacology data clearly show target saturation at 200 mg given once every 3 weeks. First, PK data in KN001 evaluating target-mediated drug disposition conclusively demonstrated saturation of PD-1 in systemic circulation at doses much lower than 200 mg given once every 3 weeks. Second, a physiologically-based PK analysis was conducted to predict tumor PD-1 saturation over a wide range of tumor penetration and PD-1 expressions. This evaluation concluded that pembrolizumab at 200 mg given once every 3 weeks achieves full PD-1 saturation in both blood and tumor.

Finally, population PK analysis of pembrolizumab which characterized the influence of body weight and other subject covariates on exposure, has shown that fixed dosing provides similar control of PK variability as weight-based dosing, with considerable overlap in the distribution of exposures from the 200-mg given once every 3 weeks dose and the 2-mg/kg given once every 3 weeks 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 given once every 3 weeks fixed dose was selected for evaluation across all pembrolizumab protocols.

No dose reduction is allowed for pembrolizumab in this trial.

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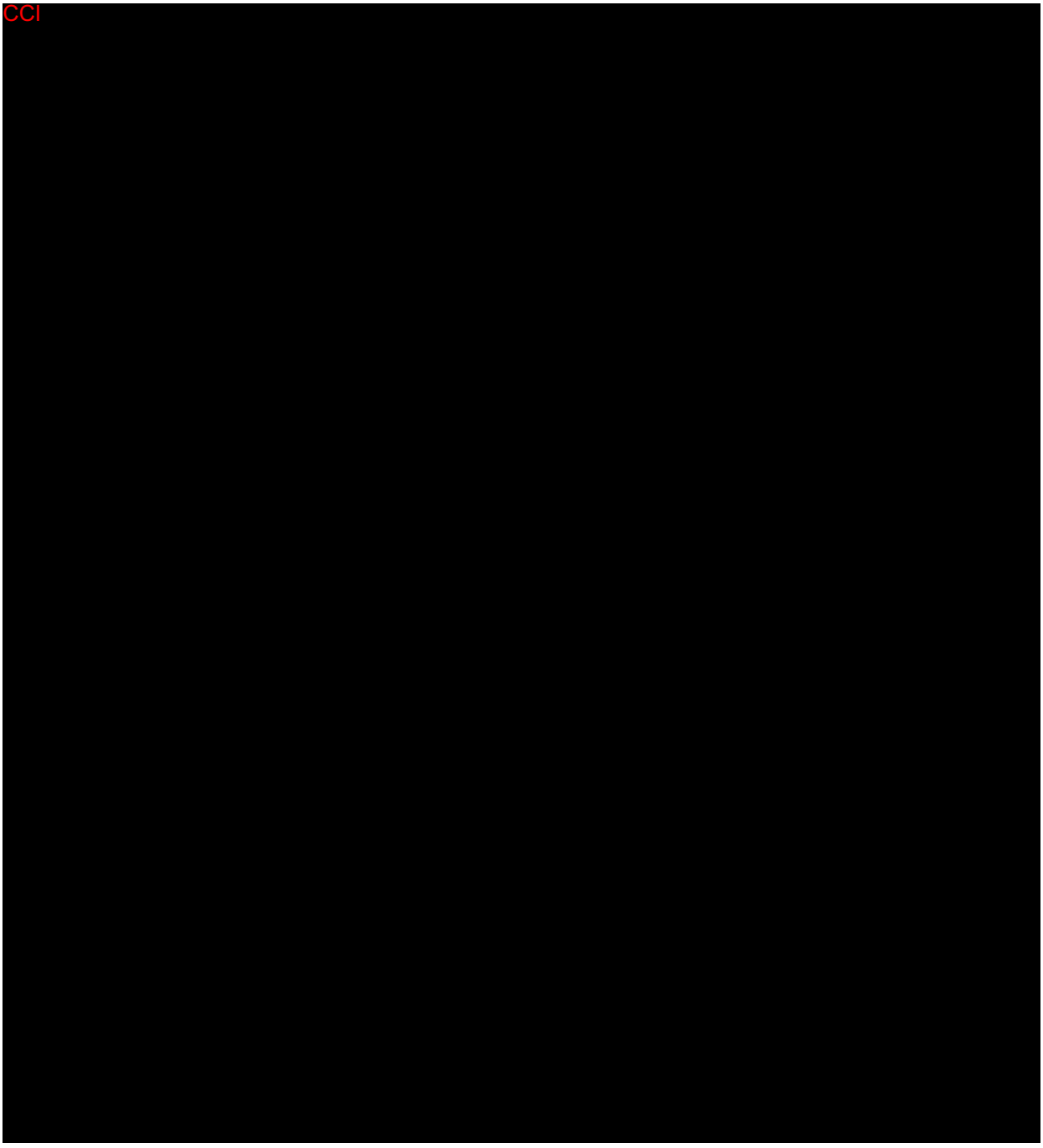

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[redacted]

4.2.3 Rationale for Endpoints

4.2.3.1 Efficacy Endpoints

Overall response rate is a secondary efficacy endpoint for this trial. Exploratory endpoints include DOR and PFS. Tumor response will be assessed by investigators using RECIST, version 1.1. CCI

[redacted]

RECIST guidelines, initially published in 2000 (version 1) and updated in 2009 (version 1.1), were established by the RECIST working group, a collection of academic investigators, cooperative groups, industry, and government authorities. These guidelines are widely considered the gold standard for quantitative assessment of changes in tumor burden in response to anticancer therapeutic agents.

4.2.3.2 Safety Endpoints

The primary objectives of this trial include characterizing the safety and tolerability of MK-7684 when used as monotherapy and in combination with pembrolizumab CCI [redacted] in subjects with advanced solid tumors. CCI [redacted]

The primary safety analyses will be based on subjects who experience toxicities as defined by CTCAE, version 4.0. Safety will be assessed by quantifying the toxicities and grades of toxicities experienced by subjects who receive MK-7684 or CCI [redacted].

The attribution to drug, time-of-onset, duration of the event, its resolution, and any concomitant medications administered will be recorded. Safety data will include, but is not limited to, AEs, SAEs, fatal AEs, and laboratory changes. Furthermore, specific events will be collected and designated as events of clinical interest (ECIs) as described in Section 7.2.3.2.

CCI [redacted]

4.2.3.3 Pharmacokinetic Endpoints

Secondary objectives of this trial are to characterize the PK profiles of MK-7684 when used as monotherapy in Arm 1, in combination with pembrolizumab in Arm 2 CCI [redacted]

The concentrations of these agents will serve as the primary readout for the PK, and this data will be used to derive PK parameters of MK-7684 alone and in combination. Furthermore, the results of these analyses will be used in conjunction with the PD, safety, and exploratory endpoints to help assess future dosing strategies for MK-7684.

4.2.3.3.1 CCI [redacted]

[redacted]

4.2.3.4 CCI [redacted]

4.2.3.4.1 CCI [redacted]

[redacted]

4.2.3.4.2 CCI [redacted]

[redacted]

4.2.3.4.3 CCI [redacted]

[redacted]

4.2.3.5 CCI [redacted]

CCI [redacted]

CCI

[redacted]

CCI

[redacted]

4.2.3.6 Future Biomedical Research

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

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

4.3 Benefit/Risk

It cannot be guaranteed that subjects in clinical trials will directly benefit from treatment during participation as clinical trials are designed to provide information about the safety and effectiveness of an investigational medicine(s).

5.0 METHODOLOGY

5.1 Entry Criteria

5.1.1 Diagnosis/Condition for Entry into the Trial

Male and female subjects with advanced solid tumors who are at least 18 years of age 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. For Part A subjects enrolled prior to Amendment 7, must meet the following criterion:

   Have a histologically or cytologically confirmed metastatic solid tumor for which there is no available therapy that is expected to convey clinical benefit.

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[redacted]

For Part B (and for Part A, once a decision is made to restrict the tumor types in Part A) – Have one of the following tumor types:

a. Advanced metastatic non-small cell lung cancer (NSCLC) that meets the criteria described below. Subjects who have EGFR or ALK mutant tumors should have received an approved targeted therapy.

    i. [Arm 1 & Arm 2] - PD-1/PD-L1 inhibitor treatment-refractory subjects must have progressed on prior anti-PD-1/PD-L1 therapy

(Arms 1 and 2). PD-1/PD-L1 inhibitor treatment-refractory disease is defined as (subjects must meet all of the following criteria):

a. Have received at least 2 doses of anti-PD-1/PD-L1 mAb at a local regulatory agency-approved dose and schedule.

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

c. Have documented disease progression within 24 weeks of the last dose of anti-PD-1/PD-L1 mAb. Subjects who were re-treated with anti-PD-1/PD-L1 mAb and subjects who were on maintenance with anti-PD-1/PD-L1 mAb will be allowed to enter the trial as long as there is documented PD within 24 weeks of the last treatment date (with anti-PD1/PD-L1 therapy).

ii. [Arm 2] - PD-1/PD-L1 inhibitor treatment-naïve subjects (Arm 2 only) may be untreated or could have received and progressed on 1 prior platinum-containing chemotherapy regimen, but must not have received prior anti-PD-1/PD-L1 therapy.

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[redacted]

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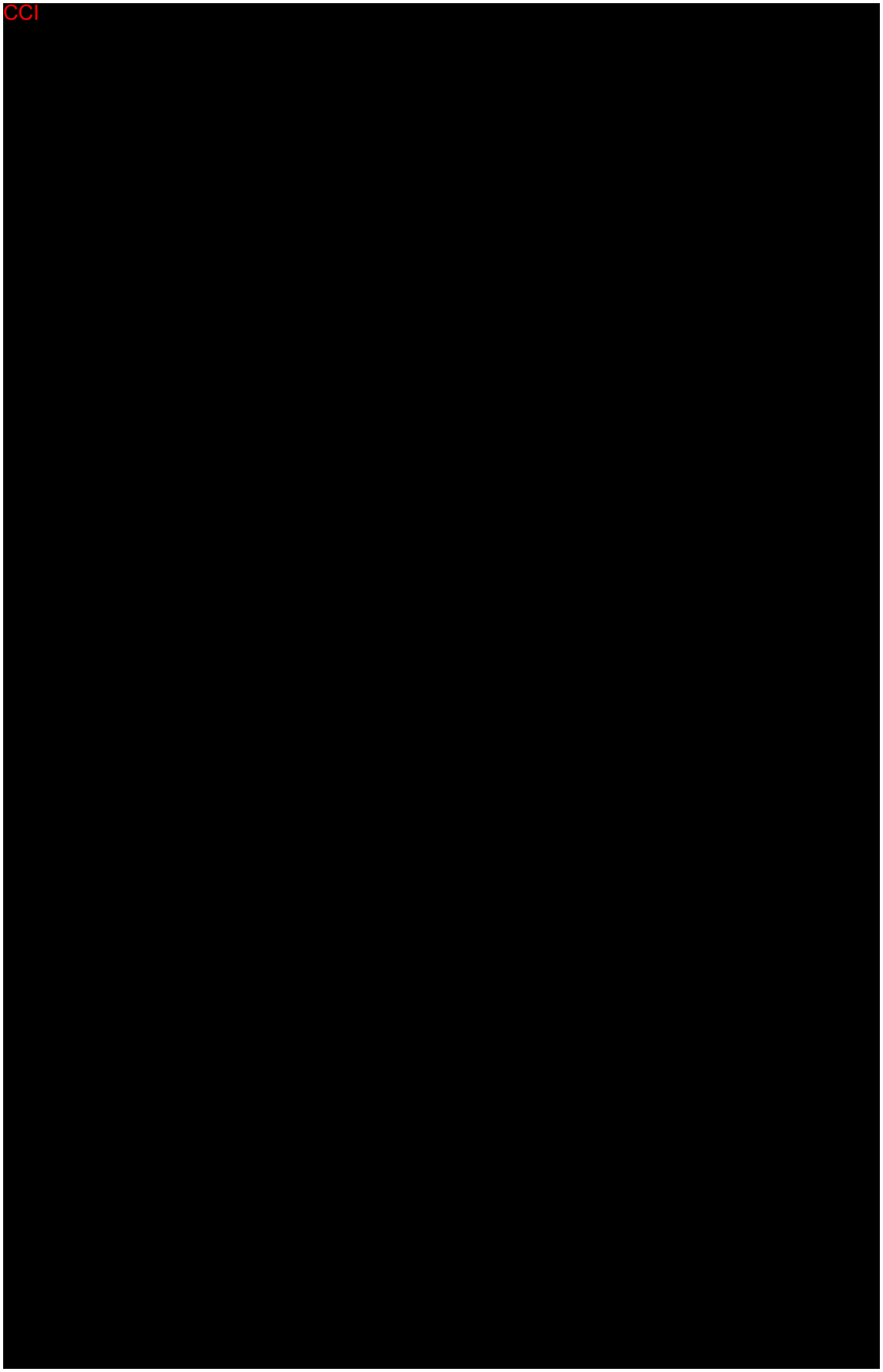

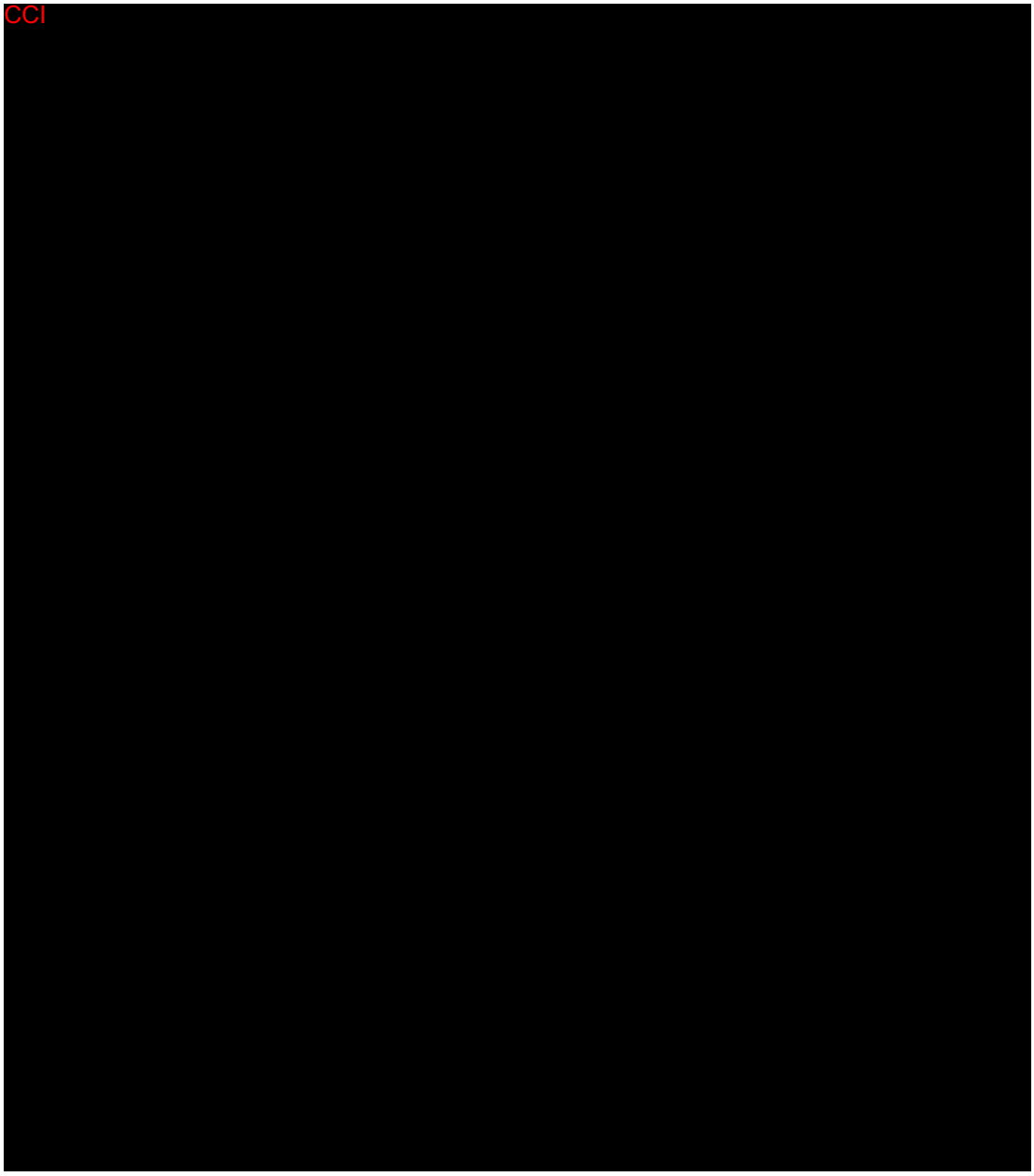

The Sponsor may prematurely terminate enrollment into a cohort for administrative reasons; in such cases, the sites will be notified via an administrative letter. All subjects already enrolled or in the screening period will be allowed to continue in the study.

2. Have measurable disease by RECIST.
3. Be male or non-pregnant and non-breast feeding female, ≥18 years of age on the day of providing documented informed consent.
4. Have an Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 1.

5. Have adequate organ function as defined in Table 3 during screening. Screening laboratory specimens must be collected within 7 days prior to the start of study treatment.

Table 3 Adequate Organ Function Laboratory Values

System / Parameter	Laboratory Value
HEMATOLOGICAL	
Absolute neutrophil count (ANC)	>1500/µL
Platelet count	>100 000/µL
Hemoglobin	≥9 g/dL or ≥5.6 mmol/L without transfusions within 2 weeks of treatment initiation
RENAL	
Creatinine **OR** Measured or calculated creatinine clearance (CrCl)[1] NOTE: Glomerular filtration rate (GFR) can be used in place of creatinine or CrCl	≤1.5 × institutional upper limit of normal (ULN) **OR** ≥50 mL/min for subjects with creatinine levels >1.5 × institutional ULN (all cohorts except ES-SCLC) ≥60 mL/min for subjects with creatinine levels >1.5 × institutional ULN (subjects with ES-SCLC enrolled as part of Amendment 12)
HEPATIC	
Total bilirubin **OR** Direct bilirubin	Total bilirubin ≤1.5 × ULN **OR** Direct bilirubin ≤ULN for subjects with total bilirubin levels >1.5 × ULN
Alanine aminotransferase (ALT) or serum glutamic pyruvic transaminase (SGPT) **AND** Aspartate aminotransferase (AST) or serum glutamic oxaloacetic transaminase (SGOT)	≤2.5 × ULN **OR** ≤5 × ULN for subjects with liver metastases
COAGULATION	
International Normalized Ratio (INR) or Prothrombin time (PT)	≤1.5 × ULN unless the subject is receiving anticoagulant therapy
Activated partial thromboplastin time (aPTT) or Partial thromboplastin time (PTT)	≤1.5 × ULN unless the subject is receiving anticoagulant therapy

Note: Assessment of adequate organ function as measured by laboratory testing will be based on laboratory results obtained locally at the site. The ULN will be based on local laboratory normal ranges.

1. Creatinine clearance should be calculated using the Cockcroft-Gault Method; refer to Appendix 12.5 for the appropriate formula.

6. Female subjects of childbearing potential must have a negative urine or serum pregnancy test within 72 hours prior the first dose of study treatment. If the urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required.

7. Female subjects of childbearing potential (Section 5.7.2) must be willing to use an adequate method of contraception as outlined in Section 5.7.2 – Contraception, for the course of the trial through 120 days after the last dose of MK-7684,

pembrolizumab, or MK-7684A OR 180 days after the last dose of chemotherapeutic agents.

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

8. Male subjects with a female partner(s) of childbearing potential must agree to use an adequate method of contraception as outlined in Section 5.7.2 – Contraception, starting with the first dose of study treatment through 120 days after the last dose of MK-7684, pembrolizumab, or MK-7684A OR 180 days after the last dose of chemotherapeutic agents.

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

9. Be willing and able to provide documented informed consent/assent for the trial. The subject may also provide consent/assent for future biomedical research (FBR); however, the subject may participate in the main trial without participating in FBR.

10. Have provided an archival tumor tissue sample or newly obtained core or excisional biopsy of a tumor lesion not previously irradiated. Formalin-fixed, paraffin-embedded tissue blocks are preferred to slides. Newly obtained biopsies are preferred to archived tissue.

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5.1.3 Subject Exclusion Criteria

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

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

not be excluded from participation in this trial. Subjects with Grade 2 or lower neuropathy may be eligible.

CCI [redacted]

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

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

3. Has received previous treatment with another agent targeting the TIGIT receptor.
4. Has received previous treatment with an immunomodulatory agent (e.g., anti-PD-1/PD-L1 or CTLA-4) and was discontinued from that treatment due to a Grade 3 or higher irAE.

   CCI [redacted]

5. Has had a severe hypersensitivity reaction to treatment with another mAb.
6. Is expected to require any other form of antineoplastic therapy while participating in the trial.
7. Has had major surgery in the past 4 weeks.
8. Is on chronic systemic steroid therapy in excess of replacement doses (e.g., ≥10 mg/day of prednisone equivalent), or on any other form of immunosuppressive medication. Subjects with reactive airway disease that require intermittent use of bronchodilators, inhaled steroids, or local steroid injections will not be excluded from the trial.
9. Has a history of a previous additional malignancy, unless potentially curative treatment has been completed with no evidence of malignancy for 5 years.

   The time requirement of 5 years with no evidence of disease does not apply to:

   - The tumor for which the subject is enrolled in the trial;
   - Subjects who underwent successful definitive resection of basal cell carcinoma of the skin;
   - Superficial bladder cancer;
   - In situ cervical cancer; or
   - Other in situ cancers.

10. Has known active central nervous system (CNS) metastases and/or carcinomatous meningitis. Subjects with previously treated brain metastases may participate

provided they are radiologically stable, i.e., without evidence of progression for at least 4 weeks by repeat imaging (note that the repeat imaging should be performed during study screening), clinically stable and without requirement of steroid treatment for at least 14 days prior to first dose of trial treatment.

CCI

[redacted]

11. Has an active autoimmune disease or a documented history of autoimmune disease, except vitiligo or resolved childhood asthma/atopy. Replacement therapy (e.g., thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency) is not considered a form of systemic treatment. Subjects receiving ongoing hormone replacement therapy for previous PD-1 or CTLA-4 inhibitor-related endocrine irAEs will not be excluded from participation in this trial.

CCI

[redacted]

12. Has an active infection requiring systemic treatment.
13. Has interstitial lung disease.
14. Has a history of (non-infectious) pneumonitis that required steroids or has current pneumonitis.
15. Has symptomatic ascites or pleural effusion. A subject who is clinically stable after treatment of these conditions (including therapeutic thoracentesis or paracentesis) will not be excluded from participation in this trial.
16. Has previously had a stem cell or bone marrow transplant.
17. Has previously had a solid organ transplant.
18. Has a history or current evidence of any condition, therapy, or laboratory abnormality that might, in the opinion of the treating investigator, confound the results of the trial, interfere with the subject's participation for the full duration of the trial, or make trial participation not in the best interest of the subject.

19. Is known to be human immunodeficiency virus (HIV)-positive (e.g., HIV 1/2 antibodies) and/or known to have active chronic or acute hepatitis B (e.g., HBsAg reactive) or hepatitis C (e.g., HCV RNA [qualitative] is detected).
20. Has a known psychiatric and/or substance abuse disorder that would make it difficult for the subject to cooperate with the requirements of the trial.
21. Is a regular user (including "recreational use") of any illicit drugs at the time of providing documented informed consent, or has a recent history (within the last year) of substance abuse (including alcohol), as determined by the treating investigator. Subjects who use cannabis for medicinal purposes or to treat specific symptoms will not be excluded unless it is being abused in the opinion of the treating investigator.
22. 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 MK-7684, pembrolizumab, or MK-7684A OR 180 days after the last dose of chemotherapeutic agents.
23. Has received a live-virus vaccine within 30 days prior to the first dose of study treatment. Seasonal flu vaccines that do not contain live virus are permitted.
24. Has had hormonal cancer therapy (e.g., tamoxifen, leuprolide). within 4 weeks prior to the first dose of study treatment.

CCI

[redacted]

5.2 Trial Treatment(s)

The treatment(s) to be used in this trial are outlined below in Table 4. Detailed instructions regarding study drug administration are provided in the Pharmacy Manual.

In the dose escalation and confirmation phase of Part A, an mTPI design with a target DLT rate of approximately 30% will be applied to identify a preliminary RPTD of MK-7684 independently in Arm 1 (MK-7684 monotherapy) and Arm 2 (MK-7684 in combination with pembrolizumab). The starting dose of MK-7684 will be 2.1 mg and may proceed, based on safety events, to a dose of 700 mg. Intermediate doses may be explored if one of the

pre-planned doses is deemed unacceptably toxic and the immediate lower dose is deemed too low. The preliminary RPTD of MK-7684 in the combination treatment arm will not exceed, but may equal, the preliminary RPTD in the MK-7684 monotherapy treatment arm.

CCI [redacted]

In Part B (expansion phase), the preliminary RPTDs identified for MK-7684 monotherapy and combination therapy with pembrolizumab using the mTPI design in Part A will be used in subjects with NSCLC, CCI [redacted] as described in Inclusion Criterion 1 (Section 5.1.2). CCI [redacted] If the dose confirmation portion of the Part A mTPI design calls for a de-escalation of one or more of these doses, the doses will be modified accordingly. The final decision for these doses will be communicated to sites via an administrative letter before enrollment into this cohort begins. Subjects in Part B with ES-SCLC will be treated with MK-7684 in combination with pembrolizumab, the investigator's choice of platinum agent (carboplatin or cisplatin), and etoposide for up to 4 cycles followed by MK-7684 and

pembrolizumab for up to an additional 31 cycles. The doses of chemotherapy will be those identified using the mTPI design in Part A.

In the combination treatment arms (Arms 2, 3, and 5), in both Part A and Part B (as applicable), the dose of pembrolizumab will remain constant at 200 mg. Pembrolizumab will be administered first on Day 1 of each cycle, with administration of MK-7684 occurring approximately 30 minutes after completion of the pembrolizumab infusion (Arms 2, 3, and 5). CCI

CCI

Table 4 Trial Treatment

Drug	Dose/Potency	Dose Frequency	Route of Administration	Regimen/ Treatment Period	Use	IMP/NIMP
Arms 1, 2, 3, and 5: MK-7684	Part A dose escalation and confirmation: 2.1 mg 7 mg 21 mg 70 mg 210 mg 700 mg (tentatively) Part A non-squamous NSCLC enrolled as part of Amendment 7: 200 mg CCI [redacted] Part B expansion phase: Preliminary RPTDs identified in Part A CCI [redacted]	Every 3 weeks	IV infusion	Day 1 of each 21-day cycle for up to 35 cycles	Experimental	IMP
Arms 2, 3, and 5: Pembrolizumab	Part A and Part B: 200 mg	Every 3 weeks	IV infusion	Day 1 of each 21-day cycle for up to 35 cycles	Experimental	IMP

Drug	Dose/Potency	Dose Frequency	Route of Administration	Regimen/ Treatment Period	Use	IMP/NIMP
CCI [redacted]						

AUC = area under the curve; IMP = investigational medicinal product; IV = intravenous; NIMP = non-investigational medicinal product; NSCLC = non-small cell lung cancer; RPTD = recommended Phase 2 dose; CCI [redacted]

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

All supplies indicated in Table 4 above will be provided centrally by the Sponsor or locally by the trial site, subsidiary or designee, depending on local country operational or regulatory requirements.

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

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 the dose escalation and confirmation phase of Part A of the trial, an mTPI design [1] with a target DLT rate of approximately 30% will be applied to identify a preliminary RPTD of MK-7684 in Arm 1 (MK-7684 monotherapy) and Arm 2 (MK-7684 in combination with pembrolizumab) in subjects with advanced solid tumors according to the rules outlined in Table 5.

Five pre-determined dose levels of MK-7684 will be explored independently in each arm: 2.1 mg, 7 mg, 21 mg, 70 mg, and 210 mg. The dose of 210 mg was chosen based on changes to hematology parameters in cynomolgus monkeys, including a transient reduction in T lymphocytes in the blood occurring within hours of dosing (see Section 4.0). If safety data demonstrate acceptable hematology parameters in humans, an additional cohort dosed at 700 mg may be added after the completion of the DLT period for 210 mg and provided that the DLT rate at 210 mg grants the decision to “escalate”. If dose escalation proceeds to the 700-mg dose, at least 6 subjects will be enrolled and complete the DLT observation period with acceptable toxicity rates in each arm before enrollment into the 700-mg cohort of Part B begins for the respective arm. At least 3 subjects must enroll at 700 mg in Arm 1 and complete the DLT period with acceptable toxicity rates prior to enrollment of subjects at the 700-mg dose level in Arm 2

Intermediate doses may be explored if one of the pre-planned doses is deemed unacceptably toxic and the immediate lower dose is deemed too low. All dose escalation decisions will be based on the occurrence of DLTs and will be made jointly by the investigators and the Sponsor. The dose of pembrolizumab in Arm 2 will remain constant at 200 mg.

Treatment allocation for Part A will be accomplished by non-random assignment. Enrollment into the MK-7684 + pembrolizumab combination treatment arm (Arm 2) will begin once 2 dose levels of MK-7684 have been tested in the MK-7684 monotherapy arm (Arm 1) and a dose escalation decision has been made so that the starting dose of MK-7684 in Arm 2 will be at least 2 levels below the dose being tested in Arm 1. When both treatment arms are open for enrollment, IVRS/IWRS will alternate subject assignment between Arm 1 and Arm 2 starting with Arm 1. For example, once the 21-mg dose cohort of Arm 1 (MK-7684 monotherapy) and the 2.1-mg dose cohort of Arm 2 (MK-7684 + pembrolizumab) are open for enrollment, the first subject will be allocated to Arm 1, the second subject will be allocated to Arm 2, the third subject will be allocated to Arm 1, etc. An observation period of at least 24 hours will occur between treatment initiation in subjects enrolled within each dose

level. Each new dose cohort will open for enrollment without delay once the 21-day DLT observation period of the previous dose cohort is completed and a dose escalation decision is made.

In Table 5, the number of subjects treated is indicated in the columns and the number of subjects who experience at least 1 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 (i.e., unacceptably toxic dose; DU).

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 5). 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.

During dose escalation, a minimum of 3 subjects are required at each dose. 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 21-day DLT assessment period. For example, if 3 subjects are enrolled at a dose and none of them 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 may 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 (i.e., 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, i.e., 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 5.

In total, 3 to 14 subjects may be enrolled at a given dose level. The dose of MK-7684 in the combination arm (Arm 2) may not be escalated to a dose that is higher than the MK-7684 dose in the MK-7684 monotherapy arm (Arm 1); however, once dose escalation of MK-7684 in Arm 1 is stopped, the dose of MK-7684 in Arm 2 may be escalated up to that dose.

To maximize enrollment efficiency, once a possible preliminary RPTD is reached, Part A will be restricted to the tumor indications specified in Inclusion Criterion 1 for Part B (Section 5.1.2), CCI [redacted]. These subjects may be used toward enrollment caps in Part B. For example, if dose escalation reaches the highest dose level and DLT data suggest ‘stay’ or ‘escalate’ based on the mTPI design (Table 5), the remaining subjects enrolled in Part A will be restricted to the tumor indications specified in Inclusion Criterion 1 for Part B (Section 5.1.2).

Dose escalation and confirmation will end after 14 subjects have been treated at any of the selected doses (including intermediate doses) as long as the decision based on Table 5 is to stay. The pool-adjacent-violators algorithm [1] that forces the DLT rate estimates to be non-decreasing with dose levels and pools adjacent violators for weighted estimates by sample size, will be used to estimate the DLT rates across doses in each treatment arm. The dose with an estimated DLT rate closest to 30% may be treated as a preliminary RPTD. The

totality of the data will be considered before deciding on the dose(s) to carry forward to Part B and the escalation schedule may be adjusted based on PD, PK, and safety data emerging throughout the trial. The preliminary RPTD of MK-7684 in the combination arm (Arm 2) will not exceed, but may equal, the preliminary RPTD in the MK-7684 monotherapy arm (Arm 1).

Note that while 30% was the target toxicity rate used to generate the guidelines in Table 5, the observed rates of subjects with DLTs at any given dose level may be slightly above or below 30%.

Table 5 Dose Escalation and Confirmation Rules Based on the Modified Toxicity Probability Interval Design

	Number of Subjects Treated at Current Dose											
Number of Subjects with at Least 1 DLT	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

E = Escalate to the next higher dose
S = Stay at the current dose
D = De-escalate to the next lower dose
DU = The current dose is unacceptably toxic
Target toxicity rate = 30%
Flat non-informative prior Beta (1,1) is used as a prior and ε1=ε2=0.03 [1], [73], [74]

CCI [redacted]

5.2.1.3 Expansion Phase

In Part B of the trial, the preliminary RPTDs identified using the mTPI design in Part A will be used in subjects with NSCLC, CCI [redacted] as described in Inclusion Criterion 1 (Section 5.1.2).

The preliminary MK-7684 RPTD(s) identified in Part A, Arm 1 will be tested in approximately 40 PD-1/PD-L1 inhibitor treatment-refractory subjects with NSCLC.

The preliminary MK-7684 RPTD(s) identified in Part A, Arm 2 in combination with a fixed dose of 200 mg of pembrolizumab will be tested as follows:

- In approximately 40 PD-1/PD-L1 inhibitor treatment-refractory subjects with NSCLC.

- In 14 to 40 PD-1/PD-L1 inhibitor treatment-naïve subjects each with NSCLC CCI [redacted], using an adaptive design. In the adaptive design, if 3 or more objective responses are observed out of the first 14 subjects in each indication based on RECIST, version 1.1, the corresponding tumor type will continue enrolling up to 40 subjects. Enrollment will not be held after the first 14 subjects; data will be analyzed on an ongoing basis.
- CCI [redacted]

CCI [redacted]

Each treatment arm will begin Part B once a preliminary RPTD for that arm is identified in Part A, CCI [redacted]. If a preliminary RPTD cannot be confidently identified in either or both of the treatment arms based on the totality of the data from the dose escalation and confirmation phase of the study (i.e., the MTD is not reached, high variability is observed for PK profiles, or target engagement cannot be confirmed), up to 2 doses of MK-7684 may be tested in a subset of the expansion phase at the Sponsor's discretion.

CCI [redacted]

Data from subjects treated at the preliminary RPTDs in Part A will be included in the analysis of Part B if they meet the specifications described in Inclusion Criterion 1 (Section 5.1.2). Final RPTDs for MK-7684, both when used as monotherapy and in combination with pembrolizumab, will be determined using PK and PD endpoints, as well as all available safety data from subjects in Part A and Part B, including DLT rates and the cumulative incidence of late toxicities (i.e., toxicities that occur after the 21-day DLT

observation period). When both treatment arms are open for enrollment to PD-1/PD-L1 inhibitor treatment-refractory NSCLC subjects in Part B, IVRS/IWRS will alternate subject assignment between Arm 1 and Arm 2 starting with Arm 1, until enrollment targets are met.

CCI

[redacted]

[redacted]

5.2.1.4 Definition of Dose-limiting Toxicity

The CTCAE, version 4.0 will be used to grade the severity of AEs in this trial.

Dose-limiting toxicities will be defined from toxicities observed during the first cycle of treatment (21 days) for each dose level explored. See Section 5.9 for rules on replacement of subjects who do not complete the DLT observation period.

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

1. Any Grade 4 non-hematological toxicity (not laboratory)
2. Any Grade 4 hematological toxicity lasting ≥7 days, except:
    - Thrombocytopenia
        - Grade 4 thrombocytopenia of any duration
        - Grade 3 thrombocytopenia associated with bleeding
    - Lymphopenia
        - Grade 4 lymphopenia lasting ≥21 days
3. Any Grade 3 non-hematological toxicity (not laboratory) lasting >3 days despite optimal supportive care
4. Any clinically significant Grade 3 or Grade 4 non-hematological laboratory abnormality, if:
    - Medical intervention is required to treat the subject, or
    - The abnormality leads to hospitalization, or
    - The abnormality persists for >1 week

5. Any Grade 3 or 4 febrile neutropenia
6. Any treatment-related AE that causes the subject to discontinue treatment during Cycle 1
7. Any treatment-related toxicity that causes a delay in Cycle 2 of >2 weeks
8. Any Grade 5 toxicity

5.2.2 Timing of Dose Administration

Study treatments in all arms will be given on Day 1 of each 3-week cycle, except etoposide which will be given on Days 1, 2, and 3 of each 3-week cycle.

In Arms 2, 3, and 5, pembrolizumab will be administered first on Day 1 of each cycle, with administration of MK-7684 occurring approximately 30 minutes after completion of the pembrolizumab infusion.

In Arm 3, the order of infusions will be as follows: pembrolizumab, MK-7684, pemetrexed, then carboplatin. Subjects should receive premedication per the approved product labels for pemetrexed and carboplatin.

In Arm 5, the order of infusions will be as follows: pembrolizumab, MK-7684, carboplatin or cisplatin, then etoposide. Subjects should receive premedication per the approved product labels for carboplatin/cisplatin and etoposide.

In Arm 1, Arm 2, and Arm 4, treatment in Cycle 2 may be administered up to 5 days after the scheduled Day 1. Beginning in Cycle 3, treatment may be administered up to 3 days before or 5 days after the scheduled Day 1 of each cycle. In Arm 3 and Arm 5, treatment in Cycles 2 through 4 may be administered up to 5 days after the scheduled Day 1. Beginning in Cycle 5, treatment may be administered up to 3 days before or 5 days after the scheduled Day 1 of each cycle. Etoposide must be administered on consecutive days (ie, Days 1, 2, and 3) without interruption.

Dose interruptions are permitted in the case of medical/surgical events or logistical reasons not related to study treatment (e.g., elective surgery, unrelated medical events, subject vacations, and/or holidays). Subjects should be placed back on study treatment within 3 weeks of the scheduled interruption, unless otherwise discussed with the Sponsor. The reason for interruption should be documented in the subject's case report form (CRF).

5.2.3 Dose Modification (Escalation/Titration/Other)

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

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

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

be managed with interruptions of pembrolizumab monotherapy, coformulation, or IO combination administration of corticosteroids and/or other supportive care. For suspected irAEs, ensure adequate evaluation to confirm etiology or exclude other causes. Additional procedures or tests such as bronchoscopy, endoscopy, skin biopsy may be included as part of the evaluation.

Attribution of Toxicity:

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

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

Holding Study Interventions:

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

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

Restarting Study Interventions:

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

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

Dose Modification and Toxicity Management Guidelines for irAEs associated with pembrolizumab monotherapy, coformulations, or IO combinations are provided in Table 6.

Table 6 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).

5.2.3.2 Toxicity Management of Infusion Reactions Related to Pembrolizumab and MK-7684/MK-7684A

Pembrolizumab and MK-7684/MK-7684A 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 the infusion. Toxicity management guidelines for treatment-related infusion reactions are provided in Table 7.

Table 7 Pembrolizumab and MK-7684/MK-7684A Infusion Reaction Treatment Guidelines

NCI CTCAE Grade	Treatment	Premedication at Subsequent Dosing
Grade 1 Mild reaction; infusion interruption not indicated; intervention not indicated	Increase monitoring of vital signs as medically indicated until the participant 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, non-steroidal anti-inflammatory drugs [NSAIDs], narcotics, IV fluids); prophylactic medications indicated for ≤24 hours
	• **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 participant 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/h to 50 mL/h). Otherwise dosing will be held until symptoms resolve and the participant should be premedicated for the next scheduled dose
	• **Participants who develop Grade 2 toxicity despite adequate premedication should be permanently discontinued from further study treatment**
		Participant may be premedicated 1.5 hours (± 30 minutes) prior to infusion with:
		• Diphenhydramine 50 mg PO (or equivalent dose of antihistamine)
		• Acetaminophen 500-1000 mg PO (or equivalent dose of analgesic)

NCI CTCAE Grade	Treatment	Premedication at Subsequent Dosing

Grade 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 participant is deemed medically stable in the opinion of the investigator
	• Hospitalization may be indicated
	• **In cases of anaphylaxis, epinephrine should be used immediately
	• **Participant is permanently discontinued from further study treatment**
		No subsequent dosing

Appropriate resuscitation equipment should be available at the bedside and a physician readily available during the period of study treatment administration. For further information, please refer to the Common Terminology Criteria for Adverse Events (CTCAE), version 4.0 at http://ctep.cancer.gov		

5.2.3.3 Dose Modification for Chemotherapy

Recommended dose modifications for key chemotherapy toxicities are outlined in Table 8 and Table 9. These serve only as a guide and do not replace investigator judgment and applicable local label recommendations, if more stringent. Please refer to Table 1 for definitions of the dose levels (DLs) for Arm 3 and Table 2 for definitions of the DLs for Arm 5.

For subjects in Arm 5, study drug-related toxicities must be resolved to baseline or Grade ≤1 (with the exception of alopecia, Grade 2 fatigue, and endocrine-related AEs requiring treatment or hormone replacement, which may be Grade ≤2, and creatinine clearance, for which the guidelines provided below may be followed) prior to administering the next dose. Subjects must not receive the next cycle of chemotherapy if any of the following apply:

- Absolute neutrophil count (ANC) <1,500/mm^3
- Platelet count <100,000/mm^3
- Hemoglobin <8 g/dL
- Total bilirubin >1.5 × ULN; and/or
- Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≥2.5 × ULN, or ≥5 × ULN if liver metastases are present

Subjects in Arm 5 are allowed to switch from cisplatin to carboplatin if they develop unexpected toxicities with the use of cisplatin (including hearing loss), become ineligible for further cisplatin therapy, and/or the investigator considers switching to carboplatin to be in the best interest of the subject. During dose escalation and confirmation, the dose of carboplatin will not be higher than the dose that is currently enrolling per the mTPI design. During dose expansion, the dose of carboplatin will not be higher than the dose that was carried forward from dose escalation and confirmation.

During Cycles 1 through 4 of Arm 5:

- If etoposide dosing is delayed or interrupted, MK-7684, pembrolizumab, and carboplatin/cisplatin should also be delayed/interrupted. If etoposide and/or carboplatin/cisplatin delayed or interrupted during Cycles 1 through 4, subjects should be seen weekly until toxicity resolves.
- If cisplatin/carboplatin dosing is delayed or interrupted, MK-7684, pembrolizumab, and etoposide should also be delayed/interrupted. If etoposide and/or carboplatin/cisplatin is delayed or interrupted during Cycles 1 through 4, subjects should be seen weekly until toxicity resolves.
- If MK-7684 and/or pembrolizumab dosing is delayed or interrupted, etoposide and/or carboplatin/cisplatin can continue as scheduled. MK-7684/pembrolizumab administration should be attempted at the next cycle of therapy.
- Each chemotherapy cycle may not be delayed by more than 3 weeks (>21 consecutive days) despite supportive treatment. If only 1 of the agents is thought to be causing the specified toxicity leading to a 21-day delay of administration of the next cycle, that chemotherapeutic agent can be stopped, and treatment can continue with MK-7684, pembrolizumab and the remaining chemotherapy drug. MK-7684 and/or pembrolizumab dosing can continue with 1 chemotherapy agent or alone.

Use of colony-stimulating factors (CSFs) for primary prophylaxis is permitted at the investigator's discretion. Refer to the American Society of Clinical Oncology (ASCO) guidelines for use of CSFs [75]. CCI [redacted]

Table 8 Recommended Dose Modifications for Chemotherapy-related Hematological Toxicities

a. Arm 3

Platelets		ANC	Carboplatin	Pemetrexed
			Dose level from Table 1	
≥50,000/mcL	AND	≥500/mcL	DL 0	DL 0
≥50,000/mcL	AND	<500/mcL	DL -1	DL -1
<50,000/mcL without bleeding	AND	ANY	DL -1	DL -1
<50,000/mcL with Grade ≥2 bleeding	AND	ANY	DL -2	DL -2
ANY	AND	<1000/mcL + fever ≥38.5°C (101°F)	DL -1	DL -1

b. Arm 5

Drug Related Toxicity[a]	Carboplatin	Cisplatin	Etoposide
	Dose Level from Table 2		
Neutrophils (ANC) <500/mm^3 without fever	DL -1	DL -1	DL -1
Febrile neutropenia (fever ≥38.5°C and ANC <1000/mm^3)	DL -1	DL -1	DL -1
Platelets <50,000/mm^3 without significant bleeding or requiring blood transfusion	DL -1	DL -1	DL -1
Platelets <50,000/mm^3 with Grade ≥2 hemorrhage or requiring blood transfusion	DL -2	DL -2	DL -2
Grade 4 hemoglobin	DL -1	DL -1	DL -1

ANC=absolute neutrophil count; DL=dose level

Note: If toxicity can clearly be attributed to one of the drugs, the investigator may choose to only reduce the dose of one of the chemotherapy agents. Investigators may decide to use supportive measures/treatment and/or secondary prophylaxis as per institutional standards (eg, filgrastim, pegfilgrastim, transfusions) instead of dose reductions for the next cycle, if considered in the best interest of the subject.

[a] Should the hematologic toxicity recur, the dose of the agent could be reduced further; not more than 2 dose reductions per chemotherapy agent are permitted.

Table 9 Recommended Dose Modifications for Chemotherapy-related Non-hematological Toxicities

a. Arm 3

Event	CTCAE Grade	Carboplatin	Pemetrexed
		Dose level from Table 1	
Nausea or vomiting	Grade 3or 4	DL 0	DL 0
Diarrhea	Grade 3or 4	DL 0	DL -1
Mucositis	Grade 3or 4	DL 0	DL -2
Neurotoxicity	Grade 2	DL 0	DL 0
	Grade 3or 4	DL -1	DL -1
Transaminase elevation	Grade 3	DL -1	DL -1
	Grade 4	Discontinue treatment	Discontinue treatment
Other non-hematological toxicities	Grade 3or 4	DL -1	DL -1

b. Arm 5

Drug-Related Toxicity[a]	CTCAE Grade	Carboplatin	Cisplatin	Etoposide
		Dose Level from Table 2		
Nausea or vomiting	Grade ≥3[b]	DL -1	DL -1	DL 0
Mucositis	Grade ≥3[b]	DL -1	DL -1	DL -1
Diarrhea	Grade ≥3[b]	DL -1	DL -1	DL -1
Peripheral neuropathy	Grade 2	No modification	DL -1[c]	No modification
	Grade 3	DL -1	Discontinue[d]	No modification
	Grade 4	DL -1	Discontinue	No modification
Total bilirubin	Grade 2	No modification	No modification	DL -2
	Grade 3	No modification	No modification	Discontinue
	Grade 4	No modification	No modification	Discontinue
Transaminase elevation	Grade 3	DL -1	DL -1	DL -1
	Grade 4	Discontinue	Discontinue	Discontinue
Other non-hematological toxicities (except fatigue and transient arthralgia and myalgia)	Grade ≥3	DL -1	DL -1	DL -1

CTCAE=Common Terminology Criteria for Adverse Events; DL=dose level
Note: If considered in the best interest of the subject, and consistent with local practice, investigators may decide to use supportive measures/treatment, and/or secondary prophylaxis instead of dose reductions for the next cycle. Also, if toxicity can clearly be attributed to one of the drugs, the investigator may choose to only reduce the dose of one of the chemotherapy agents.
[a] Should the toxicity recur, the dose of the agent could be reduced further; not more than 2 dose reductions per chemotherapy agent are permitted.
[b] The first occurrence of Grade ≥3 nausea/vomiting, mucositis, and diarrhea should be managed symptomatically with optimal medical therapy, and improve to Grade ≤1 prior to proceeding with additional therapy. Should these events recur despite aggressive management, a dose modification can be employed once the AE improves to Grade ≤1.
[c] If Grade 2 neurotoxicity recurs after DL -1, drug will be given at DL -2 or switch can be made to the appropriate dose of carboplatin at the discretion of the investigator in consultation with the Sponsor. If Grade 2 neurotoxicity persists after 2 dose level reductions and a 21-day hold, switch can be made to the appropriate dose of carboplatin at the discretion of the investigator in consultation with the Sponsor.
[d] If Grade 3 neurotoxicity occurs, cisplatin will be discontinued and, upon improvement, a switch can be made to the appropriate dose of carboplatin at the discretion of the investigator in consultation with the Sponsor.

Creatinine clearance (CrCl) for subjects in Arm 3: CrCl will be based on the original weight-based Cockcroft-Gault Method or institutional standard. CrCl must be ≥45 mL/min prior to the administration of chemotherapy. Carboplatin and/or pemetrexed may be delayed for up to 42 days to allow the participant time to recover from the toxicity. If a participant's CrCl value has not returned to ≥45 mL/min within 42 days after the previous dose, carboplatin and/or pemetrexed must be discontinued.

CrCl for subjects in Arm 5: CrCl will be based on the original weight-based Cockcroft-Gault Method or institutional standard.

For subjects receiving cisplatin, the scheduled dose of cisplatin may only be administered if the calculated CrCl is ≥50 mL/min:

- If CrCl falls to <50 mL/min, delay the start of that cycle for ≤21 days. In the interim, monitor renal function weekly and consider IV hydration. When CrCl improves to ≥50 mL/min, decrease cisplatin to DL -1 (Table 2). Alternatively, if in the investigator's judgment it is in the best interest of the subject, cisplatin can be switched to carboplatin if the calculated CrCl is appropriate, and in consultation with the Sponsor.
- At the second occurrence of CrCl <50 mL/min, decrease cisplatin to DL -2 upon improvement of CrCl to ≥50 mL/min. Alternatively, if in the investigator's judgment it is in the best interest of the subject, cisplatin can be switched to carboplatin if the calculated CrCl is appropriate, and in consultation with the Sponsor.
- At the third occurrence of CrCl <50 mL/min, cisplatin should be discontinued. If in the investigator's judgment it is in the best interest of the subject, cisplatin can be switched to carboplatin if the calculated CrCl is appropriate, at the discretion of the investigator and in consultation with the Sponsor.

For subjects receiving carboplatin, the scheduled dose of carboplatin may only be administered if the calculated CrCl is ≥40 mL/min:

- If CrCl falls to <40 mL/min, delay the start of that cycle for ≤21 days. In the interim, monitor renal function weekly and consider IV hydration. When CrCl improves to ≥40 mL/min, decrease carboplatin to DL -1 (Table 2).
- At the second occurrence of CrCl <40 mL/min, decrease carboplatin to DL -2 upon improvement of CrCl to ≥40 mL/min.
- At the third occurrence of CrCl <40 mL/min, carboplatin should be discontinued.

5.2.3.4 Management Guidelines for Overlapping Toxicities

For overlapping toxicities where it is unclear if the event is related to one or a combination of drugs, it is recommended to hold all applicable drugs, and initiate management per Table 6. Standard of care should be followed for management of toxicities deemed related to chemotherapy.

5.2.4 Trial Blinding

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

5.3 Randomization or Treatment Allocation

During the dose escalation and confirmation phase of Part A, subjects with advanced solid tumors of all types will be allocated to 1 of 2 treatment arms: MK-7684 monotherapy (Arm 1) or MK-7684 in combination with pembrolizumab (Arm 2) by non-random assignment using an IVRS/IWRS. Enrollment into the MK-7684 + pembrolizumab combination treatment arm (Arm 2) will begin once 2 dose levels of MK-7684 have been tested in the MK-7684 monotherapy arm (Arm 1) and a dose escalation decision has been made so that the starting dose of MK-7684 in Arm 2 will be at least 2 levels below the dose being tested in Arm 1. When both treatment arms are open for enrollment, IVRS/IWRS will alternate subject assignment between Arm 1 and Arm 2 starting with Arm 1. For example, once the 21-mg dose cohort of Arm 1 (MK-7684 monotherapy) and the 2.1-mg dose cohort of Arm 2 (MK-7684 + pembrolizumab) are open for enrollment, the first subject will be allocated to Arm 1, the second subject will be allocated to Arm 2, the third subject will be allocated to Arm 1, etc. An observation period of at least 24 hours will occur between treatment initiation in subjects enrolled within each dose level. Each new dose cohort will open for enrollment without delay once the 21-day DLT observation period of the previous dose cohort is completed and a dose escalation decision is made.

CCI

[redacted]

During Part B (expansion phase), subjects with PD-1/PD-L1 inhibitor treatment-refractory NSCLC will be allocated to MK-7684 monotherapy (Arm 1) or MK-7684 in combination with pembrolizumab (Arm 2) by non-random assignment using an IVRS/IWRS. Each treatment arm will begin Part B once a preliminary RPTD for that arm is identified in Part A. When both treatment arms are open for enrollment to PD-1/PD-L1 inhibitor treatment-refractory NSCLC subjects, IVRS/IWRS will alternate subject assignment between Arm 1 and Arm 2 starting with Arm 1, until enrollment targets are met.

Part B subjects with PD-1/PD-L1 inhibitor treatment-naïve NSCLC, CCI

[redacted]

CCI will be allocated to MK-7684 in combination with pembrolizumab (Arm 2) using IVRS/IWRS until enrollment targets are met.

CCI

Each treatment arm will begin Part B once a preliminary RPTD for that arm is identified in Part A.

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

5.5.1 Acceptable Concomitant Medications/Procedures

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.

Palliative and supportive care is permitted during the course of the trial for underlying medical conditions and management of symptoms. Surgery or radiotherapy for tumor control is not permitted during the trial; however, radiotherapy or procedures for symptom management is allowed. In cases of melanoma, local surgical excision may be allowed after discussion with the Sponsor.

Seasonal influenza vaccines for injection are generally killed virus vaccines and are allowed.

All concomitant medication will be recorded on the CRF including all prescription medication, over-the-counter (OTC) medication, herbal supplements, and IV medications and fluids. Documentation of drug dosage, frequency, route, start/stop dates, and indication will be included on the CRF and all changes to these parameters will also be recorded. All concomitant medications received within 30 days before the first dose of study treatment through the Post-Treatment Safety Follow-Up visit should be recorded. After the Safety Follow-Up visit, only medications taken for reportable SAEs and ECIs as defined in Section 7.2 should be recorded.

5.5.2 Prohibited Concomitant Medications

Subjects are prohibited from receiving the following therapies during the screening and treatment phases of this trial:

- Immunotherapy not specified in this protocol
- Antineoplastic systemic chemotherapy or biological therapy not specified in this protocol
- Investigational agents not specified in this protocol
- Radiation therapy (radiotherapy for symptom management is allowed and PCI is permitted in Arm 5 subjects achieving CR or PR after Cycle 4.)
- Hormonal cancer therapy (e.g., tamoxifen, leuprolide)
- Live vaccines within 30 days before the first dose of study treatment and while participating in the trial. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, chickenpox, yellow fever, rabies, Bacillus Calmette-Guérin (BCG), and typhoid vaccines. Seasonal influenza vaccines for injection are generally killed virus vaccines and are allowed. Intranasal influenza vaccines (e.g., FluMist®) are live attenuated vaccines, and are not allowed.
- Glucocorticoids other than to modulate symptoms from an immune-mediated AE and/or as pre/post-medication to prevent AEs associated with chemotherapy. Chronic systemic replacement doses of steroids and non-systemic steroids including inhaled steroids, topical steroids, intra-nasal steroids, intra-articular, and ophthalmic steroids are allowed. Systemic glucocorticoids are also allowed as required during and after

PCI in Arm 5 subjects; subjects requiring chronic glucocorticoid use (>7 days) after completion of PCI should be discontinued from study treatment.

- Phenytoin during treatment with carboplatin
- Subjects taking NSAIDs or salicylates will not take the NSAID or salicylate (other than an aspirin dose ≤1.3 g per day) for 2 days before, the day of, and 2 days after receiving pemetrexed. Subjects taking NSAIDs or salicylates with a long half-life (for example, naproxen, piroxicam, diflunisal, or nabumetone) will not take the NSAID or salicylates for 5 days before, the day of, and 2 days after pemetrexed.

Subjects who, in the opinion of the investigator, require the use of any of the prohibited therapies during the screening and treatment phases of this trial for clinical management should be removed from the trial. Subjects may receive other medications that the investigator deems to be medically necessary.

The exclusion criteria describe other medications that are prohibited in this trial.

There are no prohibited therapies after the Post-Treatment Safety Follow-Up visit.

5.6 Rescue Medications & Supportive Care

Subjects should receive appropriate supportive care measures as deemed necessary by the treating investigator. Suggested supportive care measures for the management of AEs with potential immunologic etiology are outlined in Section 5.2.3.2, Table 6. 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 study treatment.

Note: If after evaluation of the event, it is determined not to be related to MK-7684 and/or pembrolizumab (or MK-7684A), the investigator does not need to follow the treatment guidance.

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

5.6.1.1 Antiemetic Use

For participants receiving chemotherapy, antiemetic therapy should follow Multinational Association of Supportive Care in Cancer ([MASCC]; Section 12.7) or appropriate local guidelines and should, for the first 4 cycles, include a 5-HT3 receptor antagonist, dexamethasone (or equivalent), and aprepitant (or equivalent NK-1 receptor antagonist) as per the guideline followed.

5.6.1.2 Colony-stimulating Factors

For participants receiving chemotherapy, the ASCO guidelines for use of CSFs, or local equivalent, should be used for patient management [75]. Use of CSFs for primary

prophylaxis is permitted at the investigator's discretion. CCI [redacted]

5.6.1.3 Pemetrexed Premedication

All participants must receive the appropriate supplementation of Vitamin B12, folic acid, and corticosteroid prophylaxis as listed below or per the local label:

- Folic acid, 350 µg to 1000 µg orally: At least 5 doses of folic acid must be taken during the 7 days preceding the first dose of pemetrexed, through the full course of therapy, and for 21 days after the last dose of pemetrexed.
- Vitamin B12, 1000 µg by intramuscular (IM) injection: Vitamin B12 must be given in the week preceding the first dose of pemetrexed and once every 3 cycles thereafter. Subsequent Vitamin B12 injections may be given on the same day as pemetrexed.
- Dexamethasone prophylaxis, 4 mg orally twice per day (or equivalent): Dexamethasone may be taken the day before, day of, and day after pemetrexed administration. Higher or additional doses are permitted for antiemetic prophylaxis during Cycles 1 through 4 but are not to exceed doses in MASCC guidelines (or local equivalent).

5.7 Diet/Activity/Other Considerations

5.7.1 Diet

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

5.7.2 Contraception

MK-7684, pembrolizumab, and MK-7684A may have adverse effects on a fetus in utero. Furthermore, it is not known if these drugs have transient adverse effects on the composition of sperm.

Female and male subjects of reproductive potential must agree to avoid becoming pregnant or impregnating a partner, respectively, starting with the first dose of study treatment (or 14 days prior to the first dose of study treatment for oral contraception) through 120 days after the last dose of MK-7684, pembrolizumab, or MK-7684A OR 180 days after the last dose of chemotherapeutic agents by complying with one of the following:

1. Practice abstinence from heterosexual activity

   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 IRBs/ Independent Ethics Committees (IECs). Periodic abstinence (e.g., calendar, ovulation, sympto-thermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception.

OR

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

   Acceptable methods of contraception are:

   - Intrauterine device (IUD);
   - Vasectomy of a female subject's male partner;
   - Contraceptive rod implanted into the skin; or
   - A combination 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 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)

   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 those countries/regions.

   Note: Male subjects with pregnant partners must agree to use a condom; no additional method of contraception is required for the pregnant partner.

In addition, during treatment and up to 180 days after the last dose of treatment with chemotherapeutic agents, female participants must also agree not to donate eggs (ova, oocytes) to others or freeze/store eggs for their own use for the purpose of reproduction, and male participants must refrain from donating sperm and agree to use a male condom when engaging in any activity that allows for passage of ejaculate to another person of any sex.

If there is any question that a subject with reproductive potential will not reliably comply with the requirements for contraception, that subject should not be entered into the trial.

Female subjects will be considered of non-childbearing potential if they:

1. Are postmenopausal

   Postmenopausal is defined as at least 12 months with no menses without an alternative medical cause. In women <45 years of age, a high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a 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.

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. Have a congenital or acquired condition that prevents childbearing.

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

5.7.3 Use in Pregnancy

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

5.7.4 Use in Nursing Women

It is unknown whether or not MK-7684, pembrolizumab, or MK-7684A are excreted in human milk. Since many drugs are excreted in human milk, and because of the potential for serious adverse reactions in the nursing infant, subjects who are breastfeeding are not eligible for enrollment into the trial.

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 the Trial Flow Charts (Section 6) –and Section 7.1.5.3 – Post-Treatment Period.

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.

- Confirmed disease progression per response assessment criteria (see Section 7.1.2.6).
- Clinical progression.
- Unacceptable adverse event(s).
- Intercurrent illness that prevents further administration of study treatment.
- Investigator's decision to withdraw the subject from treatment.
- The subject has a confirmed positive serum pregnancy test.
- Noncompliance with trial treatment or procedure requirements.
- The subject completes study treatment (i.e., 35 cycles of MK-7684 monotherapy [Arm 1], 35 cycles of MK-7684 in combination with pembrolizumab [Arm 2], 35 cycles of MK-7684, pembrolizumab, and pemetrexed, and 4 cycles of carboplatin [Arm 3], 35 cycles of MK-7684A [Arm 4], or 35 cycles of MK-7684 and pembrolizumab, and 4 cycles of carboplatin or cisplatin and etoposide [Arm 5]as applicable).
- Administrative reasons.

Subjects who discontinue MK-7684 in the monotherapy arm due to disease progression may, at the investigator's discretion and after consultation with the Sponsor, cross over to combination treatment (Arm 2). Subjects eligible for cross-over must have received at least 2 cycles of MK-7684 monotherapy and must have radiographic imaging to document disease progression by RECIST, version 1.1 and to establish a new imaging baseline prior to cross-over. Subjects who permanently discontinue MK-7684 monotherapy for any reason other than radiologic disease progression are not eligible for cross-over. If cross-over is being considered, the subject must be re-consented and the risks and benefits of continuing treatment after disease progression should be reviewed prior to performing any cross-over-related procedures. The subject will receive the dose of MK-7684 that has been determined to be safe in the combination arm (e.g., 1 dose level below the dose being tested if in Part A) at the time of treatment cross-over. The MK-7684 dose will not exceed the dose the subject received in the monotherapy arm. The first dose of combination treatment must occur no less than 21 days and no more than 42 days after the last dose of MK-7684 monotherapy treatment. Any deviations from this time frame must be approved by the Sponsor. The total duration of treatment (monotherapy and combination therapy) will not exceed 35 cycles. Specific details regarding procedures to be performed are provided in the Cross-Over Flow Chart in Section 6.1.

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

In order to evaluate safety and allow for dose escalation decisions, subjects who meet one or more of the following criteria will be replaced and will not be counted toward the cohort total for DLT evaluation:

- Subjects who are enrolled but not treated;
- Subjects who receive less than 75% of the total MK-7684, pembrolizumab, or MK-7684A infusion in Cycle 1 (e.g., because the infusion had to be discontinued due to an infusion reaction) and do not experience a DLT;
- Subjects who discontinue from the trial before completing all the safety evaluations in Cycle 1 for reasons other than treatment-related AEs; or
- Subjects who discontinue from the trial before completing Cycle 1 and do not experience a DLT before discontinuation.

5.10 Beginning and End of the Trial

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

5.11 Clinical Criteria for Early Trial Termination

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

1. The incidence or severity of adverse drug reactions in this, or other, trials suggest a potential health hazard to subjects;
2. Plans emerge to modify or discontinue the development of the trial drug(s);
3. There is poor adherence to the protocol and/or regulatory requirements; and/or
4. The quality or quantity of data recording is inaccurate or incomplete.

Ample notification will be provided to the sites if the Sponsor decides not to continue to supply MK-7684, MK-7684A, or pembrolizumab.

6.0 TRIAL FLOW CHART

Visit / Treatment Cycle	Screening	Treatment Period Cycle = 21 days													End of Treatment	Post-Treatment Period		
		Cycle 1						Cycles 2-4							Cycles ≥5	Treatment dis-continuation	Safety Follow-Up	Disease Status Follow-Up	Survival Follow-Up
Visit Timing / Cycle Day	Up to 28 days prior to 1st dose	1	2	3	5	8	15	1	2[1]	3[1]	5[1]	8[1]	15[1]	Every 9 weeks	1		30 days after the last dose[2]	Every 9 weeks	Every 12 weeks
Visit Window (Days)	-28 to -1				+/- 1	+/- 2	+/- 3				+/- 1	+/- 2	+/- 3	+/- 7			+/- 7	+/- 7	+/- 14
Administrative Procedures																			
Informed Consent[3]	X																		
Informed Consent for Future Biomedical Research[4]	X																		
Inclusion/Exclusion Criteria	X																		
Subject Identification Card	X																		
Demographics and Medical History	X																		
Oncology Disease Status and Prior Oncology Treatment History	X																		
Concomitant Medication Review	X	X	X			X	X	X	X[1]			X[1]	X[1]		X	X	X		
Clinical Procedures/Assessments																			
Full Physical Examination	X	X[5]						X[5]							X[5]	X	X		
Height	X																		
Weight	X	X						X							X	X	X		
Vital Signs[6]	X	X	X	X		X	X	X	X[1]	X[1]		X[1]	X[1]		X	X	X		
Pulse Oximetry (SpO_2; subjects in Japan ONLY)	X	X	X	X		X	X	X	X[1]	X[1]		X[1]	X[1]		X	X	X		
ECOG Performance Status	X	X[5]						X[5]							X[5]	X	X		
12-Lead Electrocardiogram[7]	X	X[5]						X[5]											
MK-7684 Drug Administration (Arm 1 and Arm 2)[8]		X						X							X				

Visit / Treatment Cycle	Screening	Treatment Period Cycle = 21 days													End of Treatment	Post-Treatment Period		
		Cycle 1						Cycles 2-4						Cycles ≥5	Treatment dis-continuation	Safety Follow-Up	Disease Status Follow-Up	Survival Follow-Up
Visit Timing / Cycle Day	Up to 28 days prior to 1st dose	1	2	3	5	8	15	1	2[1]	3[1]	5[1]	8[1]	15[1]	Every 9 weeks	1	30 days after the last dose[2]	Every 9 weeks	Every 12 weeks
Visit Window (Days)	-28 to -1				+/- 1	+/- 2	+/- 3				+/- 1	+/- 2	+/- 3	+/- 7		+/- 7	+/- 7	+/- 14
Pembrolizumab Drug Administration (Arm 2)[8,9]		X						X							X			
CCI [redacted]		X						X							X			
Adverse Event Monitoring[10]	X	X	X	X		X	X	X	X[1]	X[1]		X[1]	X[1]		X	X	X[10]		
Tumor Imaging and RECIST, version 1.1 Response Assessment[11]	X													X	X			X	
New Anticancer Therapy Status																X	X	X
Survival Status[12]		←													→			X
Laboratory Procedures/Assessments – LOCAL																		
Hematology[13]	X[14]	X[5]	X			X	X	X[5]				X[1]	X[1]		X[5]	X	X		
Chemistry Panel[13]	X[14]	X[5]	X			X	X	X[5]				X[1]	X[1]		X[5]	X	X		
Prothrombin Time (PT)/International Normalized Ratio (INR) and Activated Partial Thromboplastin Time (aPTT)[15]	X[14]																		
Lactate Dehydrogenase (LDH) and Gamma Glutamyl Transferase (GGT)	X[14]	X[5]						X[5]							X[5]				
Thyroid Function Testing (T4, T3, TSH)[16]		X[5]						X[5, 16]							X[5,16]		X		
Immunoglobulins (IgA, IgG, IgM)		X[5]						X[5]							X[5]				

Visit / Treatment Cycle	Screening	Treatment Period Cycle = 21 days													End of Treatment	Post-Treatment Period		
		Cycle 1						Cycles 2-4						Cycles ≥5	Treatment dis-continuation	Safety Follow-Up	Disease Status Follow-Up	Survival Follow-Up
Visit Timing / Cycle Day	Up to 28 days prior to 1st dose	1	2	3	5	8	15	1	2[1]	3[1]	5[1]	8[1]	15[1]	Every 9 weeks	1	30 days after the last dose[2]	Every 9 weeks	Every 12 weeks
Visit Window (Days)	-28 to -1				+/- 1	+/- 2	+/- 3				+/- 1	+/- 2	+/- 3	+/- 7		+/- 7	+/- 7	+/- 14
Pregnancy Test (urine or serum β-human chorionic gonadotropin [β-hCG]) - if applicable[17]	X	X[5]													X			
HIV/Hepatitis Screen (at the discretion of the investigator)[18]	X																	
CCI	X[14]	X[5]						X							X			
	X[14]	X[5]						X							X			
	X																	
	X																	
	X																	
	X																	
	X																	
Urinalysis	X[14]																	
Laboratory Procedures/Assessments – CENTRAL																		
Serum for Cytokine Testing[23]	X	X	X			X		X	X[1]			X[1]			X			

Visit / Treatment Cycle	Screening	Treatment Period Cycle = 21 days													End of Treatment	Post-Treatment Period		
		Cycle 1						Cycles 2-4						Cycles ≥5	Treatment dis-continuation	Safety Follow-Up	Disease Status Follow-Up	Survival Follow-Up
Visit Timing / Cycle Day	Up to 28 days prior to 1st dose	1	2	3	5	8	15	1	2[1]	3[1]	5[1]	8[1]	15[1]	Every 9 weeks	1	30 days after the last dose[2]	Every 9 weeks	Every 12 weeks
Visit Window (Days)	-28 to -1				+/- 1	+/- 2	+/- 3				+/- 1	+/- 2	+/- 3	+/- 7		+/- 7	+/- 7	+/- 14
CCI																		

Visit / Treatment Cycle	Screening	Treatment Period Cycle = 21 days													End of Treatment	Post-Treatment Period		
		Cycle 1						Cycles 2-4						Cycles ≥5	Treatment dis-continuation	Safety Follow-Up	Disease Status Follow-Up	Survival Follow-Up
Visit Timing / Cycle Day	Up to 28 days prior to 1st dose	1	2	3	5	8	15	1	2[1]	3[1]	5[1]	8[1]	15[1]	Every 9 weeks	1	30 days after the last dose[2]	Every 9 weeks	Every 12 weeks
Visit Window (Days)	-28 to -1				+/- 1	+/- 2	+/- 3				+/- 1	+/- 2	+/- 3	+/- 7		+/- 7	+/- 7	+/- 14
CCI [redacted]																		

1. As of Amendment 9 for subjects in Part B and Amendment 10 for subjects in Part A, all assessments on Days 2, 3, 5, 8, and 15 of Cycles 2 through 4 are not required.
2. If a subject initiates a new anticancer therapy within 30 days after the last dose of study treatment, the Post-Treatment Safety Follow-Up visit should occur before the first dose of the new therapy.
3. Documented informed consent must be obtained prior to performing any protocol-specific procedures. Tests performed prior to the subject providing consent as part of routine clinical management are acceptable in lieu of a screening test if performed within the specified timeframe.
4. Consent for future biomedical research (FBR) is optional, and may be provided at any time during the subject's participation in the trial. Detailed instructions for the collection and management of FBR specimens are provided in the Procedure Manual.
5. Procedure/sample collection may be performed up to 72 hours prior to dosing. Screening procedures/sample collections done within this timeframe do not need to be repeated for the Cycle 1, Day 1 assessment.
6. Vital signs include body temperature, pulse, respiratory rate, and blood pressure. Vital signs should be measured at screening, and prior to dosing, and 2 hours, 4 hours, and 6 hours after the start of the MK-7684 infusion on Day 1, and once daily on Day 2, Day 3, Day 8, and Day 15 of Cycles 1 through 4. Beginning in Cycle 5, vital signs should be measured prior to dosing on Day 1 only. Vitals signs should also be measured at the End of Treatment visit and at the Post-Treatment Safety Follow-Up visit. As of Amendment 10, vital signs for subjects in Part A and Part B should be measured at screening, prior to dosing and 2 hours, 4 hours, and 6 hours after the start of the MK-7684 infusion (or MK-7684A infusion, as of Amendment 11) on Day 1, and once daily on Day 2, Day 3, Day 8, and Day 15 of Cycle 1. Beginning in Cycle 2, vital signs should be measured prior to dosing on Day 1 only. Vitals signs should also be measured at the End of Treatment visit and at the Post-Treatment Safety Follow-Up visit.
7. A 12-lead electrocardiogram (ECG) should be performed at screening and prior to dosing and within 30 minutes after the end of the MK-7684 or MK-7684A infusion on Day 1 of Cycles 1 through 4.
8. Subjects may receive up to 35 cycles of study treatment (MK-7684 in Arm 1, MK-7684 and pembrolizumab in Arm 2, CCI [redacted] In Cycle 2, study treatment may be administered up to 5 days after the scheduled Day 1. Beginning in Cycle 3, study treatment may be administered up to 3 days before or 5 days after the scheduled Day 1 of each cycle.

9. In Arm 2, pembrolizumab will be administered first on Day 1 of each cycle, with administration of MK-7684 occurring approximately 30 minutes after completion of the pembrolizumab infusion.
10. Adverse events and serious adverse events will be recorded from the time of treatment allocation. All adverse events and serious adverse events that occur after documented informed consent is provided 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 trial procedure. After treatment discontinuation, subjects will be monitored for adverse events and serious adverse events for 90 days, 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. The investigator will make every attempt to follow all subjects with non-serious adverse events for outcome. All subjects with serious adverse events must be followed up for outcome.
11. Tumor imaging should be performed within 28 days prior to the first dose of study treatment. Tumor imaging and response assessment should be performed 9 weeks after the first dose of study treatment and every 9 weeks thereafter, until disease progression. The timing of imaging assessments should not be adjusted for delays in cycle starts. Subjects who discontinue treatment for reasons other than confirmed disease progression will have post-treatment follow-up for disease status until disease progression, initiating a new anticancer therapy, withdrawing consent for trial participation, or becoming lost to follow-up, whichever occurs first. The same imaging technique should be used on a subject throughout the trial. Scans used for tumor measurements may be requested for potential central review.
12. Upon Sponsor request, participants may be contacted for survival status at any time during the course of the study. After confirmed disease progression, each subject will be contacted by telephone every 12 weeks for survival until withdrawal of consent to participate in the trial, becoming lost to follow-up, death, or the end of the trial, whichever occurs first.
13. Samples for hematology and chemistry panel should be collected at screening, and prior to dosing and 4 hours after the start of the MK-7684 infusion on Day 1 of Cycles 1 through 4. In Cycle 1, samples should also be collected once daily on Day 2, Day 8, and Day 15. In Cycles 2 through 4, samples will also be collected once daily on Day 8 and Day 15. Beginning in Cycle 5, samples for hematology and chemistry panel should be collected prior to dosing on Day 1 only. Samples should also be collected at the End of Treatment visit and at the Post-Treatment Safety Follow-Up visit. As of Amendment 10, samples for subjects in Part A and Part B should be collected at screening, and prior to dosing and 4 hours after the start of the MK-7684 infusion (or MK-7684A infusion, as of Amendment 11) on Day 1 of Cycles 1 through 4. In Cycle 1, samples should also be collected once daily on Day 2, Day 8, and Day 15. Beginning in Cycle 5, samples for hematology and chemistry panel should be collected prior to dosing on Day 1 only. Samples should also be collected at the End of Treatment visit and at the Post-Treatment Safety Follow-Up visit.
14. Laboratory tests at screening are to be performed within 7 days prior to the first dose of study treatment.
15. 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.
16. Samples for thyroid function testing should be collected on Day 1 of Cycle 1, every other cycle thereafter, and at the Post-Treatment Safety Follow-Up visit.
17. For women of reproductive potential, a urine pregnancy test will be performed at screening, within 72 hours prior to the first dose of study treatment, and at treatment discontinuation. A urine pregnancy test may also be performed whenever an expected menstrual cycle is missed or when pregnancy is otherwise suspected, and as required locally. If a urine pregnancy test cannot be confirmed as negative, a serum pregnancy test is required.
18. HIV testing should include HIV Type 1 and Type 2 (e.g., 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.

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6.1 Cross-over Flow Chart

Subjects who discontinue MK-7684 in the monotherapy arm due to radiographic disease progression may, at the investigator's discretion and after consultation with the Sponsor, cross over to combination treatment (Arm 2). The list and schedule of procedures to be performed are provided in the following flow chart.

Visit / Treatment Cycle	Treatment Period[1, 2] Cycle = 21 days					End of Treatment	Post-Treatment Period		
	Cycle 1			Cycles ≥2			Safety Follow-Up	Disease Status Follow-Up	Survival Follow-Up
Visit Timing / Cycle Day	1[3]	8	15	1	Every 9 weeks	Treatment dis-continuation	30 days after the last dose[4]	Every 9 weeks	Every 12 weeks
Visit Window (Days)		+/- 2	+/- 3		+/- 7		+/- 7	+/- 7	+/- 14
Administrative Procedures									
Informed Consent[5]									
Concomitant Medication Review	X			X		X	X		
Clinical Procedures/Assessments									
Full Physical Examination	X[6]			X[6]		X	X		
Weight	X			X		X	X		
Vital Signs[7]	X			X		X	X		
ECOG Performance Status	X[6]			X[6]		X	X		
12-Lead Electrocardiogram[8]	X[6]			X[6]					
MK-7684 Drug Administration[9,10]	X			X					
Pembrolizumab Drug Administratio[10,11]	X			X					
Adverse Event Monitoring[12]	X			X		X	X[12]		
Tumor Imaging and RECIST, version 1.1 Response Assessment[13]					X			X	
New Anticancer Therapy Status							X	X	X
Survival Status[14]	←								→ X
Laboratory Procedures/Assessments – LOCAL									
Hematology[15]	X[6]	X	X	X[6]		X	X		
Chemistry Panel[15]	X[6]	X	X	X[6]		X	X		
Lactate Dehydrogenase (LDH) and Gamma Glutamyl Transferase (GGT)	X[6]			X[6]					
Thyroid Function Testing (T4, T3, TSH)[16]	X[6]			X[6,16]			X		
Immunoglobulins (IgA, IgG, IgM)	X[6]			X[6]					

Visit / Treatment Cycle	Treatment Period[1, 2] Cycle = 21 days					End of Treatment	Post-Treatment Period		
	Cycle 1			Cycles ≥2			Safety Follow-Up	Disease Status Follow-Up	Survival Follow-Up
Visit Timing / Cycle Day	1[3]	8	15	1	Every 9 weeks	Treatment dis-continuation	30 days after the last dose[4]	Every 9 weeks	Every 12 weeks
Visit Window (Days)		+/- 2	+/- 3		+/- 7		+/- 7	+/- 7	+/- 14
Pregnancy Test (urine or serum β-human chorionic gonadotropin [β-hCG]) - if applicable[17]	X					X			
CCI	X[6]			X					
	X[6]			X					
CCI									

1. Any subject receiving anticoagulant therapy should continue to have coagulation factors (PT/INR and aPTT) monitored closely throughout the trial.
2. Subjects will be requested to provide a post-treatment tumor biopsy sample between Day 8 and Day 15 of Cycle 2. Leftover tissue may also be saved for future biomedical research (FBR) if the subject provides documented informed consent for FBR.
3. Cycle 1, Day 1 of combination treatment for subjects who cross over will not occur less than 21 days and no more than 42 days after the last dose of MK-7684 monotherapy the subject received in Arm 1. The Cycle 1, Day 1 visit in the combination treatment for cross-over subjects will replace the End of Treatment visit for the monotherapy arm. Any deviations from this timing must be approved by the Sponsor.
4. If a subject initiates a new anticancer therapy within 30 days after the last dose of study treatment, the Post-Treatment Safety Follow-Up visit should occur before the first dose of the new therapy.
5. If cross-over is being considered, the subject must be re-consented and the risks and benefits of continuing treatment after disease progression should be reviewed prior to performing any cross-over-related procedures.
6. Procedure/sample collection may be performed up to 72 hours prior to dosing.
7. Vital signs include body temperature, pulse, respiratory rate, and blood pressure. Vital signs should be measured prior to dosing, and 2 hours, 4 hours, and 6 hours after the start of the MK-7684 infusion on Day 1 of Cycle 1. Beginning in Cycle 2, vital signs should be measured prior to dosing on Day 1 only. Vitals signs should also be measured at the End of Treatment visit and at the Post-Treatment Safety Follow-Up visit.
8. A 12-lead electrocardiogram (ECG) should be performed prior to dosing and within 30 minutes after the end of the MK-7684 infusion on Day 1 of Cycles 1 through 4.

9. Subjects who cross over from the monotherapy arm will receive the dose of MK-7684 that has been determined to be safe in the combination arm (e.g., 1 dose level below the dose being tested) at the time of treatment cross-over. The MK-7684 dose will not exceed the dose the subject received in the monotherapy arm.
10. Subjects may receive a total of up to 35 cycles of study treatment (number of cycles received in Arm 1 + number of cycles received in Arm 2). Beginning in Cycle 2, study treatment may be administered up to 3 days before or 5 days after the scheduled Day 1 of each cycle.
11. Pembrolizumab will be administered first on Day 1 of each cycle, with administration of MK-7684 occurring approximately 30 minutes after completion of the pembrolizumab infusion.
12. Adverse events and serious adverse events will be recorded from the time of treatment allocation. After treatment discontinuation, subjects will be monitored for adverse events and serious adverse events for 90 days, 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. The investigator will make every attempt to follow all subjects with non-serious adverse events for outcome. All subjects with serious adverse events must be followed up for outcome.
13. Tumor imaging and response assessment should be performed 9 weeks after the first dose of combination treatment and every 9 weeks thereafter, until disease progression. The timing of imaging assessments should not be adjusted for delays in cycle starts. Subjects who discontinue treatment for reasons other than confirmed disease progression will have post-treatment follow-up for disease status until disease progression, initiating a new anticancer therapy, withdrawing consent for trial participation, or becoming lost to follow-up, whichever occurs first. The same imaging technique should be used on a subject throughout the trial. Scans used for tumor measurements may be requested for potential central review.
14. Upon Sponsor request, participants may be contacted for survival status at any time during the course of the study. After confirmed disease progression, each subject will be contacted by telephone every 12 weeks for survival until withdrawal of consent to participate in the trial, becoming lost to follow-up, death, or the end of the trial, whichever occurs first.
15. Samples for hematology and chemistry panel should be collected prior to dosing and 4 hours after the start of the MK-7684 infusion on Day 1, and once daily on Day 8 and Day 15 of Cycle 1. Beginning in Cycle 2, samples for hematology and chemistry panel should be collected prior to dosing on Day 1 only. Samples should also be collected at the End of Treatment visit and at the Post-Treatment Safety Follow-Up visit.
16. Samples for thyroid function testing should be collected on Day 1 of Cycle 1, every other cycle thereafter, and at the Post-Treatment Safety Follow-Up visit.
17. For women of reproductive potential, a urine pregnancy test will be performed within 72 hours prior to the first dose of cross-over treatment, and at treatment discontinuation. A urine pregnancy test may also be performed whenever an expected menstrual cycle is missed or when pregnancy is otherwise suspected, and as required locally. If a urine pregnancy test cannot be confirmed as negative, a serum pregnancy test is required.

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6.2 CCI [redacted]

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6.3 CCI [redacted]

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6.4 CCI [redacted]

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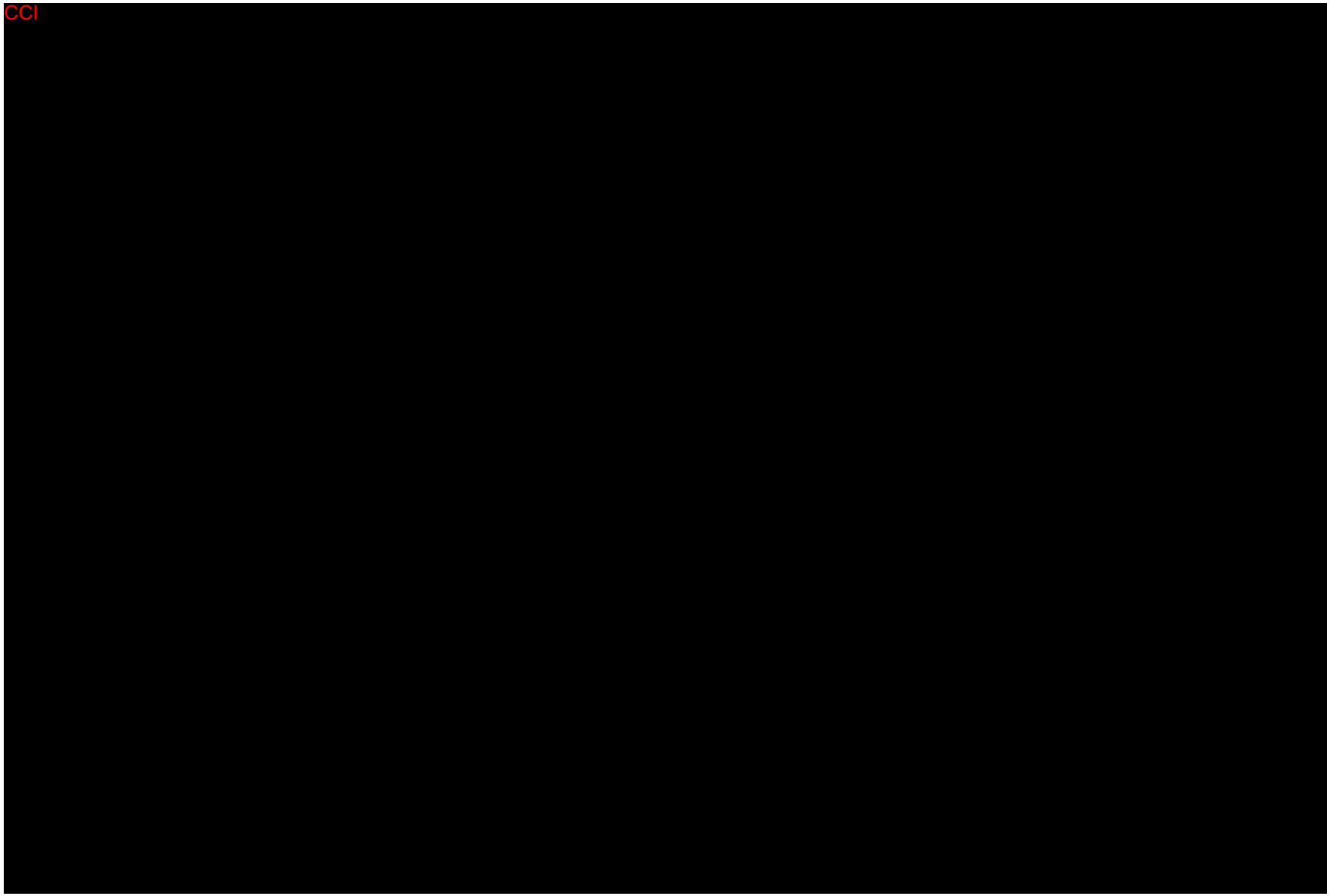
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7.0 TRIAL PROCEDURES

7.1 Trial Procedures

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

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

7.1.1 Administrative Procedures

7.1.1.1 Informed Consent

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

7.1.1.1.1 General Informed Consent

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

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

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

If the investigator recommends continuation of study intervention beyond disease progression, the subject or the subject's legally acceptable representative will be asked to provide documented informed consent.

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

Informed consent will adhere to IRB/IEC 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 medically qualified designee will explain the future biomedical research consent to the subject, or the subject's legally acceptable representative, answer all of his/her questions, and obtain documented informed consent before performing any procedure related to future biomedical research. A copy of the informed consent will be given to the subject before performing any procedure related to future biomedical research.

7.1.1.2 Inclusion/Exclusion Criteria

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

7.1.1.3 Subject Identification Card

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

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

7.1.1.4 Medical History

A medical history will be obtained by the investigator or qualified designee. Medical history will include all active conditions, and any condition diagnosed within the previous 10 years that are considered clinically significant by the investigator. Details regarding the disease for which the subject has been enrolled in the trial will be recorded separately (see Section 7.1.1.5.1) and should not be listed in medical history.

7.1.1.5 Disease Details and Treatments

7.1.1.5.1 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

7.1.1.5.2 Prior Oncology Treatment History

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

7.1.1.6 Prior and Concomitant Medications Review

7.1.1.6.1 Prior Medications

The investigator or qualified designee will review prior medication use, including any protocol-specified washout requirement, and record prior medication taken by the subject within 30 days before the first dose of study treatment. Treatment of the disease for which the subject has been enrolled in this trial will be recorded separately (see Section 7.1.1.5.2) and should not be listed in prior medications.

7.1.1.6.2 Concomitant Medications

The investigator or qualified designee will record medications, if any, taken by the subject during the trial and through to the Post-Treatment Safety Follow-Up visit. After the Safety Follow-Up visit, all medications related to reportable SAEs and ECIs should be recorded.

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

In Arms 1 and 2 of Part A and Part B, subjects will be allocated by non-random assignment. Allocation will alternate between the 2 arms when both arms are open for enrollment (see Section 5.3). CCI [redacted] All eligible subjects in Parts A and B will receive a treatment/randomization number. 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. 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 (Medication)

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 full physical examination during the screening period. Clinically significant findings from the screening examination should be recorded as medical history.

A full physical examination should be repeated at the timepoints outlined in the Trial Flow Charts (Section 6). After the first dose of study treatment, new clinically significant abnormal findings should be recorded as AEs.

7.1.2.2 Height, Weight, and Vital Signs

Height will be measured at screening only.

Weight will be measured at the timepoints outlined in the Trial Flow Charts (Section 6).

The investigator or qualified designee will measure vital signs at the timepoints outlined in the Trial Flow Charts (Section 6). 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 (Appendix 12.4) of the subject at the timepoints outlined in the Trial Flow Charts (Section 6).

7.1.2.4 Electrocardiogram

A 12-lead electrocardiogram (ECG) will be performed by the investigator or qualified designee at the timepoints outlined in the Trial Flow Charts (Section 6).

7.1.2.5 Administration of Study Treatment

MK-7684 and pembrolizumab (or MK-7684A) will be administered by IV infusion on Day 1 of each 21-day cycle. The Pharmacy Manual contains specific instructions for the preparation and administration of the infusion solutions.

Designated site personnel will be responsible for preparing and administering MK-7684 and pembrolizumab (or MK-7684A). They will also be required to record limited information during each infusion (e.g., infusion date/time, lot number and expiry date for product administered, total dose/volume administered). See Pharmacy Manual for further details.

In the combination treatment arm (Arm 2), pembrolizumab will be administered first on Day 1 of each cycle, with administration of MK-7684 occurring approximately 30 minutes after completion of the pembrolizumab infusion.

Subjects may receive up to 35 cycles of study treatment with MK-7684 in Arm 1, MK-7684 and pembrolizumab in Arm 2, and MK-7684A in Arm 4.

Subjects who discontinue MK-7684 in the monotherapy arm due to radiologic disease progression may, at the investigator's discretion and after consultation with the Sponsor, cross over to combination treatment (Arm 2). The total duration of treatment (monotherapy and combination therapy) will not exceed 35 cycles.

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7.1.2.6 Disease Assessments

Initial imaging (e.g., CT scan, MRI, PET-CT, etc.) 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 disease progression, initiating a new anticancer therapy, withdrawing consent for trial participation, or becoming lost to follow-up, whichever occurs first. CCI

[redacted]

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

Scans used for tumor measurements may be requested for potential central review.

Response will be based on RECIST, version 1.1 as assessed by investigator review.

Immunotherapeutic agents, such as MK-7684 and pembrolizumab (or MK-7684A), 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 who have initial evidence of radiologic progressive disease (PD) by RECIST after starting study treatment, should, at the discretion of the investigator, continue on study treatment until repeat imaging is obtained ≥4 weeks later to confirm PD. This clinical judgment decision should be based on the subject's overall clinical condition, including performance status, clinical symptoms, and laboratory data. Clinical stability is defined as the following:

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

(2) No decline in ECOG performance status;

(3) Absence of rapid progression of disease; and

(4) Absence of progressive tumor at critical anatomical sites (e.g., spinal cord compression).

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

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

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

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

At the investigator's discretion and after consultation with the Sponsor, subjects who discontinue MK-7684 in the monotherapy arm due to radiologic disease progression may cross over to the combination arm (Arm 2) as described in Section 5.8.1. Subjects will continue to undergo disease assessments on a routine basis as described in the Cross-Over Flow Chart (Section 6.1). For cross-over subjects, disease burden will continue to be assessed by RECIST, version 1.1 after initiation of combination treatment. From an imaging perspective, management of these subjects will be identical to management of new subjects entering the study. Subjects who have initial evidence of radiologic PD by RECIST after starting cross-over combination treatment, should, at the discretion of the investigator, continue on study treatment until repeat imaging is obtained ≥4 weeks later to confirm PD.

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

- Tumor burden remains ≥20% and there is at least a 5 mm absolute increase compared to the nadir;

- Non-target disease resulting in initial PD is qualitatively worse;
- New lesion resulting in initial PD is qualitatively worse;
- Additional new lesion(s) are identified since the last evaluation; OR
- Additional new non-target progression is identified since the last evaluation.

7.1.2.7 Brain Imaging

CCI [redacted] In addition, repeat brain imaging is to be performed at all post-baseline imaging assessments in subjects with brain metastases at diagnosis who have undergone treatment and as clinically indicated in subjects without brain metastases at diagnosis.

7.1.2.8 CCI [redacted]

CCI [redacted]

7.1.2.9 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 Charts (Section 6), and more frequently, if clinically indicated. Adverse events will be graded according to the CTCAE, version 4.0. Toxicities will be characterized in terms of seriousness, causality, toxicity grade, and action taken with regard to study treatment(s).

Since this is a dose escalation trial to establish the RPTDs of MK-7684 when used as monotherapy and in combination with pembrolizumab, each dose escalation decision will be based on the safety and tolerability experienced by subjects at each dose level. Safety and tolerability for the DLT evaluation period in each cohort will be reviewed by the Sponsor and Principal Investigators independently in each treatment arm prior to the start of the next cohort to determine the appropriateness of dose escalation. 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. The total amount of blood/tissue to be drawn/collected over the course of the trial (from pre-trial to post-trial visits), including approximate blood/tissue volumes drawn/collected by visit and by sample type per subject can be found in the Procedure Manual. The schedule of laboratory assessments is outlined in the Trial Flow Charts (Section 6).

7.1.3.1 Laboratory Safety Evaluations (Hematology, Chemistry and Urinalysis)

Laboratory tests for hematology, chemistry, and urinalysis will be performed at the local laboratory. Parameters to be measured are outlined in Table 10.

Table 10 Laboratory Tests

Hematology	Chemistry	Urinalysis	Other
Red blood cell (RBC) count	Total protein	Blood	Prothrombin time (PT)/International normalized ratio (INR)[5]
Hemoglobin	Albumin	Glucose	Activated partial thromboplastin time (aPTT)[5]
Hematocrit	Alanine aminotransferase (ALT)	Protein	Thyroid function testing (T4, T3, TSH)[6]
White blood cell (WBC) count (total and differential)	Aspartate aminotransferase (AST)	Specific gravity	Immunoglobulins (IgA, IgG, IgM)
Absolute neutrophil count (ANC)	Alkaline phosphatase	Microscopic exam, if abnormal results are noted	Serum β-human chorionic gonadotropin (β-hCG)[4]
Platelet count	Total bilirubin	Urine pregnancy test[4]	Follicle stimulating hormone (FSH)[7]
	Direct bilirubin, if total bilirubin is above the upper limit of normal		Human immunodeficiency virus (HIV; HIV Type 1 and Type 2)[8]
	Bicarbonate / Carbon dioxide (CO_2)[1]		Hepatitis (HCV, RNA [qualitative], or Hepatitis C antibody, and HBsAg)[8]
	Calcium		CCI [redacted]
	Chloride		
	Phosphorus		
	Potassium		
	Sodium		
	Glucose		
	Creatinine		
	Blood urea nitrogen (BUN)/Urea[2]		
	Uric acid		
	Amylase		
	Lipase		
	Lactate dehydrogenase (LDH)[3]		
	Gamma glutamyl transferase (GGT)[3]		

Hematology	Chemistry	Urinalysis	Other

1. If bicarbonate/CO_2 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. LDH and GGT need to be tested at screening and on Day 1 of each cycle only.
4. 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.
5. 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.
6. Total T4 is preferred; if not available free T4 may be tested Total T3 is preferred; if not available free T3 may be tested.
7. In women <45 years of age, a high follicle stimulating hormone (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.
8. Testing is at the discretion of the investigator.

CCI [redacted]

Laboratory tests will be performed at the timepoints outlined in the Trial Flow Charts (Section 6). Results must be reviewed by the investigator or qualified designee and found to be acceptable prior to administration of each dose of trial treatment. Note: Dosing will not be delayed for immunoglobulin test results that are not available at the time of dosing.

7.1.3.2 CCI [redacted]

CCI [redacted]

7.1.3.3 Pharmacokinetic/Pharmacodynamic Evaluations

To evaluate the immunogenicity and exposure of MK-7684 and pembrolizumab in these indications, sample collections for analysis of ADAs and PK are currently planned as shown in the Trial Flow Charts (Section 6). Blood samples collected for ADA and PK may only be stored at this time. Further analysis may be performed if required. If ongoing ADA and/or PK sampling is deemed to be unnecessary by the Sponsor, it may be reduced or discontinued.

7.1.3.3.1 Blood Collection for MK-7684

Samples for PK/PD evaluations will be collected at the timepoints outlined in the Trial Flow Charts (Section 6). Collection, storage, and shipment instructions for blood samples will be provided in the Procedure Manual.

7.1.3.3.2 Blood Collection for Pembrolizumab (Arms 2, 3, 4, and 5 only)

Samples for PK/PD evaluations will be collected at the timepoints outlined in the Trial Flow Charts (Section 6). Collection, storage, and shipment instructions for blood samples will be provided in the Procedure Manual.

7.1.3.3.3 Sample Collection for Exploratory Biomarkers

Samples for exploratory biomarkers will be collected at the timepoints outlined in the Trial Flow Charts (Section 6). Collection, storage, and shipment instructions will be provided in the Procedure Manual. Any leftover samples will be stored for FBR if the subject provides documented informed consent for FBR.

7.1.3.4 Tumor Tissue Collection

Subjects will be required to provide a pretreatment tumor sample (archival or newly obtained). CCI [redacted]. If an archival sample is not available, new biopsy should be performed if possible. If biopsy cannot be performed without significant risk to the patient, the biopsy requirement may be omitted after Sponsor consultation. All subjects will be requested to provide a post-treatment tumor biopsy sample as outlined in the Trial Flow Charts (Section 6).

Collection, storage, and shipment instructions for tumor samples will be provided in the Procedure 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.

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 Procedure Manual.

7.1.3.6 Future Biomedical Research Sample Collection

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

- DNA for future research

  Leftover RNA

  Leftover serum

  Leftover main study tumor

7.1.4 Other Procedures

7.1.4.1 Withdrawal/Discontinuation

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

When a subject discontinues/withdraws from participation in the trial, all applicable activities scheduled for the End of Treatment visit should be performed at the time of discontinuation. Any adverse events which are present at the time of discontinuation/withdrawal should be followed in accordance with the safety requirements outlined in Section 7.2 - Assessing and Recording Adverse Events.

7.1.4.1.1 Withdrawal From Future Biomedical Research

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

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

7.1.4.1.2 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:

1. 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.
2. The investigator or designee must make every effort to regain contact with the subject at each missed visit (e.g., 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 pre-specified data handling and analysis guidelines.

7.1.4.2 Blinding/Unblinding

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

7.1.4.3 Calibration of Equipment

The investigator or qualified designee has the responsibility to ensure that any device or instrument used for a clinical evaluation/test during a clinical 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.

Documented informed consent must be provided prior to performing any protocol-specific procedures. Results of tests performed as part of routine clinical management prior to the subject providing documented informed consent are acceptable in lieu of a screening test if performed within the specified timeframe.

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 that are to be performed within 7 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 trial participation will be allocated to a treatment arm and assigned to receive a dose of MK-7684 or MK-7684A by the Sponsor. Subjects in Arms 2, 3 and 5 will receive 200 mg of pembrolizumab in addition to their assigned dose of MK-7684. CCI [redacted]

Study visits will occur as outlined in the Trial Flow Charts (Section 6). Subjects may be seen more frequently, if clinically indicated. Tumor imaging and response assessment will occur every 9 weeks after the first dose of study treatment. CCI [redacted]

Study treatment in all arms will be given on Day 1 of each 3-week cycle, except etoposide which will be given on Days 1, 2, and 3 of each 3-week cycle. Study treatment with MK-7684 (Arms 1-5), pembrolizumab (Arms 2-5), and MK-7684A (Arm 4) may be

administered for up to 35 cycles. CCI [redacted]

Subjects who discontinue MK-7684 in the monotherapy arm due to disease progression may, at the investigator's discretion and after consultation with the Sponsor, cross over to combination treatment (Arm 2). Subjects eligible for cross-over must have received at least 2 cycles of MK-7684 monotherapy and must have radiographic imaging to document disease progression by RECIST, version 1.1 and to establish a new imaging baseline prior to cross-over. The total duration of treatment (monotherapy and combination therapy) will not exceed 35 cycles. Specific details regarding procedures to be performed are provided in the Cross-Over Flow Chart in Section 6.1.

7.1.5.3 Post-treatment 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 for post-treatment follow-up visits to monitor safety. The Post-Treatment Safety Follow-Up visit should occur approximately 30 days after the last dose of study treatment. If a subject initiates a new anticancer therapy within 30 days after the last dose of study treatment, the Post-Treatment Safety Follow-Up visit should occur before the first dose of the new therapy.

After treatment discontinuation, subjects will be monitored for AEs and SAEs for 90 days. Subjects who initiate new anticancer therapy less than 30 days after study treatment discontinuation will be monitored for AEs/SAEs for 30 days. Subjects who initiate new anticancer therapy between 30 days and 90 days after study treatment discontinuation will be monitored for AEs/SAEs until the day new anticancer therapy is initiated.

Subjects who discontinue treatment for reasons other than confirmed disease progression will have post-treatment follow-up for disease status until disease progression, initiating a new anticancer therapy, withdrawing consent for trial participation, or becoming lost to follow-up, whichever occurs first.

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

7.1.5.4 Survival Status

To ensure current and complete survival data is available, updated survival status may be requested by the Sponsor during the course of the study. Upon Sponsor notification, all participants who do not/will not have a scheduled study visit or study contact during the Sponsor-defined time period will be contacted for their survival status (excluding participants 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 (i.e., any clinically significant adverse change in frequency and/or intensity) of a preexisting condition that is temporally associated with the use of the Sponsor's product, is also an adverse event.

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

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

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

All adverse events that occur after documented informed consent is provided 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 90 days following cessation of treatment, all adverse events must be reported by the investigator. Subjects who initiate new anticancer therapy less than 30 days after study treatment discontinuation will be monitored for adverse events for 30 days. Subjects who initiate new anticancer therapy between 30 days and 90 days after study treatment discontinuation will be monitored for adverse events until the day new anticancer therapy is initiated. Adverse events will be recorded at each examination on the Adverse Event case report forms/worksheets. 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 the purpose of this trial, an overdose of MK-7684 or MK-7684A will be defined as any dose exceeding the prescribed dose by ≥20%. An overdose of pembrolizumab will be defined as any dose ≥1000 mg (i.e., ≥5 times the indicated dose).

No specific information is available on the treatment of overdose of MK-7684, MK-7684A, 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 documented informed consent is provided 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 30 days following cessation of Sponsor's product 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 11 for additional details regarding each of the above criteria.

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

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

All serious adverse events will be recorded from the time of treatment allocation. Subjects will be monitored for serious adverse events 90 days after treatment discontinuation. Subjects who initiate anticancer therapy less than 30 days after study treatment discontinuation will be monitored for serious adverse events for 30 days. Subjects who initiate new anticancer therapy between 30 days and 90 days after study treatment discontinuation will be monitored for serious adverse events until the day new anticancer therapy is initiated.

Serious adverse events or follow up to a serious adverse event, including death due to any cause, whether or not related to the Sponsor’s product, must be reported within 24 hours to the Sponsor either by electronic media or paper. Electronic reporting procedures can be found in the EDC data entry guidelines. Paper reporting procedures can be found in the Investigator Trial File Binder (or equivalent).

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

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

7.2.3.2 Events of Clinical Interest

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

For the time period beginning when documented informed consent is provided 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).
3. a Grade 3 or higher infusion-related reaction.

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

Table 11 Evaluating Adverse Events

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

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

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

7.2.5 Sponsor Responsibility for Reporting Adverse Events

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

8.0 STATISTICAL ANALYSIS PLAN

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

If, after the trial 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 non-confirmatory analyses made after the protocol has been finalized, but prior to the conduct of any analyses, will be documented in the sSAP as needed and referenced in the Clinical Study Report (CSR) for the trial. 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 (SAP), Section 8.2 to Section 8.12.

Trial Design Overview	Phase 1/1b trial of MK-7684 monotherapy and MK-7684 in combination with pembrolizumab in subjects with advanced solid tumors. The trial applies an mTPI design for dose escalation and confirmation of preliminary RPTDs, followed by an expansion phase with CCI (NSCLC, CCI [redacted] Final RPTDs for MK-7684 when used as monotherapy and in combination with pembrolizumab will be determined using PK and PD endpoints, as well as all available safety data.
Analysis Populations	Safety (Primary): All-Subjects-as-Treated (ASaT) PK (Secondary): Per-Protocol (PP) Efficacy (Secondary & Exploratory): Full Analysis Set (FAS)
Primary Endpoint(s)	Safety: all available safety data from subjects in Part A and Part B, including DLT rates and the cumulative incidence of late toxicities (i.e., toxicities that occur after the 21-day DLT observation period)

Key Secondary Endpoints	PK parameters of MK-7684 monotherapy, MK-7684 in combination with pembrolizumab, CCI [redacted] ORR in subjects treated with MK-7684 monotherapy, MK-7684 in combination with pembrolizumab, CCI [redacted]
Statistical Methods for Key Efficacy/ Pharmacokinetic Analyses	Efficacy analyses are documented in the sSAP. PK concentrations of study treatments will be summarized by planned visit and time for each dose separately; PK parameters of MK-7684 will be summarized by dose.
Treatment Assignment	In all subjects in Part A CCI [redacted] and in all subjects in Part B CCI [redacted] subjects will be allocated by non-random assignment to receive MK-7684 monotherapy (Arm 1) or MK-7684 in combination with pembrolizumab (Arm 2) centrally through an IVRS/IWRS. Allocation will alternate between the 2 arms when both arms are open for enrollment. CCI [redacted] The trial 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 2-dimensional pool-adjacent-violators algorithm [1] that forces the DLT rate estimates to be non-decreasing with dose levels and to be no higher in the MK-7684 monotherapy arm (Arm 1) than in the combination therapy arm (Arm 2) will be used to estimate the DLT rates across doses. The estimates of the DLT rates among subjects treated at the preliminary RPTDs of MK-7684 when used as monotherapy and when used in combination with pembrolizumab and the 80% Bayesian credible intervals with prior distribution Beta (1, 1) for the estimates will be provided.
Interim Analyses	CCI [redacted]
Multiplicity	No multiplicity adjustment is planned for this Phase 1/1b trial.
Sample Size and Power	The overall sample size for this trial depends on the observed DLT profiles of MK-7684 monotherapy (Arm 1), MK-7684 in combination with pembrolizumab (Arm 2), CCI [redacted] A maximum sample size of 492 subjects will be used for trial planning purposes.

8.2 Responsibility for Analyses/In-house Blinding

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

The trial is open-label, i.e., subjects, investigators, and Sponsor personnel will be aware of subject treatment assignment after each subject is enrolled and treatment is assigned.

8.3 Trial Objectives

Objectives of the trial are outlined in Section 3.0.

8.4 Analysis Endpoints

8.4.1 Efficacy/Pharmacokinetic Endpoints

Overall response rate is a secondary endpoint of the trial. Overall response rate is defined as the proportion of subjects in the analysis population who experience CR or PR at any time during the trial using RECIST, version 1.1 as assessed by investigator review. For subjects with ES-SCLC treated in Arm 5, 6-month PFS rate is also a secondary endpoint. PFS is

defined as the time from the first dose of study treatment to the first documented disease progression per RECIST 1.1 as assessed by investigator review or death due to any cause, whichever occurs first. The 6-month PFS rate is defined as the percentage of subjects who achieve a 6-month PFS as estimated by the Kaplan-Meier method. CCI [redacted]

Pharmacokinetic endpoints include serum concentrations of MK-7684 (Arms 1 through 5) and pembrolizumab (Arms 2 through 5), as well as any derived PK parameters.

CCI [redacted]

8.4.2 Safety Endpoints

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

A description of safety measures is provided in Section 7.0.

8.5 Analysis Populations

8.5.1 Safety Analysis Population

The All-Subjects-as-Treated (ASaT) population will be used for the analysis of safety data in this trial. The ASaT population consists of all subjects who received at least one dose of study treatment. In case of treatment administration errors, subjects will be analyzed according to the treatment they actually received. For DLT evaluation, ASaT subjects that were observed for safety for 21 days after the first dose of assigned treatment or experienced a DLT prior to 21 days after the first dose of assigned treatment will be used. Data from subjects who experienced disease progression in the monotherapy arm and crossed over into the combination arm will be presented separately; data from these subjects will not be included in the DLT evaluation.

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

8.5.2 Pharmacokinetic Analysis and Target Engagement Populations

The Per-Protocol (PP) population will be used for the analysis of the PK and target engagement data in this trial. The PP population consists of the subset of subjects who

complied with the protocol sufficiently to ensure that the data they generated will be likely to exhibit the effects of treatment, according to the underlying scientific model. Compliance covers such considerations as exposure to treatment, availability of measurements, and absence of major protocol violations. Major protocol violators will be identified, to the extent possible, by individuals responsible for data collection/compliance, and its analysis and interpretation. Any subjects or data values excluded from analysis will be identified in the CSR, along with the reasons for exclusion. At the end of the trial, all subjects who were compliant with the trial procedures and have available data from at least one treatment may be included in the PP analysis dataset. Data from subjects who experienced disease progression in the monotherapy arm and crossed over into the combination arm will be presented separately.

8.5.3 Efficacy Analysis Populations

The Full Analysis Set (FAS) population will be used for the analysis of secondary and exploratory efficacy data in this trial. The FAS population consists of all subjects with a baseline scan with measurable disease by investigator assessment who were administered a dose of study treatment regardless of dose level. Data from subjects who experienced disease progression in the monotherapy arm and crossed over into the combination arm will be presented separately.

8.6 Statistical Methods

8.6.1 Statistical Methods for Efficacy Analyses

For the secondary endpoint of ORR, the point estimate and 95% CI will be evaluated separately in subjects treated with MK-7684 monotherapy and subjects treated with MK-7684 in combination with pembrolizumab CCI

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 by 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] that forces the DLT rate estimates to be non-decreasing with dose levels and pools adjacent violators for weighted estimates by sample size, will be used to estimate the DLT rates across doses in Arm 1 and Arm 2. The estimates of the DLT

rates among subjects treated at the preliminary RPTDs and the 80% Bayesian credible intervals based on a prior distribution of Beta (1,1) for the estimates will be provided.

CCI [redacted]

8.6.3 Summaries of Baseline Characteristics, Demographics, and Other Analyses

8.6.3.1 Demographic and Baseline Characteristics

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

8.6.3.2 Population Pharmacokinetic/Pharmacodynamic Analyses

Pharmacokinetic and PD modeling analyses will be done on an ongoing basis throughout the trial and at the end of the trial. These analyses will be used to explore the relationships among PK, target engagement, exploratory biomarkers, and tumor response measurements.

CCI [redacted]

8.7 Interim Analyses

CCI [redacted]

8.8 Multiplicity

There will be no multiplicity control in this trial.

8.9 Sample Size and Power Calculations

During Part A (dose escalation and confirmation), approximately 102 subjects (38 subjects each in Arm 1 and Arm 2, CCI [redacted] are expected to be enrolled. The actual sample size will depend on the safety profiles of MK-7684 in each treatment arm, but is expected to be in line with a typical Phase 1 first-in-human oncology trial.

In Part B (expansion phase), approximately 338 to 390 subjects (94 to 120 subjects with NSCLC, CCI [redacted] are expected to be enrolled. Data from subjects treated at the preliminary RPTDs in Part A will be included in the analysis of Part B if they meet the specifications described in Inclusion Criterion 1 (Section 5.1.2).

A maximum sample size of 492 subjects will be used for trial planning purposes.

CCI [redacted]

8.10 Subgroup Analyses and Effect of Baseline Factors

Subgroup analyses of the secondary efficacy endpoint (ORR) will be conducted by treatment arm, dose level, and tumor type. CCI [redacted]

CCI

[redacted]

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.

9.0 LABELING, PACKAGING, STORAGE AND RETURN OF CLINICAL SUPPLIES

9.1 Investigational Product

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

Clinical Supplies will be provided by the Sponsor as summarized in Table 12. Chemotherapy will be sourced locally by the site.

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

Treatment Group(s)	Product Name and Potency	Dose(s)	Route of Administration and Frequency	Source
Arms 1, 2, 3, and 5	MK-7684 50 mg/mL, 2.0-mL vial, solution for infusion	Escalating doses based on pre-specified dose-limiting toxicity (DLT) criteria / RPTD(s)	Intravenous infusion on Day 1 of each 21-day cycle	Centrally by the Sponsor
Arms 2, 3, and 5	Pembrolizumab (MK-3475) 25 mg/mL, 4.0-mL vial, solution for infusion	200 mg	Intravenous infusion on Day 1 of each 21-day cycle	Centrally by the Sponsor
CCI [redacted]				

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 kits of MK-7684, MK-3475/pembrolizumab, CCI [redacted] as outlined in the Procedure Manual. Each kit of MK-7684 will contain 1 vial. Each kit of MK-3475/pembrolizumab will contain 2 vials. CCI [redacted].

9.3 Clinical Supplies Disclosure

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

9.4 Storage and Handling Requirements

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

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

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

9.5 Discard/Destruction/Returns and Reconciliation

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

9.6 Standard Policies

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

10.0 ADMINISTRATIVE AND REGULATORY DETAILS

10.1 Confidentiality

10.1.1 Confidentiality of Data

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

10.1.2 Confidentiality of Subject Records

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

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

10.1.3 Confidentiality of Investigator Information

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

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

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

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

10.1.4 Confidentiality of IRB/IEC Information

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

10.2 Compliance with Financial Disclosure Requirements

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

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

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

10.3 Compliance with Law, Audit and Debarment

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

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

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

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

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

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

The investigator must maintain copies of all documentation and records relating to the conduct of the trial in compliance with all applicable legal and regulatory requirements. This

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

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

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

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

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

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

10.4 Compliance with Trial Registration and Results Posting Requirements

Under the terms of the Food and Drug Administration 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. MSD, as Sponsor of this trial, will review this protocol and submit the information necessary to fulfill these requirements. MSD entries are not limited to 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. MSD will post a synopsis of trial results for approved

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

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

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

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

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

11.0 LIST OF REFERENCES

[1] Ji Y, Li Y, Bekele BN. Dose-finding in phase l clinical trials based on toxicity probability intervals. Clin Trials 2007;4:235-44.

[2] Disis ML. Immune regulation of cancer. J Clin Oncol 2010;28(29):4531-8.

[3] Dong H, Strome SE, Salomao DR, Tamura H, Hirano F, Flies DB, et al. Tumor-associated B7-H1 promotes T-cell apoptosis: a potential mechanism of immune evasion. Nat Med 2002;8(8):793-800.

[4] Hino R, Kabashima K, Kato Y, Yagi H, Nakamura M, Honjo T, et al. Tumor cell expression of programmed cell death-1 ligand 1 is a prognostic factor for malignant melanoma. Cancer 2010;116:1757-66.

[5] Topalian SL, Hodi FS, Brahmer JR, Gettinger SN, Smith DC, McDermott DF, et al. Safety, activity, and immune correlates of anti-PD-1 antibody in cancer. N Engl J Med 2012;366(26):2443-54.

[6] Patnaik A, Kang SP, Tolcher AW, Rasco DW, Papadopoulos KP, Beeram M, et al. 2012 ASCO Annual Meeting: Phase I study of MK-3475 (anti-PD-1 monoclonal antibody) in patients with advanced solid tumors.

[7] Hodi FS, O'Day SJ, McDermott DF, Weber RW, Sosman JA, Haanen JB, et al. Improved survival with ipilimumab in patients with metastatic melanoma. N Engl J Med 2010;363(8):711-23.

[8] Chapman PB, Hauschild A, Robert C, Hannen JB, Ascierto P, Larkin J, et al. Improved survival with vemurafenib in melanoma with BRAF V600E mutation. N Engl J Med 2011;364(26):2507-16.

[9] Robert C, Thomas L, Bondarenko I, O'Day S, Weber J, Garbe C, et al. Ipilimumab plus dacarbazine for previously untreated metastatic melanoma. N Engl J Med 2011;364(26):2517-26.

[10] Sasaki A, Tanaka F, Mimori K, Inoue H, Kai S, Shibata K, et al. Prognostic value of tumor-infiltrating FOXP3+ regulatory T cells in patients with hepatocellular carcinoma. EJSO 2008;34:173-9.

[11] Shen Z, Zhou S, Wang Y, Li R, Zhong C, Liang C, et al. Higher intratumoral infiltrated Foxp3+ Treg numbers and Foxp3+/CD8+ ratio are associated with adverse prognosis in resectable gastric cancer. J Cancer Res Clin Oncol 2010;136:1585-95.

[12] Levin SD, Taft DW, Brandt CS, Bucher C, Howard ED, Chadwick EM, et al. Vstm3 is a member of the CD28 family and an important modulator of T-cell function. Eur J Immunol. 2011 Apr;41(4):902-15.

[13] Dardalhon V, Schubart AS, Reddy J, Meyers JH, Monney L, Sabatos CA, et al. CD226 is specifically expressed on the surface of Th1 cells and regulates their expansion and effector functions. J Immunol. 2005 Aug 1;175(3):1558-65.

[14] Stanietsky N, Rovis TL, Glasner A, Seidel E, Tsukerman P, Yamin R, et al. Mouse TIGIT inhibits NK-cell cytotoxicity upon interaction with PVR. Eur J Immunol. 2013 Aug;43(8):2138-50.

[15] Carlsten M, Bjorkstrom NK, Norell H, Bryceson Y, van Hall T, Baumann BC, et al. DNAX accessory molecule-1 mediated recognition of freshly isolated ovarian carcinoma by resting natural killer cells. Cancer Res. 2007 Feb 1;67(3):1317-25.

[16] Hirota T, Irie K, Okamoto R, Ikeda W, Takai Y. Transcriptional activation of the mouse Necl-5/Tage4/PVR/CD155 gene by fibroblast growth factor or oncogenic Ras through the Raf-MEK-ERK-AP-1 pathway. Oncogene. 2005 Mar 24;24(13):2229-35.

[17] Masson D, Jarry A, Baury B, Blanchardie P, Laboisse C, Lustenberger P, et al. Overexpression of the CD155 gene in human colorectal carcinoma. Gut. 2001 Aug;49(2):236-40.

[18] Soriani A, Zingoni A, Cerboni C, Iannitto ML, Ricciardi MR, Di Gialleonardo V, et al. ATM-ATR-dependent up-regulation of DNAM-1 and NKG2D ligands on multiple myeloma cells by therapeutic agents results in enhanced NK-cell susceptibility and is associated with a senescent phenotype. Blood. 2009 Apr 9;113(15):3503-11.

[19] Stanietsky N, Simic H, Arapovic J, Toporik A, Levy O, Novik A, et al. The interaction of TIGIT with PVR and PVRL2 inhibits human NK cell cytotoxicity. Proc Natl Acad Sci U S A. 2009 Oct 20;106(42):17858-63.

[20] Chauvin JM, Pagliano O, Fourcade J, Sun Z, Wang H, Sander C, et al. TIGIT and PD-1 impair tumor antigen-specific $CD8^+$ T cells in melanoma patients. J Clin Invest. 2015 May;125(5):2046-58.

[21] Johnston RJ, Comps-Agrar L, Hackney J, Yu X, Huseni M, Yang Y, et al. The immunoreceptor TIGIT regulates antitumor and antiviral CD8(+) T cell effector function. Cancer Cell. 2014 Dec 8;26(6):923-37.

[22] Talmadge JE, Donkor M, Scholar E. Inflammatory cell infiltration of tumors: Jekyll or Hyde. Cancer Metastasis Rev 2007;26(3-4):373-400.

[23] Usubütün A, Ayhan A, Uygur MC, Özen H, Toklu C, Ruacan S. Prognostic factors in renal cell carcinoma. J Exp Clin Cancer Res 1998;17(1):77-81.

[24] Zhang X, Schwartz J-CD, Guo X, Bhatia S, Cao E, Chen L, et al. Structural and functional analysis of the costimulatory receptor programmed death-1. Immunity 2004;20:337-47.

[25] Okazaki T, Maeda A, Nishimura H, Kurosaki T, Honjo T. PD-1 immunoreceptor inhibits B cell receptor-mediated signaling by recruiting src homology 2-domain-containing tyrosine phosphatase 2 to phosphotyrosine. Proc Natl Acad Sci U S A 2001;98(24):13866-71.

[26] Chemnitz JM, Parry RV, Nichols KE, June CH, Riley JL. SHP-1 and SHP-2 associate with immunoreceptor tyrosine-based switch motif of programmed death 1 upon primary human T cell stimulation, but only receptor ligation prevents T cell activation. J Immunol 2004;173:945-54.

[27] Sheppard K-A, Fitz LJ, Lee JM, Benander C, George JA, Wooters J, et al. PD-1 inhibits T-cell receptor induced phosphorylation of the ZAP70/CD3zeta signalosome and downstream signaling to PKCtheta. FEBS Lett. 2004;574:37-41.

[28] Riley JL. PD-1 signaling in primary T cells. Immunol Rev 2009;229:114-25.

[29] Nobili C, Degrate L, Caprotti R, Franciosi C, Leone BE, Trezzi R, et al. Prolonged survival of a patient affected by pancreatic adenocarcinoma with massive lymphocyte and dendritic cell infiltration after interleukin-2 immunotherapy. Report of a case. Tumori 2008;94(3):426-30.

[30] Hiraoka N. Tumor-infiltrating lymphocytes and hepatocellular carcinoma: molecular biology. Int J Clin Oncol 2010;15(6):544-51.

[31] Globocan 2012: Lung Cancer Estimated Incidence, Mortality and Prevalence Worldwide in 2012 [Internet]. Lyon (FR): World Health Organization, International Agency for Research on Cancer (IARC). c2014 – [updated 2014 Oct 3]. Available from: http://globocan.iarc.fr/Pages/fact_sheets_cancer.aspx

[32] SEER*Stat [Internet]. Bethesda (MD): National Cancer Institute. 2018. Cancer stat facts: lung and bronchus cancer; [about 12 screens]. Available from: https://seer.cancer.gov/statfacts/html/lungb.html.

[33] Sulpher JA, Owen SP, Hon H, Tobros K, Shepherd FA, Sabri E, et al. Factors influencing a specific pathologic diagnosis of non-small-cell lung carcinoma. Clin Lung Cancer. 2013 May;14(3):238-44.

[34] National Comprehensive Cancer Network (NCCN). Clinical Practice Guidelines in Oncology: Non-small cell lung cancer: version 5.2017. Fort Washington, PA: NCCN; 2017.

[35] Reck M, Rodriguez-Abreu D, Robinson AG, Hui R, Csoszi T, Fulop A, et al. Pembrolizumab versus Chemotherapy for PD-L1-Positive Non-Small-Cell Lung Cancer. N Engl J Med. 2016 Oct 8. [Epub ahead of print].

[36] Langer CJ, Gadgeel SM, Borghaei H, Papadimitrakopoulou VA, Patnaik A, Powell SF, et al. Carboplatin and pemetrexed with or without pembrolizumab for advanced, non-squamous non-small-cell lung cancer: a randomised, phase 2 cohort of the open-label KEYNOTE-021 study. Lancet Oncol. 2016 Nov;17:1497-508.

[37] Borghaei H, Langer S, Gadgeel S, Papadimitrakopoulou V, Patnaik A, Powell S, et al. Pemetrexed-carboplatin plus pembrolizumab as first-line therapy for advanced nonsquamous NSCLC: KEYNOTE-021 cohort G update. J Thorac Oncol. 2017 Nov;12(11 suppl 2):S1791. Abstract no. OA 17.01.

[38] Gandhi L, Rodriguez-Abreu D, Gadgeel S, Esteban E, Felip E, De Angelis F, et al. Pembrolizumab plus chemotherapy in metastatic non-small-cell lung cancer. N Engl J Med. 2018 May 31;378(22):2078-92.

[39] Varghese AM, Zakowski MF, Yu HA, Won HH, Riely GJ, Krug LM, et al. Small-cell lung cancers in patients who never smoked cigarettes. J Thorac Oncol. 2014 Jun;9(6):892-6.

[40] Ou SH, Ziogas A, Zell JA. Prognostic factors for survival in extensive stage small cell lung cancer (ED-SCLC): the importance of smoking history, socioeconomic and marital statuses, and ethnicity. J Thorac Oncol. 2009 Jan;4(1):37-43.

[41] American Cancer Society. Cancer facts and figures 2014 [Internet]. Atlanta: American Cancer Society; 2014. Available from: http://www.cancer.org/acs/groups/content/@research/documents/webcontent/acspc-042151.pdf.

[42] Gaspar LE, McNamara EJ, Gay EG, Putnam JB, Crawford J, Herbst RS, et al. Small-cell lung cancer: prognostic factors and changing treatment over 15 years. Clin Lung Cancer. 2012 Mar;13(2):115-22.

[43] Horn L, Mansfield AS, Szczesna A, Havel L, Krzakowski M, Hochmair MJ, et al. First-line atezolizumab plus chemotherapy in extensive-stage small-cell lung cancer. N Engl J Med. 2018 Dec 6;379(23):2220-2229.

[44] Reck M, Liu SV, Mansfield AS, Mok T, Scherpereel A, Reinmuth N, et al. Impower133: updated overall survival (OS) analysis of first-line (1L) atezolizumab (atezo) + carboplatin + etoposide in extensive-stage SCLC (ES-SCLC). Slides presented at: 44th European Society for Medical Oncology (ESMO) 2019 Congress; 2019 Sep 27-Oct 1; Barcelona (Spain).

[45] Paz-Ares L, Dvorkin M, Chen Y, Reinmuth N, Hotta K, Trukhin D, et al. Durvalumab plus platinum-etoposide versus platinum-etoposide in first-line treatment of extensive-stage small-cell lung cancer (CASPIAN): a randomised, controlled, open-label, phase 3 trial. Lancet. 2019 Nov 23;394(10212):1929-1939

[46] Paz-Ares LG, Dvorkin M, Chen Y, Reinmuth N, Hotta K, Trukhin D, et al. Durvalumab ± tremelimumab + platinum-etoposide in first-line extensive-stage SCLC (ES-SCLC): updated results from the phase III CASPIAN study [abstract]. Presented at: 2020 American Society of Clinical Oncology (ASCO) Virtual Scientific Program; 2020 May 29-31; [online meeting]. J Clin Oncol. 2020;38(15 suppl). Abstract no. 9002.

[47] Rudin CM, Awad MM, Navarro A, Gottfried M, Peters S, Csoszi T, et al. Pembrolizumab or placebo plus etoposide and platinum as first-line therapy for extensive-stage small-cell lung cancer: randomized, double-blind, phase III KEYNOTE-604 study. J Clin Oncol. 2020 Jul 20;38(21):2369-2379.

[48] Xu Y, Cui G, Jiang Z, Li N, Zhang X. Survival analysis with regard to PD-L1 and CD155 expression in human small cell lung cancer and a comparison with associated receptors. Oncol Lett. 2019;17:2960-8.

[49] Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2018;68:394-424.

[50] Cortez AJ, Tudrej P, Kujawa KA, Lisowska KM. Advances in ovarian cancer therapy. Cancer Chemother Pharmacol. 2018;81:17-38.

[51] Matulonis UA, Penson RT, Domchek SM, Kaufman B, Shapira-Frommer R, Audeh MW, et al. Olaparib monotherapy in patients with advanced relapsed ovarian cancer and a germline BRCA1/2 mutation: a multistudy analysis of response rates and safety. Ann Oncol. 2016 Jun;27(6):1013-9.

[52] Matulonis UA, Shapira-Frommer R, Santin AD, Lisyanskaya AS, Pignata S, Vergote I, et al. Antitumor activity and safety of pembrolizumab in patients with advanced recurrent ovarian cancer: results from the phase II KEYNOTE-100 study. Ann Oncol. 2019;30(7):1080-7.

[53] Pujade-Lauraine E, Hilpert F, Weber B, Reuss A, Poveda A, Kristensen G, et al. Bevacizumab combined with chemotherapy for platinum-resistant recurrent ovarian cancer: The AURELIA open-label randomized phase III trial. J Clin Oncol. 2014 May 1;32(13):1302-8. Erratum in: J Clin Oncol. 2014 Dec 10;32(35):4025.

[54] Pölcher M, Braun M, Friedrichs N, Rudlowski C, Bercht E, Fimmers R, et al. Foxp3(+) cell infiltration and granzyme B(+)/Foxp3(+) cell ratio are associated with outcome in neoadjuvant chemotherapy-treated ovarian carcinoma. Cancer Immunol Immunother 2010;59(6):909-19.

[55] Ropponen KM, Eskelinen MJ, Lipponen PK, Alhava E, Kosma V-M. Prognostic value of tumour-infiltrating lymphocytes (TILs) in colorectal cancer. J Pathol 1997;182(3):318-24.

[56] Dudley ME, Wunderlich JR, Yang JC, Sherry RM, Topalian SL, Restifo NP, et al. Adoptive cell transfer therapy following non-myeloablative but lymphodepleting chemotherapy for the treatment of patients with refractory metastatic melanoma. J Clin Oncol 2005;23(10):2346-57.

[57] Hunder NN, Wallen H, Cao J, Hendricks DW, Reilly JZ, Rodmyre R, et al. Treatment of metastatic melanoma with autologous CD4+ T cells against NY-ESO-1. N Engl J Med 2008;358(25):2698-703.

[58] Greenwald RJ, Freeman GJ, Sharpe AH. The B7 family revisited. Annu Rev Immunol 2005;23:515-48.

[59] Nishimura H, Okazaki T, Tanaka Y, Nakatani K, Hara M, Matsumori A, et al. Autoimmune dilated cardiomyopathy in PD-1 receptor-deficient mice. Science 2001;291:319-22.

[60] Nishimura H, Nose M, Hiai H, Minato N, Honjo T. Development of lupus-like autoimmune dieseases by disruption of the PD-1 gene encoding an ITIM motif-carrying immunoreceptor. Immunity 1999;11:141-51.

[61] Ansari MJI, Salama AD, Chitnis T, Smith RN, Yagita H, Akiba H, et al. The programmed death-1 (PD-1) pathway regulates autoimmune diabetes in nonobese diabetic (NOD) mice. J Exp Med 2003;198(1):63-9.

[62] Emens LA, Middleton G. The interplay of immunotherapy and chemotherapy: harnessing potential synergies. Cancer Immunol Res. 2015 May;3(5):436-43.

[63] Galluzzi L, Buque A, Kepp O, Zitvogel L, Kroemer G. Immunological effects of conventional chemotherapy and targeted Anticancer agents. Cancer Cell. 2015 Dec 14;28(6):690-714.

[64] Vincent J, Mignot G, Chalmin F, Ladoire S, Bruchard M, Chevriaux A, et al. 5-Fluorouracil selectively kills tumor-associated myeloid-derived suppressor cells resulting in enhanced T cell-dependent antitumor immunity. Cancer Res. 2010 Apr 15;70(8):3052-61.

[65] Besse B, Adjei A, Baas P, Meldgaard P, Nicolson M, Paz-Ares L, et al. 2nd ESMO consensus conference on lung cancer: non-small-cell lung cancer first-line/second and further lines of treatment in advanced disease. Ann Oncol. 2014 Aug;25(8):1475-84.

[66] Matulonis UA, Shapira-Frommer R, Santin A, Lisyanskaya AS, Pignata S, Vergote I, et al. Antitumor activity and safety of pembrolizumab in patients with advanced recurrent ovarian cancer: interim results from the phase 2 KEYNOTE-100 study [abstract]. Presented at: 2018 American Society of Clinical Oncology (ASCO) Annual Meeting; 2018 Jun 1-5; Chicago, IL. J Clin Oncol. 2018;36(15 suppl). Abstract no. 5511.

[67] Nanda R, Specht J, Dees EC, Berger B, Gupta S, Geva R, et al. Pembrolizumab for metastatic triple-negative breast cancer (mTNBC): long-lasting responses in the phase Ib KEYNOTE-012 study [abstract]. Presented at: European CanCer Organisation (ECCO): 2017 European Cancer Congress; 2017 Jan 27-30; Amsterdam (Netherlands). Eur J Cancer. 2017 Feb;72(suppl 1):S38. Abstract no. 243.

[68] Schellens JHM, Marabelle A, Zeigenfuss S, Ding J, Pruitt SK, Chung HC, et al. Pembrolizumab for previously treated advanced cervical squamous cell cancer: preliminary results from the phase 2 KEYNOTE-158 study [abstract]. Presented at: 2017 American Society of Clinical Oncology (ASCO) Annual Meeting; 2017 Jun 2-6; Chicago, IL. J Clin Oncol. 2017;35(15 suppl). Abstract no. 5514.

[69] O'Neil BH, Wallmark JM, Lorente D, Elez E, Raimbourg J, Gomez-Roca C, et al. Safety and antitumor activity of the anti-PD-1 antibody pembrolizumab in patients with advanced colorectal carcinoma. PLoS One. 2017 Dec 28;12(12):e0189848.

[70] Fuchs SC, Doi T, Jang RWJ, Muro K, Satoh T, Machado M, et al. KEYNOTE-059 cohort 1: efficacy and safety of pembrolizumab (pembro) monotherapy in patients with previously treated advanced gastric cancer [abstract]. Presented at: 2017 American Society of Clinical Oncology (ASCO) Annual Meeting; 2017 Jun 2-6; Chicago, IL. J Clin Oncol. 2017;35(15 suppl). Abstract no. 4003.

[71] KEYTRUDA (pembrolizumab) Investigator's Brochure, Edition Number 17, 26-JUL-2019.

[72] Hammond ME, Hayes DF, Dowsett M, Allred DC, Hagerty KL, Badve S, et al. American Society of Clinical Oncology/College Of American Pathologists guideline recommendations for immunohistochemical testing of estrogen and progesterone receptors in breast cancer. J Clin Oncol. 2010 Jun 1;28(16):2784-95.

[73] Ji Y, Li Y, Li B, Bekele N. Dose-finding in phase I clinical trials based on toxicity probability intervals. Clin Trials 2007;4:235-44.

[74] Ji Y, Wang S-J. Modified toxicity probability interval design: a safer and more reliable method than the 3 + 3 design for practical phase I trials. J Clin Oncol 2013;31:1-12.

[75] Smith TJ, Khatcheressian J, Lyman GH, Ozer H, Armitage JO, Balducci L, et al. 2006 update of recommendations for the use of white blood cell growth factors: An evidence-based clinical practice guideline. J Clin Oncol 2006;24(19):3187-205.

[76] Miettinen O, Nurminen M. Comparative analysis of two rates. Stat Med 1985;4:213-26.

12.0 APPENDICES

12.1 Code of Conduct for Clinical Trials

Merck Sharp & Dohme LLC, Rahway, NJ, USA (MSD)
Code of Conduct for Interventional Clinical Trials

I. Introduction

A. Purpose

MSD, through its subsidiaries, conducts clinical trials worldwide to evaluate the safety and effectiveness of our products. As such, we are committed to designing, implementing, conducting, analyzing, and reporting these trials in compliance with the highest ethical and scientific standards. Protection of participants in clinical trials is the overriding concern in the design and conduct of clinical trials. In all cases, MSD clinical trials will be conducted in compliance with local and/or national regulations (including all applicable data protection laws and regulations), and International Council for Harmonisation Good Clinical Practice (ICH-GCP), and also in accordance with the ethical principles that have their origin in the Declaration of Helsinki.

B. Scope

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

II. Scientific Issues

A. Trial Conduct

1. Trial Design

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

The design (i.e., participant population, duration, statistical power) must be adequate to address the specific purpose of the trial and shall respect the data protection rights of all participants, trial site staff and, where applicable, third parties. All trial protocols are and will be assessed for the need and capability to enroll underrepresented groups. Participants must meet protocol entry criteria to be enrolled in the trial.

2. Site Selection

MSD's clinical trials are conducted globally in many different countries and in diverse populations, including people of varying age, race, ethnicity, gender, and accounting for other potential disease related factors. MSD selects investigative sites based on medical expertise, access to appropriate participants, adequacy of facilities and staff, previous performance in clinical trials, as well as budgetary considerations. Prior to trial initiation, sites are evaluated by MSD personnel (or individuals acting on behalf of MSD) to assess the ability to successfully conduct the trial.

Where appropriate, and in accordance with regulatory authority guidance, MSD will make concerted efforts to raise awareness of clinical trial opportunities in various communities. MSD will seek to engage underrepresented groups and those disproportionately impacted by the disease under study. MSD will support clinical trial investigators to enroll underrepresented groups and expand access to those who will ultimately use the products under investigation.

3. Site Monitoring/Scientific Integrity

Investigative trial sites are monitored to assess compliance with the trial protocol and Good Clinical Practice (GCP). MSD reviews clinical data for accuracy, completeness, and consistency. Data are verified versus source documentation according to standard operating procedures. Per MSD policies and procedures, if potential fraud, scientific/research misconduct, privacy incidents/breaches or Clinical Trial-related Significant Quality Issues are reported, such matters are investigated. When necessary, appropriate corrective and/or preventative actions are defined and regulatory authorities and/or ethics review committees are notified.

B. Publication and Authorship

Regardless of trial outcome, MSD commits to publish the primary and secondary results of its registered trials of marketed products in which treatment is assigned, according to the pre-specified plans for data analysis. To the extent scientifically appropriate, MSD seeks to publish the results of other analyses it conducts that are important to patients, physicians, and payers. 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 such as multiplicity.

MSD's policy on authorship is consistent with the recommendations published by the International Committee of Medical Journal Editors (ICMJE). In summary, authorship should reflect significant contribution to the design and conduct of the trial, performance or interpretation of the analysis, and/or writing of the manuscript. All named authors must be able to defend the trial results and conclusions. MSD funding of a trial will be acknowledged in publications.

III. Participant Protection

A. Regulatory Authority and Ethics Committee Review (Institutional Review Board [IRB]/Independent Ethics Committee [IEC])

All protocols and protocol amendments will be submitted by MSD for regulatory authority acceptance/authorization prior to implementation of the trial or amendment, in compliance with local and/or national regulations.

The protocol, protocol amendment(s), informed consent form, investigator's brochure, and other relevant trial documents must be reviewed and approved by an IRB/IEC before being implemented at each site, in compliance with local and/or national regulations. Changes to the protocol that are required urgently to eliminate an immediate hazard and to protect participant safety may be enacted in anticipation of ethics committee approval. MSD will inform regulatory authorities of such new measures to protect participant safety, in compliance with local and/or national regulations.

B. Safety

The guiding principle in decision-making in clinical trials is that participant welfare is of primary importance. Potential participants 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.

All participation in MSD clinical trials is voluntary. Participants enter the trial only after informed consent is obtained. Participants may withdraw from an MSD trial at any time, without any influence on their access to, or receipt of, medical care that may otherwise be available to them.

C. Confidentiality

MSD is committed to safeguarding participant confidentiality, to the greatest extent possible, as well as all applicable data protection rights. Unless required by law, only the investigator, Sponsor (or individuals acting on behalf of MSD), ethics committee, and/or regulatory authorities will have access to confidential medical records that might identify the participant by name.

D. Genomic Research

Genomic research will only be conducted in accordance with a protocol and informed consent authorized by an ethics committee.

IV. Financial Considerations

A. Payments to Investigators

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

MSD does not pay for participant referrals. However, MSD may compensate referring physicians for time spent on chart review and medical evaluation to identify potentially eligible participants.

B. Clinical Research Funding

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

C. Funding for Travel and Other Requests

Funding of travel by investigators and support staff (e.g., to scientific meetings, investigator meetings, etc.) will be consistent with local guidelines and practices.

V. Investigator Commitment

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

12.2 Collection and Management of Specimens for Future Biomedical Research

1. Definitions

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

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

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

d. DNA: Deoxyribonucleic acid.

e. RNA: Ribonucleic acid.

2. Scope of Future Biomedical Research

The specimens collected in this trial as outlined in Section 7.1.3.6 – Future Biomedical Research Sample Collection7.1.3.6 – Future Biomedical Research Sample Collection will be used to study various causes for how subjects may respond to a drug/vaccine. Future biomedical research specimen(s) will be stored to provide a resource for future trials conducted by the Sponsor focused on the study of biomarkers responsible for how a drug/vaccine enters and is removed by the body, how a drug/vaccine works, other pathways a drug/vaccine may interact with, or other aspects of disease. The specimen(s) may be used for future assay development and/or drug/vaccine development.

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

3. Summary of Procedures for Future Biomedical Research

a. Subjects for Enrollment

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

b. Informed Consent

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

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

c. eCRF Documentation for Future Biomedical Research Specimens

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

d. Future Biomedical Research Specimen Collections

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

4. Confidential Subject Information for Future Biomedical Research

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

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

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

5. Biorepository Specimen Usage

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

6. Withdrawal From Future Biomedical Research

Subjects may withdraw their consent for Future Biomedical Research and have their specimens and all derivatives destroyed. Subjects may withdraw consent at any time by contacting the principal investigator for the main trial. If medical records for the main trial are still available, the investigator will contact the Sponsor using the designated

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

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

7. Retention of Specimens

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

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

8. Data Security

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

9. Reporting of Future Biomedical Research Data to Subjects

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

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

through appropriate mechanisms (e.g., scientific publications and/or presentations). Subjects will not be identified by name in any published reports about this study or in any other scientific publication or presentation.

10. Future Biomedical Research Study Population

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

11. Risks Versus Benefits of Future Biomedical Research

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

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

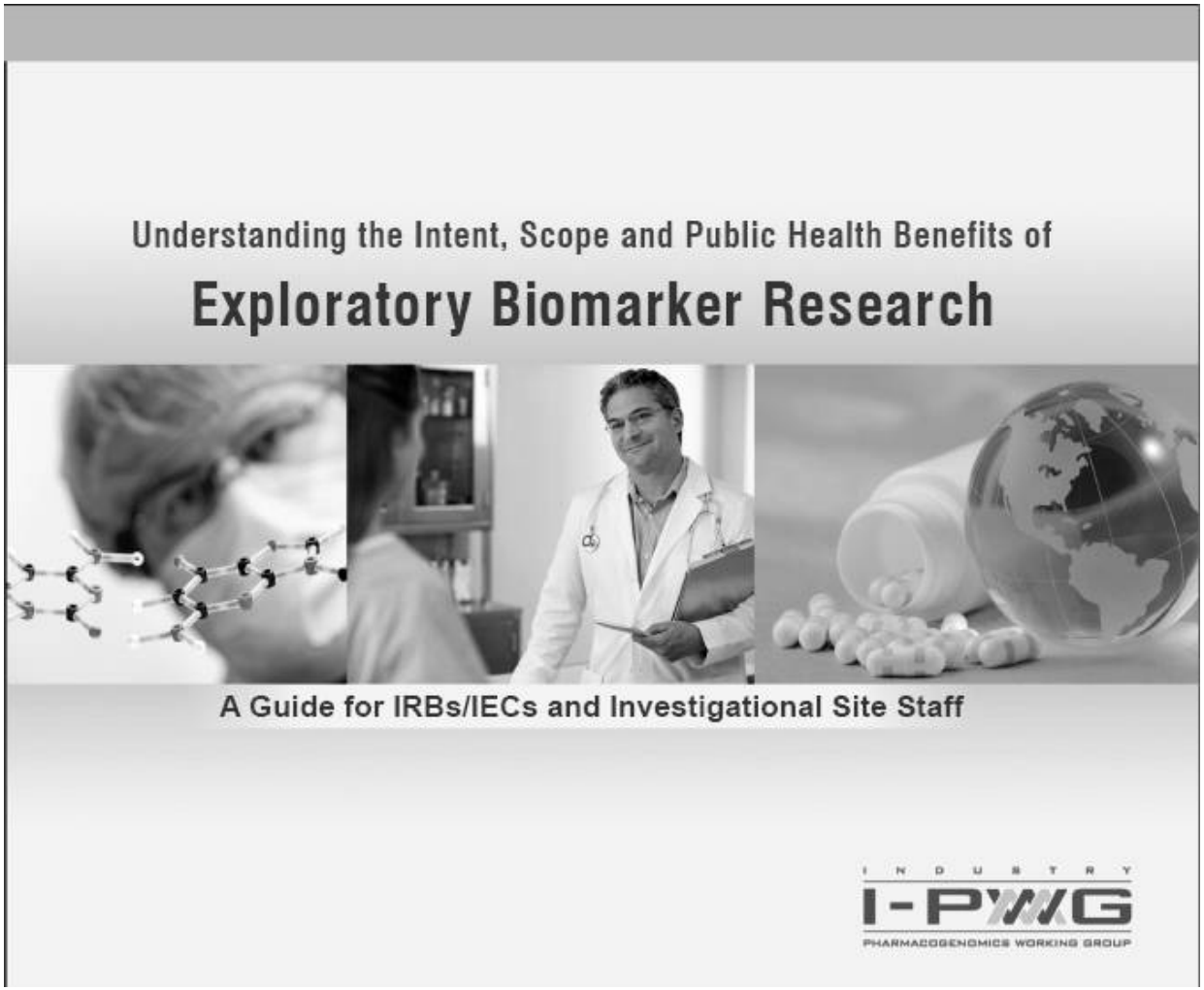
12. Questions

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

13. References

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

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



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

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

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

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

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

2. Why is Biomarker Research Important?

Importance to Patients and Public Health

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

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

Importance to Drug Development

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

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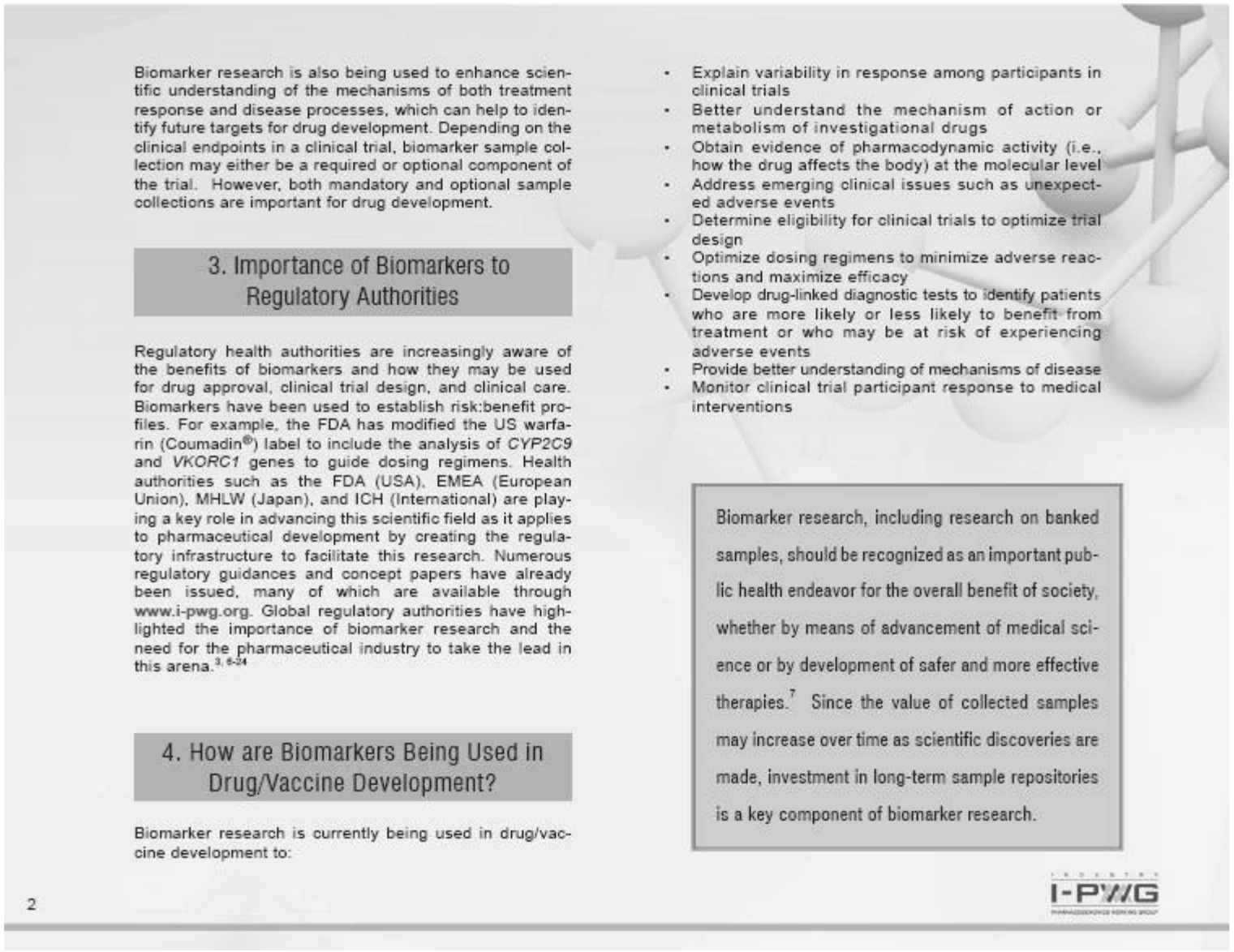
Biomarker research is also being used to enhance scientific understanding of the mechanisms of both treatment response and disease processes, which can help to identify future targets for drug development. Depending on the clinical endpoints in a clinical trial, biomarker sample collection may either be a required or optional component of the trial. However, both mandatory and optional sample collections are important for drug development.
3. Importance of Biomarkers to Regulatory Authorities
Regulatory health authorities are increasingly aware of the benefits of biomarkers and how they may be used for drug approval, clinical trial design, and clinical care. Biomarkers have been used to establish risk:benefit profiles. For example, the FDA has modified the US warfarin (Coumadin®) label to include the analysis of CYP2C9 and VKORC1 genes to guide dosing regimens. Health authorities such as the FDA (USA), EMEA (European Union), MHLW (Japan), and ICH (International) are playing a key role in advancing this scientific field as it applies to pharmaceutical development by creating the regulatory infrastructure to facilitate this research. Numerous regulatory guidances and concept papers have already been issued, many of which are available through www.i-pwg.org. Global regulatory authorities have highlighted the importance of biomarker research and the need for the pharmaceutical industry to take the lead in this arena.[3, 6-24]
4. How are Biomarkers Being Used in Drug/Vaccine Development?
Biomarker research is currently being used in drug/vaccine development to:
• Explain variability in response among participants in clinical trials
• Better understand the mechanism of action or metabolism of investigational drugs
• Obtain evidence of pharmacodynamic activity (i.e., how the drug affects the body) at the molecular level
• Address emerging clinical issues such as unexpected adverse events
• Determine eligibility for clinical trials to optimize trial design
• Optimize dosing regimens to minimize adverse reactions and maximize efficacy
• Develop drug-linked diagnostic tests to identify patients who are more likely or less likely to benefit from treatment or who may be at risk of experiencing adverse events
• Provide better understanding of mechanisms of disease
• Monitor clinical trial participant response to medical interventions
Biomarker research, including research on banked samples, should be recognized as an important public health endeavor for the overall benefit of society, whether by means of advancement of medical science or by development of safer and more effective therapies.[7] Since the value of collected samples may increase over time as scientific discoveries are made, investment in long-term sample repositories is a key component of biomarker research.
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5. Biomarkers are Already a Reality in Health Care

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

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

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

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

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

6. Biomarker Samples from Clinical Trials: An Invaluable Resource

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

7. Informed Consent for Collection & Banking of Biomarker Samples

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

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and regulations for legally-appropriate informed consent vary on national, state, and local levels, but are generally based on internationally recognized pillars of ethical conduct for research on human subjects.[26-31]

Optional vs. Required Subject Participation

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

Consent for Future Research Use

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

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

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

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

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

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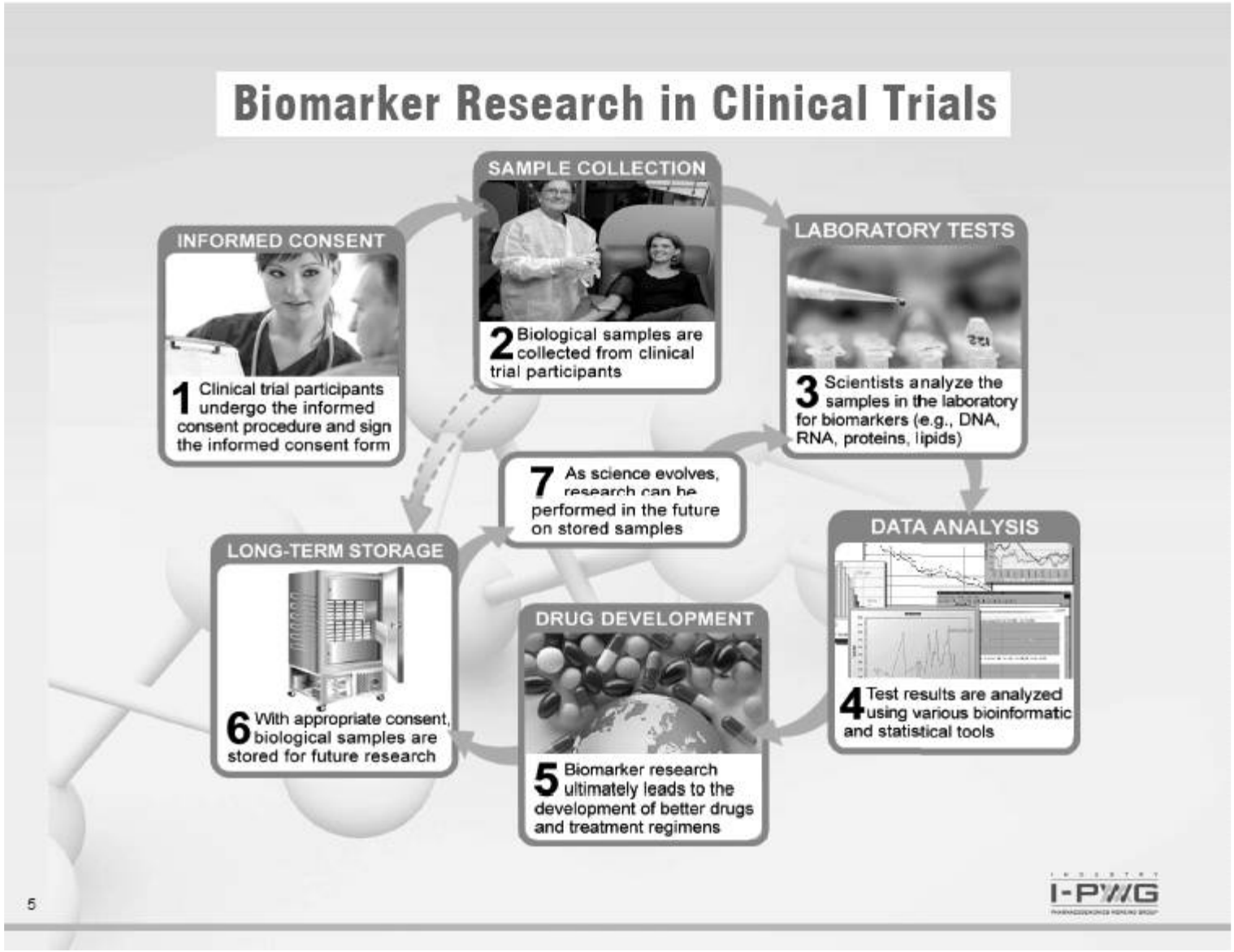
Biomarker Research in Clinical Trials
SAMPLE COLLECTION
2 Biological samples are collected from clinical trial participants
INFORMED CONSENT
1 Clinical trial participants undergo the informed consent procedure and sign the informed consent form
LABORATORY TESTS
3 Scientists analyze the samples in the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

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

9. Return of Research Results to Study Participants

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

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

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

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

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

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

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

10. Benefits and Risks Associated with Biomarker Research

Benefits

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

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

Risks

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

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

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

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

11. Privacy, Confidentiality, and Patient Rights

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

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

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

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

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

12.Where to Get More Information?

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

13. What is I-PWG?

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

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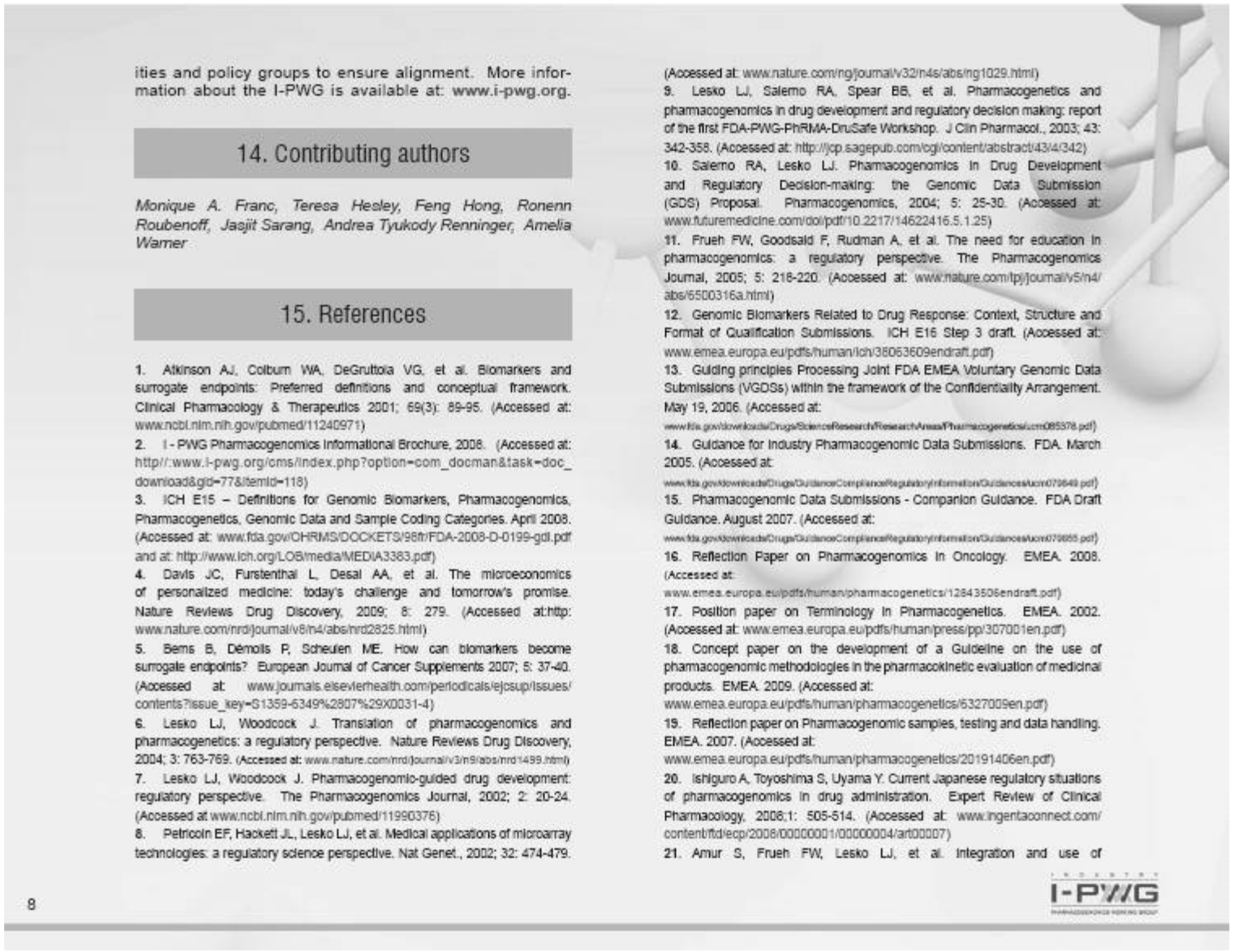

ities and policy groups to ensure alignment. More information about the I-PWG is available at: www.i-pwg.org.

14. Contributing authors

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15. References

1. Atkinson AJ, Colburn WA, DeGruttola VG, et al. Biomarkers and surrogate endpoints: Preferred definitions and conceptual framework. Clinical Pharmacology & Therapeutics 2001; 69(3): 89-95. (Accessed at: www.ncbi.nlm.nih.gov/pubmed/11240971)
2. I - PWG Pharmacogenomics Informational Brochure, 2008. (Accessed at: http//:www.i-pwg.org/cms/index.php?option=com_docman&task=doc_download&gid=77&Itemid=118)
3. ICH E15 – Definitions for Genomic Biomarkers, Pharmacogenomics, Pharmacogenetics, Genomic Data and Sample Coding Categories. April 2008. (Accessed at: www.fda.gov/OHRMS/DOCKETS/98fr/FDA-2008-D-0199-gdl.pdf and at: http://www.ich.org/LOB/media/MEDIA3383.pdf)
4. Davis JC, Furstenthal L, Desai AA, et al. The microeconomics of personalized medicine: today's challenge and tomorrow's promise. Nature Reviews Drug Discovery, 2009; 8: 279. (Accessed at:http: www.nature.com/nrd/journal/v8/n4/abs/nrd2825.html)
5. Bems B, Démolis P, Scheulen ME. How can biomarkers become surrogate endpoints? European Journal of Cancer Supplements 2007; 5: 37-40. (Accessed at: www.journals.elsevierhealth.com/periodicals/ejcsup/issues/contents?issue_key=S1359-6349%2807%29X0031-4)
6. Lesko LJ, Woodcock J. Translation of pharmacogenomics and pharmacogenetics: a regulatory perspective. Nature Reviews Drug Discovery, 2004; 3: 763-769. (Accessed at: www.nature.com/nrd/journal/v3/n9/abs/nrd1499.html)
7. Lesko LJ, Woodcock J. Pharmacogenomic-guided drug development: regulatory perspective. The Pharmacogenomics Journal, 2002; 2: 20-24. (Accessed at www.ncbi.nlm.nih.gov/pubmed/11990376)
8. Petricoin EF, Hackett JL, Lesko LJ, et al. Medical applications of microarray technologies: a regulatory science perspective. Nat Genet., 2002; 32: 474-479. (Accessed at: www.nature.com/ng/journal/v32/n4s/abs/ng1029.html)
9. Lesko LJ, Salerno RA, Spear BB, et al. Pharmacogenetics and pharmacogenomics in drug development and regulatory decision making: report of the first FDA-PWG-PhRMA-DruSafe Workshop. J Clin Pharmacol., 2003; 43: 342-358. (Accessed at: http://jcp.sagepub.com/cgi/content/abstract/43/4/342)
10. Salerno RA, Lesko LJ. Pharmacogenomics in Drug Development and Regulatory Decision-making: the Genomic Data Submission (GDS) Proposal. Pharmacogenomics, 2004; 5: 25-30. (Accessed at: www.futuremedicine.com/doi/pdf/10.2217/14622416.5.1.25)
11. Frueh FW, Goodsaid F, Rudman A, et al. The need for education in pharmacogenomics: a regulatory perspective. The Pharmacogenomics Journal, 2005; 5: 216-220. (Accessed at: www.nature.com/tpj/journal/v5/n4/abs/6500316a.html)
12. Genomic Biomarkers Related to Drug Response: Context, Structure and Format of Qualification Submissions. ICH E16 Step 3 draft. (Accessed at: www.emea.europa.eu/pdfs/human/ich/38063609endraft.pdf)
13. Guiding principles Processing Joint FDA EMEA Voluntary Genomic Data Submissions (VGDSs) within the framework of the Confidentiality Arrangement. May 19, 2006. (Accessed at: www.fda.gov/downloads/Drugs/ScienceResearch/ResearchAreas/Pharmacogenetics/ucm085378.pdf)
14. Guidance for Industry Pharmacogenomic Data Submissions. FDA. March 2005. (Accessed at: www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm079849.pdf)
15. Pharmacogenomic Data Submissions - Companion Guidance. FDA Draft Guidance. August 2007. (Accessed at: www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm079865.pdf)
16. Reflection Paper on Pharmacogenomics in Oncology. EMEA. 2008. (Accessed at: www.emea.europa.eu/pdfs/human/pharmacogenetics/12843506endraft.pdf)
17. Position paper on Terminology in Pharmacogenetics. EMEA. 2002. (Accessed at: www.emea.europa.eu/pdfs/human/press/pp/30700en.pdf)
18. Concept paper on the development of a Guideline on the use of pharmacogenomic methodologies in the pharmacokinetic evaluation of medicinal products. EMEA. 2009. (Accessed at: www.emea.europa.eu/pdfs/human/pharmacogenetics/6327009en.pdf)
19. Reflection paper on Pharmacogenomic samples, testing and data handling. EMEA. 2007. (Accessed at: www.emea.europa.eu/pdfs/human/pharmacogenetics/2019406en.pdf)
20. Ishiguro A, Toyoshima S, Uyama Y. Current Japanese regulatory situations of pharmacogenomics in drug administration. Expert Review of Clinical Pharmacology, 2008;1: 505-514. (Accessed at: www.ingentaconnect.com/content/bfd/ecp/2008/00000001/00000004/art00007)
21. Amur S, Frueh FW, Lesko LJ, et al. Integration and use of

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biomarkers in drug development, regulation and clinical practice: A US regulatory practice. Biomarkers Med. 2008; 2, 305-311. (Accessed at: www.ingentaconnect.com/content/fm/bmm/2008/00000002/00000003/art00010?crawler=true)

22. Mendrick DL, Brazell C, Mansfield EA, et al. Pharmacogenomics and regulatory decision making: an international perspective. The Pharmacogenomics Journal. 2006; 6(3), 154-157. (Accessed at: www.nature.com/tpj/journal/v6/n3/abs/6500364a.html)

23. Pendergast MK. Regulatory agency consideration of pharmacogenomics. Exp Biol Med (Maywood). 2008; 233:1498-503. (Accessed at: www.ebmonline.org/cgi/content/abstract/233/12/1496)

24. Goodsaid F, Frueh F. Process map proposal for the validation of genomic biomarkers. Pharmacogenomics., 2006; 7(5):773-82 (Accessed at: www.futuremedicine.com/doi/abs/10.2217/14622416.7.5.773)

25. FDA Table of Valid Genomic Biomarkers in the Context of Approved Drug Labels. (Accessed at: www.fda.gov/Drugs/ScienceResearch/ResearchAreas/Pharmacogenetics/ucm083378.htm)

26. International Serious Adverse Event Consortium. (Accessed at: www.saeconsortium.org)

27. Predictive Safety Testing Consortium. (Accessed at: www.c-path.org/pstc.cfm)

28. Nuremberg code. (Accessed at: http://ohsr.od.nih.gov/guidelines/nuremberg.html)

29. Declaration of Helsinki. (Accessed at: http://ohsr.od.nih.gov/guidelines/helsinki.html)

30. Belmont report. (Accessed at: http://ohsr.od.nih.gov/guidelines/belmont.html)

31. ICH E6(R1) – Guideline for Good Clinical Practice. June 1996. (Accessed at: www.ich.org/LOB/media/MEDIA482.pdf)

32. Barnes M, Heffernan K. The "Future Uses" Dilemma: Secondary Uses of Data and Materials by Researchers for Commercial Research Sponsors. Medical Research Law & Policy, 2004; 3: 440-450.

33. Eriksson S, Helgesson G. Potential harms, anonymization, and the right to withdraw consent to biobank research. Eur J Hum Genet., 2005; 13:1071-1076. (Accessed at: www.nature.com/ejhg/journal/v13/n9/pdf/5201458a.pdf)

34. Renegar G, Webster CJ, Stuerzebecher S, et al. Returning genetic research results to individuals: points-to-consider. Bioethics 2006; 20: 24-36. (Accessed at: http://www3.interscience.wiley.com/cgi-bin/fulltext/118562753/PDFSTART)

35. Article 29 Data Protection Working Party. (Accessed at: www.ec.europa.eu/justice_home/fsj/privacy/workinggroup/index_en.htm)

36. Human Tissue Act 2004 (UK). (Accessed at: www.opsi.gov.uk/acts/acts2004/en/ukpgaen_20040030_en_1)

37. Genetic Information Nondiscrimination Act. (Accessed at: http://webgate.access.gpo.gov/cgi-bin/getdoc.cgi?dbname=110_cong_public_laws&docid=f:pub1233.110.pdf)

38. Guidance for Sponsors, Clinical Investigators, and IRBs Data Retention When Subjects Withdraw from FDA-Regulated Clinical Trials. FDA October 2008 www.fda.gov/OHRMS/DOCKETS/98fr/FDA-2008-D-0576-gdl.pdf

39. Anderson C, Gomez-Mancilla B, Spear BB, Barnes DM, Cheeseman K, Shaw P, Friedman J, McCarthy A, Brazell C, Ray SC, McHale D, Hashimoto L, Sandbrink R, Watson ML, Salerno RA, on behalf of The Pharmacogenetics Working Group. Elements of Informed Consent for Pharmacogenetic Research; Perspective of the Pharmacogenetics Working Group. Pharmacogenomics Journal 2002;2:284-92. (Accessed at: www.nature.com/tpj/journal/v2/n5/abs/6500131a.html)

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12.4 ECOG Performance Status

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

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

12.5 Cockcroft-Gault Formula

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

12.6 Abbreviations

Abbreviation/Term	Definition
ADA	Anti-drug antibody
AE	Adverse event
ALK	Anaplastic lymphoma kinase
ALT	Alanine aminotransferase
ANC	Absolute neutrophil count
aPTT	Activated partial thromboplastin time
ASaT	All Subjects as Treated
ASCO	American Society of Clinical Oncology
AST	Aspartate aminotransferase
AUC	Area under the curve
BCG	Bacillus Calmette-Guérin
β-hCG	β-human chorionic gonadotropin
BRCA1/2	Breast cancer susceptibility gene 1/2
BUN	Blood urea nitrogen
CA 125	Cancer antigen 125
CD3ζ	CD3 zeta
CE	Conformité Européene
CEA	Carcinoembryonic antigen
CFR	Code of Federal Regulations
CI	Coordinating investigator
C_{max}	Maximum concentration
CNS	Central nervous system
CO_2	Carbon dioxide
CPS	Combined positive score
CR	Complete response
CRC	Colorectal cancer
CrCl	Creatinine clearance
CRF	Case report form
CRU	Clinical research unit
CSF	Colony-stimulating factor
CSR	Clinical Study Report
CT	Computed tomography
CTCAE	Common Toxicity Criteria for Adverse Events
CTLA-4	Cytotoxic T-lymphocyte-associated antigen-4
C_{trough}	Trough concentration in blood
DCR	Disease control rate
DL	Dose level
DLT	Dose-limiting toxicity
DNA	Deoxyribonucleic acid
DOR	Duration of response
ECG	Electrocardiogram
ECI	Event of clinical interest

Abbreviation/Term	Definition
ECOG	Eastern Cooperative Oncology Group
EDC	Electronic data capture
EGFR	Epidermal growth factor receptor
ER	Estrogen receptor
ERC	Ethics Review Committee
ES-SCLC	Extensive-stage small cell lung cancer
FAS	Full analysis set
FBR	Future biomedical research
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act
FDAMA	Food and Drug Administration Modernization Act
FSH	Follicle stimulating hormone
GCP	Good Clinical Practice
GEP	Gene expression profile
GFR	Glomerular filtration rate
GGT	Gamma glutamyl transferase
GI	Gastrointestinal
HBsAg	Hepatitis B surface antigen
HCV	Hepatitis C virus
HER2	Human epidermal growth factor receptor 2
HIV	Human immunodeficiency virus
HPV	Human papillomavirus
IB	Investigator's Brochure
ICF	Informed consent form
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IFNγ	Interferon gamma
Ig	Immunoglobulin
IgV	Immunoglobulin variable
IHC	Immunohistochemistry
IL	Interleukin
ILD	Interstitial lung disease
IM	Intramuscular
INR	International normalized ratio
irAE	Immune-related adverse event
IRB	Institutional Review Board
irRECIST	Immune-related Response Evaluation Criteria in Solid Tumors
ITIM	Immunoreceptor tyrosine-based inhibition motif
ITT	Immunoglobulin tail tyrosine
IUD	Intrauterine device
IV	Intravenous
IVD	In vitro diagnostic
IVRS	Interactive Voice Response System
IWRS	Integrated Web Response System

Abbreviation/Term	Definition
Km	Michaelis-Menten constant
LDH	Lactate dehydrogenase
LS-SCLC	Limited-stage small cell lung cancer
mAb	Monoclonal antibody
MASCC	Multinational Association of Supportive Care in Cancer
MCP-1	Monocyte chemoattractant protein 1
MRI	Magnetic resonance imaging
mRNA	Messenger ribonucleic acid
MSI	Microsatellite instability
MTD	Maximum tolerated dose
mTPI	Modified toxicity probability interval
NCI	National Cancer Institute
NK cell	Natural killer cell
NKT cell	Natural killer T cell
NOAEL	No observed adverse effect level
NSAID	Non-steroidal anti-inflammatory drug
NSCLC	Non-small cell lung cancer
ORR	Overall response rate
OS	Overall survival
OTC	Over-the-counter
PBMC	Peripheral blood mononuclear cell
PCI	Prophylactic cranial irradiation
PCR	Polymerase chain reaction
PD	Pharmacodynamic(s) or Progressive disease
PD-1	Programmed death 1
PD-L1	Programmed cell death ligand 1
PD-L2	Programmed cell death ligand 2
PET	Positron emission tomography
PFS	Progression-free survival
PI	Probability interval
PIN	Personal identification number
PK	Pharmacokinetic(s)
PKCθ	Protein kinase C-theta
PARP	Poly(ADP-ribose) polymerase
PP	Per-protocol
PR	Partial response or Progesterone receptor
PT	Prothrombin time
PTT	Partial thromboplastin time
PVR	Poliovirus receptor
PVRL	Poliovirus receptor-related 2
RA	Receptor availability
RBC	Red blood cell
RCC	Renal cell carcinoma
RECIST	Response Evaluation Criteria in Solid Tumors

Abbreviation/Term	Definition
RNA	Ribonucleic acid
RPTD	Recommended Phase 2 dose
SAC	Scientific Advisory Committee
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SCLC	Small cell lung cancer
SD	Stable disease
SGOT	Serum glutamic oxaloacetic transaminase
SGPT	Serum glutamic pyruvic transaminase
SNP	Single nucleotide polymorphism
SOC	Standard of care
SOP	Standard Operating Procedure
sSAP	Supplementary Statistical Analysis Plan
$t_{1/2}$	Half-life
TCR	T-cell receptor
T_{eff}	Effector T cell
TIGIT	T-cell immunoglobulin and immunoreceptor tyrosine-based inhibitory motif
TIL	Tumor infiltrating lymphocyte
Tim-3	T-cell immunoglobulin and mucin domain containing-3
T_{max}	Time to maximum concentration
TNBC	Triple-negative breast cancer
TNFα	Tumor necrosis factor alpha
TPI	Toxicity probability interval
TPS	Tumor Proportion Score
T_{reg}	Regulatory T cell
TSH	Thyroid stimulating hormone
ULN	Upper limit of normal
US	United States
VEGF	Vascular endothelial growth factor
WBC	White blood cell
ZAP70	Zeta-chain-associated protein kinase

12.7 MASCC 2016 Guidelines

DEXAMETHASONE		Dose and Schedule
High Risk	- Acute Emesis	20 mg once (12 mg when used with (fos)aprepitant or netupitant)**
	- Delayed Emesis	8 mg bid for 3 - 4 days (8 mg once daily when used with (fos)aprepitant or netupitant)
Moderate Risk	- Acute Emesis	8 mg once
	- Delayed Emesis	8 mg daily for 2 - 3 days (many panelists give the dose as 4 mg bid)
Low Risk	- Acute Emesis	4 - 8 mg once

* While corticosteroids other than dexamethasone are effective antiemetics, the dose and schedule of dexamethasone coupled with its wide availability in various dose forms established it as the guideline agent of choice.

** The 12 mg dose of dexamethasone is the only one tested with (fos)aprepitant/netupitant in large randomized trials.

Rolia F, Molassiotis A, Herrstedt J, et al. 2016 MASCC and ESMO guideline update for the prevention of chemotherapy- and radiotherapy-induced nausea and vomiting and of nausea and vomiting in advanced cancer patients. Ann Oncol (2016) 27 (suppl_5): v119-v133, 2016.

http://www.mascc.org/antiemetic-guidelines

Investigators may use local equivalent or more current guidelines, if available.

12.8 Country-specific Requirements

12.8.1 Japan-specific Requirements

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

Section 5.2.1.4 – Definition of Dose-limiting Toxicity

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

- Thrombocytopenia if associated with bleeding that requires a platelet transfusion.

Section 5.2.3.1 – Dose Modification and Toxicity Management for Adverse Events Associated with Pembrolizumab and MK-7684/MK-7684A

In addition to the MK-7684 dose modification and treatment discontinuation guidelines listed in Table 6, the investigator will use the guidelines in Table 13 for events of pneumonitis and/or interstitial lung disease deemed related to MK-7684 for subjects in Japan:

Table 13 Japan-specific MK-7684 Dose Modification and Treatment Discontinuation Guidelines for Treatment-related Adverse Events

Toxicity	Interrupt Treatment	Criteria for Restarting Treatment	Dose/Schedule for Restarting Treatment	Criteria for Discontinuation after Consultation with Sponsor
Pneumonitis and/or Interstitial Lung Disease[1, 2]:				
• Grade 2	Yes	MK-7684 can be resumed after AE has improved to Grade 1 or less and corticosteroid has been tapered. MK-7684 should be permanently discontinued if AE does not resolve within 12 weeks of last dose or corticosteroids cannot be reduced to ≤10 mg prednisone or equivalent per day within 12 weeks.		
• Grade 3 or 4, or recurrent Grade 2	Permanently discontinue	N/A	N/A	N/A

1. Administer corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper.
2. Monitor participants for signs and symptoms of pneumonitis/interstitial lung disease.
Evaluate participants with suspected pneumonitis/interstitial lung disease with radiographic imaging and initiate corticosteroid treatment. Add prophylactic antibiotics for opportunistic infections.

Arm 4 (treatment with co-formulated MK-7684A product) is not open to sites in Japan.

In Table 6, dose interruption/discontinuation and toxicity management guidelines listed for pneumonitis will also apply to interstitial lung disease associated with pembrolizumab.

Section 5.5.2 – Prohibited Concomitant Medications

In addition to all prohibited concomitant medications listed, the following is a prohibited concomitant medication for subjects in Japan except for subjects with ES-SCLC enrolled as part of Amendment 12:

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

Section 5.7.4 - Use in Nursing Women

In addition to the information given in Section 5.7.4, the following sentence is added for subjects in Japan:

- Subjects who have discontinued breastfeeding but wish to restart are also ineligible.

Section 6.4 - Trial Flow Chart for Subjects with ES-SCLC Enrolled as Part of Amendment 12

- To assist with early diagnosis of pneumonitis/interstitial lung disease (ILD) in study participants, the following items, such as SpO_2, CRP, KL-6, and SP-D, will be measured in this study. These items should be measured as follows:
  - SpO2 at the time of vital sign assessment.
  - CRP, KL-6, and SP-D at screening[1], prior to dosing on Day 1 of every cycle, at the End of Treatment visit and at the Post-Treatment Safety Follow-Up visit (30 days after the last dose).

    [1]Should be measured at the time of clinical laboratory tests (such as hematology/chemistry).

If pneumonitis/ILD occurs, regardless of causality with study treatment, an independent ILD evaluation committee will conduct adjudication of cases of the pneumonitis/ILD. For this purpose, relevant data, such as chest imaging (from baseline to the recovery of pneumonitis/ILD) will be submitted to MSD K.K.

Section 7.1.2 –Clinical Procedures/Assessments

For subjects in Japan only, pulse oximetry will be performed using local standard procedures by the investigator or qualified designee at the timepoints outlined in the Trial Flow Chart (Section 6.0).

Clinical Study Conduct System

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

1. Sponsor

1.1 Name and Address of Sponsor

1.2 Sponsor’s Representative

1.3 Medical Expert

1.4 Field Monitor (CRA) Representative

2. Contract Research Organization

2.1 External Monitoring Agency

2.2 Patient Registration Center

2.3 Emergency Unblinding Call Center

2.4 MSD Emergency Center

3. Central Testing Facilities
4. Investigators
5. Japan Enrollment Policy

13.0 SIGNATURES

13.1 Sponsor's Representative

TYPED NAME	
TITLE	
SIGNATURE	
DATE SIGNED	

13.2 Investigator

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

TYPED NAME	
TITLE	
SIGNATURE	
DATE SIGNED	