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TITLE:

A Phase 1 Trial of MK-1248 as Monotherapy and in Combination with Pembrolizumab in Subjects with Advanced Solid Tumors.

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SUMMARY OF CHANGES

PRIMARY REASON FOR THIS AMENDMENT:

Section Number	Section Title	Description of Change (s)	Rationale
5.2.3	Guidelines for Dose Modification due to Adverse Events	Added guidelines for dose interruption/treatment discontinuation and toxicity management in the event of myocarditis and intolerable or persistent Grade 2 drug-related toxicities.	To align with the most current label and safety information for pembrolizumab.

ADDITIONAL CHANGE(S) FOR THIS AMENDMENT:

Section Number (s)	Section Title (s)	Description of Change (s)	Rationale
4.2.2.2	Rationale for Pembrolizumab Dose	Updated to align with most current template text.	To ensure the most current information is included.
5.2.3; 5.6	Guidelines for Dose Modification due to Adverse Events; Rescue Medications & Supportive Care	These sections were re-distributed to align with the most current template text.	To align with the most current template text.
6.0; 7.1.8.4	Trial Flow Chart; Survival Status	Added text to allow the Sponsor to collect survival data throughout the study.	To allow the Sponsor to collect survival data throughout the study to support ongoing analyses of survival data as appropriate.

Section Number (s)	Section Title (s)	Description of Change (s)	Rationale
7.1.4.1; 7.1.4.2	Blood Collection for MK-1248 and Pembrolizumab PK; Blood Collection for Anti-MK-1248 Antibodies and Anti-Pembrolizumab Antibodies (ADA)	Updated to allow storage of PK and ADA samples collected and to allow the Sponsor to reduce or discontinue sample collections as needed.	To clarify that samples collected for PK and ADA may be stored and to allow the Sponsor flexibility to reduce or discontinue sample collections as needed.

1.0 TRIAL SUMMARY

Abbreviated Title	Phase 1 Trial of MK-1248 as Monotherapy and in Combination with Pembrolizumab in Subjects with Advanced Solid Tumors
Trial Phase	Phase 1
Clinical Indication	Treatment of subjects with advanced solid tumors
Trial Type	Interventional
Type of control	None
Route of administration	Intravenous
Trial Blinding	Unblinded Open-label
Treatment Groups	Subjects will be allocated by non-random assignment to one of 2 treatment arms: Arm 1: MK-1248 as monotherapy Arm 2: MK-1248 in combination with pembrolizumab
Number of trial subjects	Approximately 96 subjects will be enrolled.
Estimated duration of trial	The sponsor estimates that the trial will require approximately 4 years from the time the first subject signs the informed consent until the last subject's last visit.
Duration of Participation	Each subject will participate in the trial from the time the subject signs the Informed Consent Form (ICF) through the final contact. After a screening phase of up to 28 days, each subject will be allocated by non-random assignment into one of two arms and receive treatment with MK-1248 alone or in combination with pembrolizumab. Study treatment in both arms will begin on Day 1 of each 3-week cycle. For subjects enrolled in Arm 1 and Arm 2, treatment with MK-1248 will end after 4 cycles; treatment with pembrolizumab in Arm 2 will continue for up to 24 months. Treatment in both arms will continue until disease progression, unacceptable adverse event(s), intercurrent illness that prevents further administration of treatment, Investigators decision to withdraw treatment, subject withdraws consent, pregnancy of the subject, noncompliance with study treatment or procedure requirements, subject completes treatment, or administrative reasons requiring cessation of treatment. After the end of treatment, each subject will be followed for 30 days for adverse event monitoring (serious adverse events will be collected for 90 days after the end of treatment, or 30 days after the end of treatment if the subject initiates new anticancer therapy, whichever is earlier).

Enrollment into this study has been prematurely discontinued due to program prioritization and not related to any safety concerns. The cut-off date for enrollment is 31-Mar-2017.

Subjects who are ongoing in the study after that date and who do not yet meet established protocol discontinuation criteria, as outlined in Section 5.8, will continue to attend study visits and be followed per protocol.

Subjects who are ongoing in the study after that date and who do not yet meet established treatment discontinuation criteria, as outlined in Section 5.8, may continue to receive study treatment per protocol, provided the investigator feels such treatment is in the best interest of the subject.

2.0 TRIAL DESIGN

2.1 Trial Design

This is a non-randomized, multi-site, 2-arm, open-label trial of MK-1248 monotherapy (Arm 1) and MK-1248 in combination with pembrolizumab (Arm 2) in subjects with a histologically or cytologically confirmed diagnosis of any type of solid tumor who have measurable disease.

This trial will use an adaptive design based on the pre-specified criteria of dose limiting toxicity (DLT). For Dose Escalation (Parts B and D) a 3+3 dose escalation design will be utilized (See Section 5.2.1.4). For Dose Confirmation (Parts C and E) the toxicity probability interval (TPI) design [1] will be utilized to refine the estimate of maximum tolerated dose (MTD).

In Arm 1, MK-1248 monotherapy, dose escalation will begin with 2-subject cohorts (Part A) starting at a MK-1248 dose of 0.12 mg and will proceed based on adverse events to a dose of 10.0 mg or until a DLT occurs. If a DLT occurs, an additional subject will be enrolled and the rules of 3+3 as described in Section 5.2.1.4 will apply. Starting at a 30.0 mg dose in Part B, the study will continue with a 3+3 design to identify a preliminary maximum tolerated dose (MTD). During 3+3 dose escalation in both arms, an initial cohort of 3 subjects will be enrolled to a dose level. If none of the 3 subjects experiences a DLT, escalation to the next dose will occur. If one of the 3 subjects experiences a DLT, another 3 subjects will be enrolled at this dose level. If 1 DLT is observed among the 6 subjects, the dose escalation will continue. If $\geq$2/3 or $\geq$2/6 subjects at a dose level develop DLTs, dose escalation will be terminated, and the study will proceed to the dose confirmation stage at the previous dose level. At least 2 days of observation will occur between each of the first 3 subjects at each dose level (for Part A this applies to the 2 subjects enrolled). In Part C, dose confirmation will refine the estimate of the tolerability of the MTD (or maximum administered dose), using a toxicity probability interval.

Treatment in Arm 2, (MK-1248 in combination with pembrolizumab) will begin once 2 subjects complete 1 cycle of $\geq$3 mg dose level in Part A, and will follow a 3+3 design to identify a preliminary MTD in Part D. The starting dose of MK-1248 will be 0.12 mg and the dose of 200 mg pembrolizumab will be used in Arm 2. During 3+3 dose escalation, at least 2 days of observation will occur between each of the first 3 subjects at each dose level. There will be a one week observation period between the first and second subject treated with the combination in the first cohort of Arm 2. Dose confirmation in Part E will refine the estimate of tolerability of the MTD using a toxicity probability interval.

Enrollment to both arms will occur in parallel with treatment allocation accomplished by non-random assignment to Arm 1 or Arm 2 using an interactive voice response system/integrated web response system (IVRS/IWRS). Doses of MK-1248 used in combination will be at least 1-2 dose levels behind the monotherapy dose, and would not exceed the MTD for monotherapy. However, once the MTD or RP2D (recommended Phase 2 dose) for the monotherapy arm is established, the dose of MK-1248 in combination may continue escalation up to that dose.

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

Adverse Events (AEs) will be evaluated according to criteria outlined in the National Cancer Institute's (NCI) Common Terminology Criteria for Adverse Events (CTCAE), version 4.0.

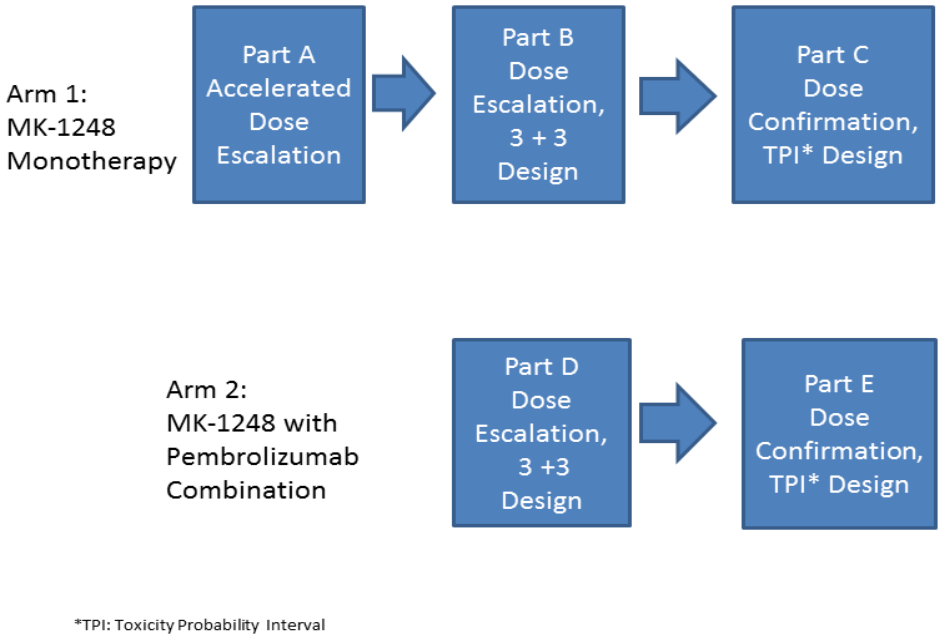
Specific procedures to be performed during the trial, as well as their prescribed times and associated visit windows, are outlined in the Trial Flow Chart - Section 6.0. Details of each procedure are provided in Section 7.0 – Trial Procedures.

Enrollment into this study has been prematurely discontinued due to program prioritization and not related to any safety concerns. The cut-off date for enrollment is 31-Mar-2017. Subjects who are ongoing in the study after that date and who do not yet meet established protocol discontinuation criteria, as outlined in Section 5.8, will continue to attend study visits and be followed per protocol. Subjects who are ongoing in the study after that date and who do not yet meet established treatment discontinuation criteria, as outlined in Section 5.8, may continue to receive study treatment per protocol, provided the investigator feels such treatment is in the best interest of the subject.

2.2 Trial Diagram

The trial design is depicted in Figure 1.

Note: Enrollment into this study has been prematurely discontinued due to program prioritization and not related to any safety concerns. The cut-off date for enrollment is 31-Mar-2017. Subjects who are ongoing in the study after that date and who do not yet meet established protocol discontinuation criteria, as outlined in Section 5.8, will continue to attend study visits and be followed per protocol. Subjects who are ongoing in the study after that date and who do not yet meet established treatment discontinuation criteria, as outlined in Section 5.8, may continue to receive study treatment per protocol, provided the investigator feels such treatment is in the best interest of the subject.



*TPI: Toxicity Probability Interval

In Arm 1, Part A, dose escalation will begin with 0.12 mg in cohorts of 2 subjects each, and will proceed based on safety events to a dose of 10.0 mg. During Part A, there will be at least 2 days observation between the first 2 subjects treated at each dose level. Starting at a 30.0 mg dose (or at a lower dose as described in Section 5.2.1.3) in Part B, the study will continue with a 3+3 design to identify a preliminary maximum tolerated dose (MTD). In Part C, dose confirmation will refine the estimate of the tolerability of the MTD (or maximum administered dose), using a toxicity probability interval.

Treatment in Arm 2, (MK-1248 in combination with pembrolizumab) will begin once 2 subjects complete 1 cycle of ≥3 mg dose level in Part A, and will follow a 3+3 design to identify a preliminary MTD in Part D. The starting dose of MK-1248 will be 0.12 mg and the dose of 200 mg pembrolizumab will be used in Arm 2. During 3+3 dose escalation in Part D, at least 2 days of observation will occur between each of the first 3 subjects at each dose level. There will be a one week observation period between the first and second subject treated with the combination in the first cohort of Arm 2. Doses of MK-1248 used in combination will be at least 1-2 dose levels behind the monotherapy dose, and would not exceed the MTD for monotherapy. However, once the MTD for the monotherapy arm is established, the dose of MK-1248 in combination may continue escalation up to that dose. Dose confirmation in Part E will refine the estimate of tolerability of the MTD using a toxicity probability interval.

Figure 1 Trial Design

3.0 OBJECTIVE(S) & HYPOTHESIS(ES)

In subjects with a histologically or cytologically confirmed diagnosis of any type of solid tumor having measurable disease:

3.1 Primary Objective(s)

1) **Objective:** To determine the safety and tolerability of MK-1248 monotherapy and to establish a maximum tolerated dose (MTD) or maximum administered dose (MAD)
2) **Objective:** To determine the safety and tolerability of MK-1248 monotherapy and to establish a maximum tolerated dose (MTD) or maximum administered dose (MAD) when given in combination with pembrolizumab

3.2 Secondary Objective(s)

1) **Objective**: To characterize the PK profile of MK-1248 alone and in combination with pembrolizumab
2) **Objective**: To characterize the PK profile of pembrolizumab following administration of MK-1248 and pembrolizumab in combination
3) **Objective**: To evaluate target engagement as measured by modulation in peripheral blood GITR receptor availability alone and in combination with pembrolizumab

3.3 Exploratory Objectives

1) **Objective:** To evaluate the antitumor activity of MK-1248 alone and in combination with pembrolizumab as determined by irRECIST as assessed by investigator review
2) **Objective**: To investigate the relationship between candidate efficacy biomarkers and anti-tumor activity of MK-1248 alone and in combination with pembrolizumab
    a. To evaluate the relationship between GITR expression levels in tumor samples and anti-tumor activity
    b. To investigate other biomarkers in circulating blood cells or in tumor tissue (e.g. tumor infiltrating lymphocytes, GITR expression, FOXP3 expression, PD-L1 expression, T-cell repertoire, ribonucleic acid signature profiles, pharmacogenetic variation) that may correlate with tumor responses
    c. To evaluate differences in tumor tissue characteristics in biopsies taken pre- and post-treatment versus baseline
3) **Objective**: To evaluate development of circulating anti-MK-1248 antibodies and anti-pembrolizumab antibodies, as appropriate, following administration of MK-1248 alone and in combination with pembrolizumab
4) **Objective**: To explore the relationship between genetic variation and response to the treatment(s) administered. Variation across the human genome will be analyzed for association with clinical data collected in this study

4.0 BACKGROUND & RATIONALE

4.1 Background

Detailed background information on MK-1248 and pembrolizumab (MK-3475) is available in the MK-1248 Investigator's Brochure (IB) and the Pembrolizumab IB.

4.1.1 Pharmaceutical and Therapeutic Background

4.1.1.1 MK-1248 Background

MK-1248 is a humanized IgG4 agonist monoclonal antibody (mAb) that targets Glucocorticoid-Induced Tumor necrosis factor Receptor -related protein (GITR). GITR is constitutively expressed at high levels on regulatory T-cells (T_{regs}) and at low levels on resting CD4+ and CD8+ T-cells, as well as NK cells and NK T-cells[2], [3]. Following T-cell activation, GITR expression is highly upregulated on CD4+ and CD8+ T-cells and NK cells, including tumor infiltrating lymphocytes [4], [5]. The natural ligand for GITR, GITR ligand (GITRL), is expressed at low levels by antigen presenting cells (APCs) such as dendritic cells, macrophages and B cells, and is upregulated upon activation with stimuli such as Toll-like receptor (TLR) ligands [6].

GITR ligation by GITRL (or anti-GITR agonist antibodies) provides a costimulatory signal that enhances both CD4+ and CD8+ T-cell proliferation and effector functions leading to enhanced cellular and humoral immunity [2], [7], [8], [9], [10]. In contrast, blocking GITR-GITRL signaling with antagonist anti-GITRL antibodies inhibits T lymphocyte activation [11]. GITR ligation signaling enhances T-cell survival by up-regulating IL-2, IL-2Rα, IFN-γ and rescue of T-cells from anti-CD3 mediated apoptosis [12], [3]. In addition, co-stimulation through GITR has been shown to render naive or effector T-cells (T_{effs}) resistant to the suppressive effects of T_{regs} [6], [7], [11], [13].

MK-1248 is a humanized agonistic mAb of the IgG4 isotype that targets human GITR and is intended for treatment of multiple human cancers. MK-1248 binds to a region on human GITR that is comparable to the region where a functionally active surrogate monoclonal antibody, DTA-1 (DTA-1), binds on mouse GITR. DTA-1 has been shown to augment antitumor T-cell responses and induce tumor rejection in syngeneic mouse tumor models (see IB for details).

Effective antitumor immunity depends on presentation of a tumor antigen, activation of protective T-cell responses, and the ability to overcome tumor-based blockade of anti-tumor responses [14]. Approaches to antigen-induced promotion of anti-tumor response were pharmacologically validated with the approval of Provenge™ (sipuleucel-T) in 2010. Approaches to reversal of tumor-based immunosuppression were pharmacologically validated by approval of Yervoy™ (ipilimumab) in 2011, and Keytruda ® (pembrolizumab) and Opdivo™ (nivolumimab) in 2014. Following these milestones in immunotherapy, agonist stimulators of anti-tumor T-cell responses represent a next important frontier for development of pharmacologic agents promoting anti-tumor immunity.

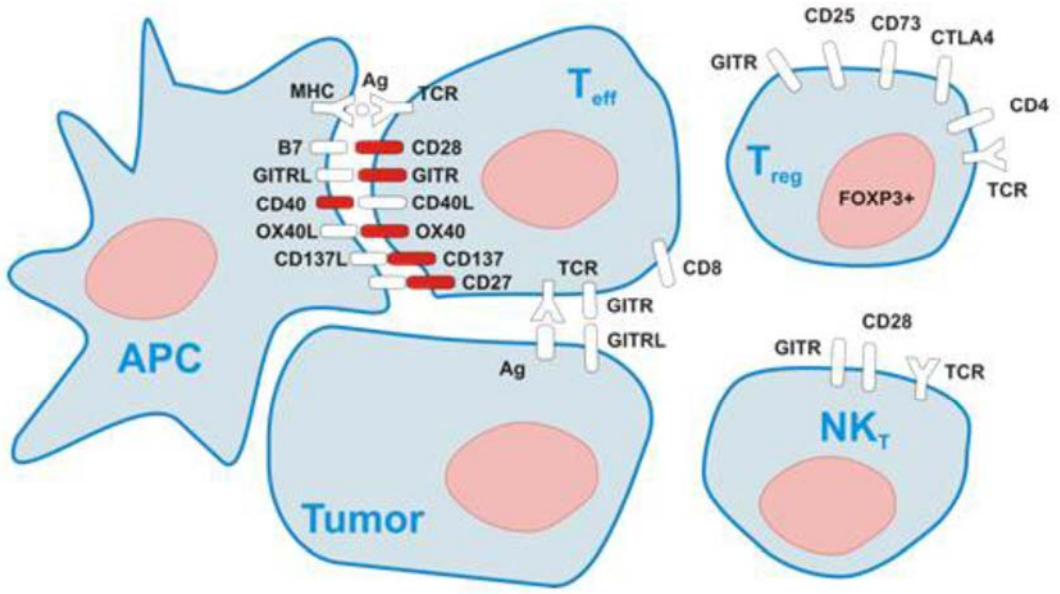


Figure 2 Schematic Diagram of Immune Stimulatory Targets

A broad range of immunostimulatory molecules have been identified and characterized [15]. Several antibodies that target these molecules have entered early pharmacologic development (Figure 2– red highlighted molecules) [16].

Initial attempts to manipulate T-cell activation focused on CD28 as the prototypic costimulatory molecule; CD28 agonists showed promise in preclinical work [17]. Unfortunately, the anti-CD28 agonist TGN1412 demonstrated unexpected toxicity when evaluated in first-in-man clinical studies [18], which urges caution for all ongoing and proposed agonist immunostimulatory antibodies.

Multiple agonist immunostimulatory molecules have entered investigational studies in humans. In early phase studies, the RP2D for CD40 agonists was established from the maximum tolerable toxicity dose (MTD) where transaminitis was the main dose-limiting toxicity (DLT) [19], [20]. Early results for an anti-CD137 (41BB) presented in abstract form (ASCO) documented no MTD for one agonist compound (BMS-663513) [21], these preliminary results further documented that <15% of subjects experienced grade 1-2 events, and 6% of subjects showed objective responses. Both anti-OX40 and anti-CD27 (NCT01460134) antibodies are in early phase clinical trials (NCT01644968). Other known anti-GITR mAbs in clinical trials include MK-4166 (Merck) and TRX-518 (GITR, Inc.).

MK-4166 is a humanized IgG1 agonist monoclonal antibody being evaluated in an ongoing Phase 1 trial in adults with advanced solid tumors. As of 01-Mar-2017, human safety data are available for a total of 81 patients: 45 patients treated with MK-4166 monotherapy and 36 patients treated with MK-4166 in combination with pembrolizumab. Dose escalation has reached 670 mg in the monotherapy treatment arm and 480 mg in the combination treatment arm. Treatment has generally been well tolerated. One DLT was reported in the MK-4166 monotherapy arm at the 30 mg dose: a patient with metastatic urethral cancer had a Grade 3 perforation of an Indiana Pouch which was considered possibly related to study drug, as the

rate of spontaneous perforation is extremely low and there is no other obvious explanation for the event. Dose escalation is continuing per protocol.

MK-1248 has a similar GITR binding region to MK-4166, while the framework for MK-1248 is an IgG4 class compared to the IgG1 class for MK-4166. As such, MK-4166 has ADCC and CDC activity related to the IgG1 backbone while MK-1248 does not. It is unknown whether the activity of the IgG1 in MK-4166 will result in increased efficacy, increased toxicity, or both. If the IgG1 class molecule results in greater toxicity related to the backbone, then an IgG4 class molecule such as MK-1248 may have a greater therapeutic index. By studying both MK-4166 and MK-1248 in clinical trials, the potential difference in therapeutic index based on the IgG subtype will be assessed and a determination made whether one subtype should be favored for further development.

4.1.1.2 Pembrolizumab (MK-3475) Background

The PD-1 receptor-ligand interaction is a major pathway hijacked by tumors to suppress immune control. The normal function of PD-1, expressed on the cell surface of activated T-cells under healthy conditions, is to down-modulate unwanted or excessive immune responses, including autoimmune reactions. PD-1 (encoded by the gene Pdcd1) is an Ig superfamily member related to CD28 and 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 (V-type) domain responsible for ligand binding and a cytoplasmic tail which is responsible for the binding of signaling molecules. The cytoplasmic tail of PD-1 contains 2 tyrosine-based signaling motifs, an immunoreceptor tyrosine-based inhibition motif (ITIM) and an immunoreceptor tyrosine-based switch motif (ITSM). Following T-cell stimulation, PD 1 recruits the tyrosine phosphatases SHP-1 and SHP-2 to the ITSM motif within its cytoplasmic tail, leading to the dephosphorylation of effector molecules such as CD3ζ, PKCθ and ZAP70 which are involved in the CD3 T-cell signaling cascade [22], [25], [26], [27]. 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 [28], [29]. PD-1 was shown to be expressed on activated lymphocytes including peripheral $CD4^+$ and $CD8^+$ T-cells, B-cells, T_{regs} and Natural Killer cells [30], [31], $CD4^-CD8^-$ (double negative) T-cells as well as subsets of macrophages and dendritic cells [32]. The ligands for PD-1 (PD-L1 and PD-L2) are constitutively expressed or can be induced in a variety of cell types, including non-hematopoietic tissues as well as in various tumors [33], [34], [35], [28]. Both ligands are type I transmembrane receptors containing both IgV- and IgC-like domains in the extracellular region and contain short cytoplasmic regions with no known signaling motifs. Binding of either PD-1 ligand to PD-1 inhibits T-cell activation triggered through the T-cell receptor. PD-L1 is expressed at low levels on various non-hematopoietic tissues, most notably on vascular endothelium, whereas PD-L2 protein is only detectably expressed on antigen-presenting cells found in lymphoid tissue or chronic inflammatory environments. PD-L2 is thought to control immune T-cell activation in lymphoid organs, whereas PD-L1 serves to dampen unwarranted T-cell function in peripheral tissues [28]. Although healthy organs express little (if any) PD-L1, a variety of cancers were demonstrated to express abundant levels of this T-cell inhibitor. High expression of PD-L1 on tumor cells (and to a lesser extent of PD-L2) has been found to correlate with poor prognosis and survival in various cancer

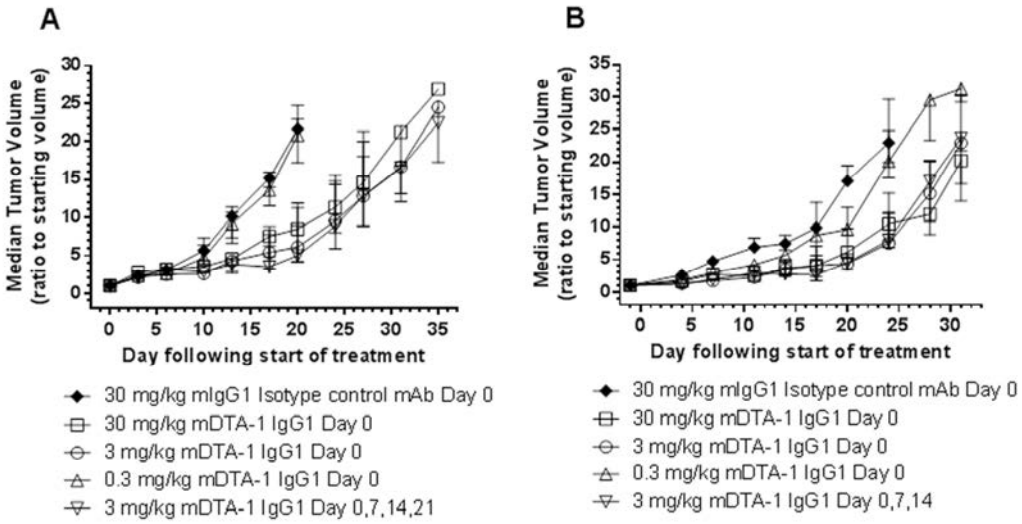
types, including RCC [36], pancreatic carcinoma [37], hepatocellular carcinoma [38], and ovarian carcinoma [39]. Furthermore, PD-1 has been suggested to regulate tumor-specific T-cell expansion in subjects with melanoma (MEL) [40]. This suggests that the PD-1/PD-L1 pathway plays a critical role in tumor immune evasion and should be considered as an attractive target for therapeutic intervention.

4.1.2 Preclinical and Clinical Trials

4.1.2.1 MK-1248 Preclinical and Clinical Trials

Published and internal Merck preclinical observations showing that GITR ligation has potent immunostimulatory effects prompted evaluation of GITR modulation as an approach to enhancement of antitumor immunity. Most of these studies used the rat anti-mouse agonist GITR mAb DTA-1 [41], [42], [43], [44]. These studies have demonstrated that DTA-1 treatment can augment anti-tumor T-cell responses and can induce tumor rejection in several mouse tumor models. In these studies, DTA-1 administration leads to an increased ratio of effector T-cells (T_{eff}) to regulatory T-cells (T_{reg}) (T_{eff}:T_{reg} ratio) and enhanced intra-tumor T_{eff} activation and function. Data from some models suggest that this shift in T_{eff}:T_{reg} ratio is dependent on direct DTA-1 interaction with both tumor-specific T_{effs} and T_{regs}. Recent studies demonstrated that the reduction in number of T_{regs} within the tumor after DTA -1 treatment was associated with decreased T_{reg} migration to the tumor as well as loss of Foxp3 expression in T_{regs} within the tumor [44]. These effects of GITR ligation on T_{regs} were not observed in draining lymph node or spleen [43], [44]. The effect of GITR modulation on intratumor T_{regs}, combined with the known co-stimulatory activity of GITR ligation on T_{effs}, provides a potentially novel dual immunomodulatory mechanism to enhance antitumor immunity. In addition, the apparent preservation of global T_{reg} function following GITR stimulation [43], [44] suggests that the loss of immune tolerance and the incidence of immune-related adverse events may be low. Thus, targeted immunomodulation of GITR appears to be a promising new approach for treatment of cancer.

The results of studies conducted at Merck using the murinized version of DTA-1 (mouse IgG1; mDTA-1 IgG1) revealed that administration of a single dose of mDTA-1 IgG1 leads to tumor growth inhibition of established (70 to 115 mm^3 in volume) subcutaneous MC38 and CT26 tumors. The maximal effective dose of mDTA -1 in these models is in the dose range of approximately 3 mg/kg (Figure 3).



The CT26 colon adenocarcinoma (**Panel A**) and MC38 colon adenocarcinoma (**Panel B**) mouse tumor cell lines were implanted subcutaneously into immunocompetent C57BL/6J and BALB/cAnN mice, respectively. Animals were assigned into treatment groups when the mean tumor volume reached approximately 74 to 110 mm^3.and 70 to 115 mm^3. Isotype control monoclonal antibody mIgG1 was administered as a single subcutaneous dose on Day 0. mDTA-1 IgG1 was administered as a single subcutaneous dose of 0.3, 3, or 30 mg/kg on Day 0, or up to 4 weekly doses of 3 mg/kg on Days 0, 7, 14, and 21. Tumors were measured approximately once weekly. Tumor volumes are presented as group median tumor volumes normalized to starting tumor volume ± 68% *CI*. There were 9 to 10 animals in each group.

Figure 3 Efficacy of a Single Dose of mDTA-1 IgG1 in Established Syngeneic Mouse Tumor Model

GITR stimulation induces humoral immune responses resulting in mechanism-based anti-drug antibody (ADA) formation in mouse models, which is also seen in non-human primates (NHP) (details in IB). This ADA response has the potential to confound drug exposures at therapeutic doses, and potentially prime for subsequent infusion-related toxicity. Analysis of serum cytokines shows no evidence of cytokine storm associated with the ADA. However, in mice, intravenous (IV) bolus administration of mDTA-1 in the presence of preexisting ADA leads to an acute infusion reaction. Studies summarized in the IB suggest that the acute infusion reactions in mice may result from rapid immune complex formation leading to an "alternative" IgG1-mediated pathway of anaphylaxis [45]. No acute infusion reactions are observed in mice after multiple sub-cutaneous (SQ) administrations of mDTA-1 or in cynomolgus monkeys after multiple 30-minute IV infusions of MK-1248 (at dose levels of 0.0005 to 200 mg/kg), suggesting that anti-GITR antibodies can be safely administered even in the presence of ADA.

4.1.2.2 Pembrolizumab (MK-3475) Preclinical and Clinical Trials

Efficacy studies in mouse models have shown that administration of antibodies blocking PD-1/PD-L1 interaction, either as a mono-therapy or in combination with other treatment modalities, enhances infiltration of tumor-specific CD8+ T-cells and leads ultimately to tumor rejection. Anti-mouse PD-1 or anti-mouse PD-L1 antibodies have demonstrated anti-tumor responses as a monotherapy in models of squamous cell carcinoma, pancreatic carcinoma, melanoma and colorectal carcinoma. Blockade of the PD-1 pathway effectively

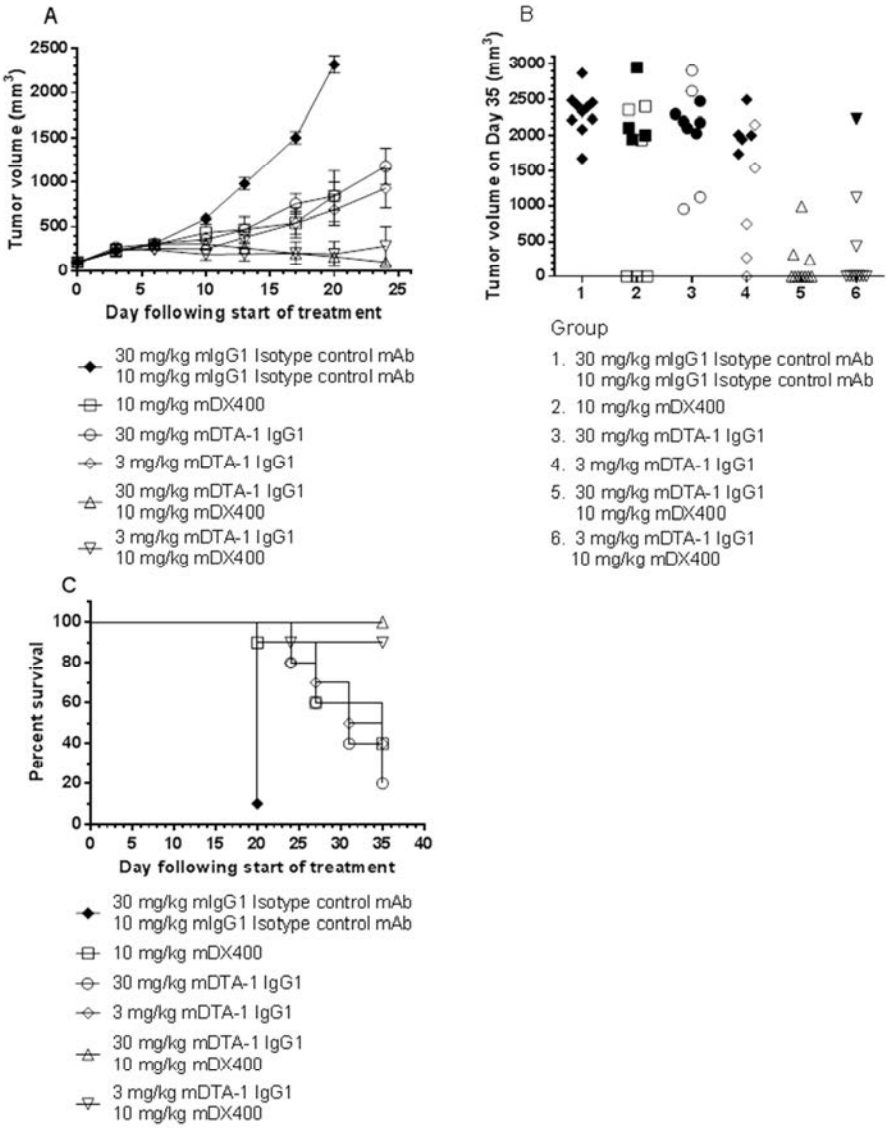
promoted CD8+ T-cell infiltration into the tumor and the presence of IFN-γ, granzyme B and perforin, indicating that the mechanism of action involved local infiltration and activation of effector T-cell function in vivo [40], [46], [45], [47]. Experiments have confirmed the in vivo efficacy of PD-1 blockade as a mono-therapy as well as in combination with chemotherapy in syngeneic mouse tumor models (see the IB).

Pembrolizumab [KEYTRUDA® (US); previously known as lambrolizumab, MK-3475 and SCH 9000475] is a potent and highly selective humanized monoclonal antibody (mAb) of the IgG4/kappa isotype designed to directly block the interaction between PD-1 and its ligands, PD-L1 and PD-L2. KEYTRUDA® (pembrolizumab) is indicated for the treatment of patients across a number of indications. For more details on specific indications refer to the IB.

4.1.2.3 MK-1248 with Pembrolizumab Combination Preclinical Trials

As MK-1248 acts to stimulate effector immune cells while pembrolizumab acts to prevent immune suppression in tumors, it is conceivable that a combination of MK-1248 and pembrolizumab may result in further stimulation of the immune system against malignant disease and thereby greater anti-tumor efficacy. This hypothesis was tested in preclinical models, the results of which provide support for the proposed clinical trial.

Studies have been conducted in the CT26 syngeneic mouse tumor model to assess the anti-tumor efficacy of treatment with mDTA-1 IgG1 (mouse surrogate for MK-1248) in combination with muDX400 (mouse surrogate for pembrolizumab). mDTA-1 IgG1 or muDX400 were administered either as monotherapy or in combination twice with a seven day interval at previously determined maximally effective monotherapeutic doses. Administration of mDTA-1 IgG1 in combination with muDX400 resulted in greater anti-tumor efficacy than administration of either antibody alone (Figure 4).



The CT26 colon adenocarcinoma cells were implanted into immunocompetent BALB/cAnN mice subcutaneously. Animals were assigned into treatment groups when the tumor volume ranged from approximately 77 to 115 mm^3. mIgG1 isotype control monoclonal antibody (mIgG1) was administered SC or IP on Days 0 and 7. muDX400 alone was administered IP on Days 0 and 7. mDTA-1 IgG1 alone was administered SC on Day 0. mDTA-1 IgG1 was administered SC in combination with muDX400 administered IP on Days 0 and 7. In panel A, mean group tumor volumes (± standard error of the mean) are presented. Statistical comparisons of tumor volume between groups are presented in panel B. In panel B, individual animal tumor volumes on Day 35 are presented. Open symbols are measured values from Day 35; solid symbols are censored data (final measurement taken before Day 35). In panel C, animal survival curves are presented. Comparison of animal survival between groups was conducted using Log-rank with Mantel-Cox test analysis. Comparisons with significant differences are shown in panel C. Tumor volumes presented are from Study 14-M320-6565. There were 10 animals in each group.

Figure 4 Efficacy of Combination Treatment with mDTA-1 IgG1 and muDX400 in Established Syngeneic Mouse Tumor Model

4.1.3 Ongoing Clinical Trials

4.1.3.1 MK-1248 Ongoing Clinical Trials

This is the first clinical trial with MK-1248. A Phase 1 clinical trial with MK-4166, an anti-GTIR humanized mAB of the IgG1 class, is ongoing as described previously in Section 4.1.1.1.

4.1.3.2 Pembrolizumab Ongoing Clinical Trials

Ongoing clinical trials with pembrolizumab are being conducted in multiple solid tumors, including melanoma, non-small cell lung cancer, head and neck cancer, triple negative breast cancer, gastric cancer, and bladder cancer, as well as hematological malignancies. In addition, multiple combinations with pembrolizumab are also being investigated, including the combination of pembrolizumab with MK-4166 (anti-GITR). For trial details please refer to the pembrolizumab IB.

4.1.4 Information on Other Trial-Related Therapy

No comparators are proposed for this trial.

4.2 Rationale

4.2.1 Rationale for the Trial and Selected Subject Population

MK-1248 is being developed for treatment of solid tumors. This trial is the first-in-human trial designed to assess the safety, tolerability, pharmacokinetics and pharmacodynamics of escalating doses of MK-1248 alone and in combination with pembrolizumab in subjects with advanced solid tumors that have failed standard therapy. The effect of MK-1248 on tumor size will also be explored. The trial will enroll subjects with solid tumors without regard to specific tumor type.

4.2.2 Rationale for Dose Selection/Regimen/Modification

MK-1248 and MK-4166 are both monoclonal antibodies with similar binding to the GITR receptor and different Fc regions; MK-4166 has a functional IgG1 domain while MK-1248 utilizes an IgG4 framework. Therefore, the dose regimen proposed for this first-in-human trial of MK-1248 is based on the experience in the MK-4166 first-in-human trial. Specifically, doses of 0.0015 to 10 mg have been administered to single-dose cohorts of subjects in MK-4166 PN 001 and no DLTs have been reported in these subjects. A dose of 30 mg MK-4166 was administered to 3 subjects, with 1 subject reporting a DLT. This DLT was a Grade 3 Indiana Pouch perforation reported in a subject with metastatic urethral cancer in which the investigator determined the event to be possibly related to study drug because of the low incidence of spontaneous perforation and no obvious explanation for the event. As of 01-Mar-2017, data are available for a total of 81 patients: 45 patients treated with MK-4166 monotherapy and 36 patients treated with MK-4166 in combination with pembrolizumab. Dose escalation has reached 670 mg in the monotherapy treatment arm and 480 mg in the combination treatment arm; dose escalation is continuing per protocol.

4.2.2.1 Starting Dose for This Trial

The starting dose of MK-1248 for this trial was determined by the following criteria:

1) MK-1248 has similar GITR binding epitope to MK-4166 while due to its IgG4 domain MK-1248 is predicted to have lesser Fc-related activity compared to the MK-4166, with its functional IgG1 domain.
2) Preclinically, cytokine release activity representing the minimum active biologic activity for MK-1248 is similar to MK-4166 (see below).
3) MK-4166 has been administered to subjects at doses ranging from 0.0015 mg to 10 mg without any DLTs. One DLT has been reported at a dose of 30 mg and dose escalation is ongoing.
4) The GITR receptor binding pharmacodynamic assay utilized in the MK-4166 protocol indicates that saturation of GITR receptors in the periphery approaches saturation as doses of 0.37 mg and higher.

Therefore, the starting dose of MK-1248 in this trial is planned to be 0.12 mg. The dose of 0.12 mg MK-1248 was chosen because safety data from the closely related MK-4166 molecule is available as doses approximately 100-fold higher than the 0.12 mg dose (i.e. at 10 mg MK-4166) without DLTs. Furthermore, while a starting dose of 0.12 mg is anticipated to have some GITR-binding pharmacodynamic activity, it is expected to be below the corresponding dose of MK-4166 at which full saturation of peripheral GITR receptors was approached (0.37 mg MK-4166).

Cynomolgus monkeys were used for studies of PK and GITR engagement as a bridging species to human administration. Cynomolgus monkeys were chosen as the relevant pharmacological species for the conduct of preclinical safety studies since MK-1248 binds to and co-activates cynomolgus monkey GITR with similar affinity and potency to that of human GITR. A broad survey of tissues from normal human and cynomolgus monkey demonstrated that GITR is expressed at low levels primarily on lymphoid cells in the blood and in lymphoid tissues in both species. In the blood, GITR expression on T-cells is comparable. However, a higher percentage of GITR-positive NK T-cells is present in cynomolgus monkey blood relative to human, and a large but variable percentage of GITR-positive NK cells is present in human while none are present in cynomolgus monkey blood. Non-linear PK properties were observed in cynomolgus monkeys at lower doses (0.0005 – 3 mg/kg). In line with changes in serum concentration-time profiles for MK-1248, a dose-dependent effect on GITR engagement in blood, as measured by a receptor (GITR) availability assay (RA assay described in IB), was observed in monkeys. Relationships between receptor (GITR) availability and MK-1248 serum concentrations were described by an inhibitory E_{max} model, which provided a preliminary estimate of a potency value ($EC_{50} \approx 6$ ng/ml) for blood GITR engagement. It should be noted that MK-4166 has a similar estimated potency value in this same model.

GITR+ T-cells in blood were evaluated for MK-1248 binding in cancer patients, normal healthy volunteers and Cynomolgus monkeys. Results from this experiment showed comparable binding potency and maximum binding capacity between humans and cynomolgus monkeys under the in vitro experimental conditions employed.

4.2.2.2 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 non-small cell lung cancer 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 study.

4.2.2.3 Maximum Dose/Exposure for This Trial

Data from mouse efficacy studies and predictions of human target engagement suggest a human efficacious dose in the range of 60 mg to 330 mg for MK-1248. Although dose escalations will depend on adverse events, a potential dose up to 900 mg is planned. While the maximum clinical dose to be evaluated in this trial is 900 mg, studies in the appropriate safety species (cynomolgus monkey) showed no adverse effects at doses where the C_{max} and AUC values were twenty-fold and five-fold higher, respectively, relative to the predicted human exposure.

4.2.2.4 Rationale for Dose Interval and Trial Design

4.2.2.4.1 MK-1248 Monotherapy

Maximal efficacy was achieved in mouse preclinical studies using 3 mg/kg doses. In the rapidly progressing syngeneic tumor models, no improvement in efficacy was observed with weekly dosing (see IB). Because preclinical data suggests that long-term chronic dosing may not be necessary for full efficacy, we plan a limited number of MK-1248 administrations. A single first dose will be followed by a 3-week (DLT) observation period during which time subjects will be monitored for toxicity (including signs of systemic cytokine release) and target engagement monitored by receptor availability. In the absence of limiting safety events, three additional doses will be administered at 21-day intervals. The 3 week dosing interval may be adjusted based on emerging data from the study, e.g., PK and receptor (GITR) availability. Subjects will also be monitored for anti-drug antibodies (ADA).

4.2.2.4.2 MK-1248 in Combination with Pembrolizumab

As described previously, the combination of the anti-mouse GITR and anti-mouse PD-1 surrogate antibodies for MK-1248 and pembrolizumab showed greater efficacy in preclinical studies than either agent alone. Therefore, the combination of MK- 1248 and pembrolizumab is planned for study in clinical trials to assess whether selected groups of patients with cancer may also derive greater benefit from the combination. As an initial step in testing the combination in clinical trials, this study will assess the safety and tolerability of the combination of MK-1248 and pembrolizumab, and determine a recommended Phase 2 dose for MK-1248 when used in combination with pembrolizumab. Similar to the preclinical studies, MK-1248 and pembrolizumab will be administered on the same day for the first 4 cycles in Arm 2 when both drugs are administered, followed by administration of pembrolizumab alone every 3 weeks for a total of 24 weeks or until a discontinuation criterion is met.

4.2.3 Rationale for Endpoints

4.2.3.1 Efficacy Endpoints

An exploratory endpoint for this trial is to evaluate the anti-tumor activity of MK-1248 and MK-1248 in combination with pembrolizumab in subjects with advanced solid malignancies. Tumor response will be accessed using irRECIST.

Immunotherapeutic agents such as MK-1248 and pembrolizumab may produce antitumor effects by potentiating endogenous cancer-specific immune responses. The response patterns seen with such an approach may extend beyond the typical time course of responses seen with typical cytotoxic agents, and can manifest a clinical response after an initial increase in tumor burden or even the appearance of new lesions. Standard response assessment criteria may not provide a comprehensive response assessment of immunotherapeutic agents such as MK-1248 and pembrolizumab. Therefore, the subject should not be discontinued from treatment unless the initial assessment of PD is confirmed at least 4 weeks later, provided the subject's clinical condition is stable, and irRECIST will thus be used to assess efficacy.

4.2.3.2 Safety Endpoints

The primary safety analysis of this trial is to characterize the safety and tolerability of MK-1248 monotherapy and in combination with pembrolizumab in subjects with advanced solid tumors. The primary safety analysis will be based on subjects who experience toxicities as defined by CTCAE criteria. Safety will be assessed by quantifying the toxicities and grades of toxicities experienced by subjects who have received MK-1248, including serious adverse events and events of clinical interest (ECIs).

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

4.2.3.3 Pharmacokinetic Endpoints

A secondary objective of this trial is to characterize the pharmacokinetic (PK) profile of MK-1248 following administration as a single agent, and MK-1248 and pembrolizumab following administration of MK-1248 and pembrolizumab in combination. The serum concentrations of each antibody will serve as the primary readout for the PK, and these data will be used to derive PK parameters of the agents alone and in combination. Furthermore, the results of these analyses will be used in conjunction with the pharmacodynamics, safety and anti-drug antibody endpoints to help assess future dosing strategies for MK-1248.

4.2.3.4 Pharmacodynamic Endpoints

4.2.3.4.1 Target Engagement (TE): Receptor Availability on Peripheral Blood Lymphocytes

Due to GITR internalization upon binding by MK-1248, direct measurement of GITR receptor occupancy is not feasible. Therefore, to evaluate GITR target engagement, a receptor (GITR) availability (RA) assay designed to assess the availability of surface GITR

following administration of MK-1248 was developed. GITR is detected on CD4+CD25+ and CD4+CD95+ T-cell sub-populations using flow cytometry and compared to pre-dose baseline. GITR target engagement is calculated as 100% - (%) receptor (GITR) availability. This assay is the primary pharmacodynamic assessment of MK-1248 target binding, and represents a secondary hypothesis for this trial. As GITR binding and internalization in the periphery is likely to saturate, this assay may not be conducted at higher doses once saturation has been confirmed.

4.2.3.5 Anti-Drug Antibody (ADA) Assay

GITR stimulation results in an induction of humoral immune responses resulting in mechanism-based anti-drug antibody (ADA) formation. This ADA response can potentially confound drug exposures at therapeutic doses, and prime for subsequent infusion-related toxicity. Anti-MK-1248 and anti-pembrolizumab ADA response at the beginning of each cycle will be determined to understand drug metabolism, exposure and safety.

4.2.3.6 Serum Cytokines

Because of the immune stimulation by an agonistic antibody and resulting potential for cytokine release triggered by anti-GITR, serum cytokines will be monitored to provide supplementary information to assist in the evaluation of any safety events (for example TNFα, IL-2 and IL-6).

4.2.3.7 Planned Exploratory Biomarker Research

Mechanistic pharmacodynamic markers of anti-GITR activity have been observed after administration of the surrogate mAb mDTA-1 in mouse syngeneic tumor efficacy models, including changes in intra-tumor CD8:T_{reg} ratios and induction of gene expression changes of various immune mediators (e.g. IFNγ, perforin and granzymes). These changes in candidate pathway biomarkers are predominantly seen within the tumor. Immunophenotyping and gene expression profiling of tumor biopsies will be performed to explore changes in lymphocyte populations. These may include T_{reg} markers (e.g. FoxP3, GITR) as well as measures of interferon-γ-pathway genes, effector T-cell response genes, T-cell repertoire immunomodulatory receptors (IMRs) and other related markers of immune response.

For Arm 1, Parts B and C and Arm 2 Parts D and E of the study, subjects will be required to provide an archival tumor tissue sample and/or a fresh biopsy of tumor before treatment for these biomarker analyses. Subjects will also be asked to agree to an optional biopsy of tumor after initiation of MK-1248 and to provide the acquired tissue for these biomarker analyses.

Immune modulatory agents may alter populations of circulating immune cells in blood. To assess the effect of MK-1248 on these cell populations, peripheral blood samples will be obtained at designated times before and after MK-1248 administration. Changes in immune cell populations will be evaluated by comparing changes from baseline in expression of immune function genes or proteins after treatment, and by evaluating changes from baseline in T-cell repertoire after treatment.

Additional host genetic factors might predict for response to the treatments in this study. Therefore, an additional blood sample will be collected for exploratory pharmacogenetic studies. This research will evaluate whether genetic variation within the clinical trial population correlates with response to the treatment(s) or adverse events under evaluation.

4.2.3.8 Planned Genetic Analysis

Understanding genetic determinants of drug response is an important endeavor during medical research. This research will evaluate whether genetic variation within a clinical trial population correlates with response to the treatment(s) under evaluation. If genetic variation is found to predict efficacy or adverse events, the data might inform optimal use of therapies in the patient population. This research contributes to understanding genetic determinants of efficacy and safety associated with the treatments in this study.

4.2.3.9 Future Biomedical Research

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

Such research is for biomarker testing to address emergent questions not described elsewhere in the protocol (as part of the main trial) and will only be conducted on specimens from appropriately consented subjects. The objective of collecting specimens for Future Biomedical Research is to explore and identify biomarkers that inform the scientific understanding of diseases and/or their therapeutic treatments. For instance, exploratory pharmacogenetic (PGt) studies may be performed if significant Pharmacokinetic/Pharmacodynamic (PK/PD) relationships are observed or adverse events are identified. Genomic markers of disease may also be investigated. Such retrospective pharmacogenetic studies will be conducted with appropriate biostatistical design and analysis and compared to PK/PD results or clinical outcomes. Any significant PGt relationships to outcome would require validation in future clinical trials. The overarching goal is to use such information to develop safer, more effective drugs/vaccines, and/or to ensure that subjects receive the correct dose of the correct drug/vaccine at the correct time. The details of this Future Biomedical Research sub-trial are presented in Section 12.2 - Collection and Management of Specimens for Future Biomedical Research. Additional informational material for institutional review boards/ethics committees (IRBs/ERCs) and investigational site staff is provided in Section 12.3.

4.3 Benefit/Risk

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

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

5.0 METHODOLOGY

5.1 Entry Criteria

5.1.1 Diagnosis/Condition for Entry into the Trial

Enrollment into this study has been prematurely discontinued due to program prioritization and not related to any safety concerns. The cut-off date for enrollment is 31-Mar-2017. Subjects who are ongoing in the study after that date and who do not yet meet established protocol discontinuation criteria, as outlined in Section 5.8, will continue to attend study visits and be followed per protocol. Subjects who are ongoing in the study after that date and who do not yet meet established treatment discontinuation criteria, as outlined in Section 5.8, may continue to receive study treatment per protocol, provided the investigator feels such treatment is in the best interest of the subject. Male/Female subjects with advanced solid tumors, of 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. Have histologically or cytologically-confirmed metastatic solid tumor for which there is no available therapy which may convey clinical benefit.
2. Have measureable disease by RECIST 1.1 criteria.
3. Be ≥18 years of age on the day of signing informed consent.
4. Have a performance status of 0 or 1 on the Eastern Cooperative Oncology Group (ECOG) Performance Scale.
5. Demonstrate adequate organ function as defined in Table 1 (labs to be obtained within 7 days of initiation of treatment).

Table 1 Adequate Organ Function Laboratory Values

System	Laboratory Value
Hematological	
Absolute neutrophil count (ANC)	≥ 1500/mcL
Platelets	≥ 100,000/ mcL
Hemoglobin	≥9 g/dL or ≥5.6 mmol/L
Renal	
Creatinine **OR** Measured or calculated creatinine clearance (GFR can also be used in place of creatinine or CrCl)	≤1.5 X upper limit of normal (ULN) **OR** ≥60 mL/min for subject with creatinine levels > 1.5 X institutional ULN *Note: Creatinine clearance should be calculated per institutional standard*
Hepatic	
Total Bilirubin	≤ 1.5 X ULN **OR** Direct bilirubin ≤ ULN for subjects with total bilirubin levels > 1.5 ULN
AST (SGOT) and ALT (SGPT)	≤ 2.5 X ULN
Coagulation	
International Normalized Ratio (INR) or Prothrombin Time (PT) Activated Partial Thromboplastin Time (aPTT)	≤1.5 X ULN ≤1.5 X ULN

6. Female subjects of childbearing potential should be willing to use 2 methods of birth control or be surgically sterile, or abstain from heterosexual activity for the course of the study through 120 days after the last dose of study medication. Subjects of childbearing potential are those who have not been surgically sterilized, or have not been free from menses for > 1 year. Male subjects should agree to use an adequate method of contraception starting with the first dose of study therapy through 180 days after the last dose of study medication. Abstinence is acceptable if this is the established and preferred contraception for this subject.
7. Female subjects of childbearing potential should have a negative urine or serum pregnancy test at Screening and again within 24 hours prior to receiving the first dose of study medication. If urine test is positive, a negative serum pregnancy test will be required.
8. Voluntarily agreed to participate by giving written informed consent. The subject may also provide consent for Future Biomedical Research. However, the subject may participate in the main trial without participating in Future Biomedical Research.

9. Submit a baseline tumor sample for analysis. If submitting unstained cut slides, freshly cut slides should be submitted to the testing laboratory within 14 days from when the slides are cut.

5.1.3 Subject Exclusion Criteria

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

1. Has had chemotherapy, radiation, or biological cancer therapy within 4 weeks prior to the first dose of study therapy, or who has not recovered to CTCAE grade 1 or better from the adverse events due to cancer therapeutics administered more than 4 weeks earlier (this includes subjects with previous immunomodulatory therapy with residual irAEs).

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

3. Has received previous treatment with another agent targeting the GITR receptor (e.g., MK-4166).

4. Have received previous treatment with an immunomudulatory therapy (e.g., anti-PD-1/PD-L1 or CTLA 4 agent) and was discontinued from that therapy due to an irAE.

5. Is expected to require any other form of antineoplastic therapy while on study.

6. Is on chronic systemic steroid therapy in excess of replacement doses, or on any other form of immunosuppressive medication.

7. Has a history of a previous, additional malignancy, unless potentially curative treatment has been completed, with no evidence of malignancy for 5 years.

    a. Note: The time requirement for no evidence of disease for 5 years does not apply to the tumor for which a subject is enrolled in the study. The time requirement does not apply to subjects who underwent successful definitive resection of basal cell carcinoma of the skin, superficial bladder cancer or in situ cervical cancer.

8. Has known active central nervous system (CNS) metastases and/or carcinomatous meningitis. Subjects with previously treated brain metastases may participate provided they are clinically stable for at least 8 weeks prior to study entry, have no evidence of new or enlarging brain metastases and are off steroids.

9. Has had a severe hypersensitivity reaction to treatment with another monoclonal antibody.

10. Has an active autoimmune disease or a documented history of autoimmune disease, except vitiligo or resolved childhood asthma/atopy, or endocrine deficiency following treatment with an immunomodulary agent.

11. Has an active infection requiring therapy.

12. Has active, or a history of non-infectious pneumonitis.

13. Has had a prior stem cell or bone marrow transplant.

14. Has a known history of Human Immunodeficiency Virus (HIV) (HIV 1/2 antibodies), active chronic or acute Hepatitis B (e.g., HBsAg reactive) or Hepatitis C (e.g., HCV RNA [qualitative] is detected).

15. Has a history or current evidence of any condition, therapy, or laboratory abnormality that might confound the results of the study, interfere with the subject's participation for the full duration of the study, or is not in the best interest of the subject to participate, in the opinion of the treating Investigator.

16. Has known psychiatric or substance abuse disorders that would interfere with cooperation with the requirements of the trial.

17. Is a regular user (including "recreational use") of any illicit drugs or had a recent history (within the last year) of substance abuse (including alcohol), at the time of signing informed consent.

18. Has symptomatic ascites or pleural effusion. A subject who is clinically stable following treatment for these conditions (including therapeutic thoraco- or paracentesis) is eligible.

19. Is pregnant or breastfeeding, or expecting to conceive or father children within the projected duration of the study.

20. Has had major surgery within 16 weeks prior to screening. Local surgery for melanoma is allowed.

21. Has received a live vaccine within 30 days prior to first dose.

22. Is or has an immediate family member (e.g., spouse, parent/legal guardian, sibling or child) who is investigational site or sponsor staff directly involved with this trial, unless prospective IRB approval (by chair or designee) is given allowing exception to this criterion for a specific subject.

5.2 Trial Treatment(s)

The treatment(s)to be used in this trial are outlined below in Table 2 and Table 3.

In Arm 1, Part A, dose escalation will begin with 0.12 mg in cohorts of 2 subjects each, and will proceed based on safety events to a dose of 10 mg. Starting at a 30 mg dose (or at a lower dose as described in Section 5.2.1.3) in Part B, dose escalation will continue with a 3+3 design to identify a preliminary maximum tolerated dose (MTD). In Part C, dose confirmation will refine the estimate of the tolerability of the MTD (or maximum administered dose), using a toxicity probability interval [1].

Enrollment to Arm 2, (MK-1248 in combination with pembrolizumab) will begin once 2 subjects complete 1 cycle of MK-1248 monotherapy at the ≥3 mg dose level in Part A, and will follow a 3+3 design to identify a preliminary MTD in Part D. The starting dose of MK-1248 will be 0.12 mg. Doses of MK-1248 will be escalated as described in Table 3 and the dose of pembrolizumab will be fixed at 200 mg. During 3+3 dose escalation, at least 2 days of observation will occur between each of the first 3 subjects at each dose level (except for the first 2 subjects receiving the combination treatment at the first dose level for which at least 7 days of observation between dosing will occur). Dose confirmation in Part E will refine the estimate of tolerability of the MTD using a toxicity probability interval [1].

Enrollment to both arms will occur in parallel with treatment allocation accomplished by non-random assignment to Arm 1 or Arm 2 using an IVRS/IWRS.

If pharmacodynamic saturation at the tissue level and/or robust clinical efficacy is observed during the dose escalation phase in either the monotherapy or combination therapy arm, initiation of the dose confirmation Parts C and E may begin. Depending on safety, efficacy and pharmacologic data, dose escalation in the monotherapy and combination therapy arms may continue concurrent with enrollment in Parts C and E. Up to a total of 14 subjects may be enrolled at a lower dose level where robust clinical activity is observed concurrent with the dose escalation phase. In either of the above cases, an administrative letter will be used to document the initiation of a dose confirmation cohort (Part C or E for the monotherapy or combination treatment, respectively), or to allow enrollment of up to a total of 14 subjects at a given dose.

Note: Enrollment into this study has been prematurely discontinued due to program prioritization and not related to any safety concerns. The cut-off date for enrollment is 31-Mar-2017. Subjects who are ongoing in the study after that date and who do not yet meet established protocol discontinuation criteria, as outlined in Section 5.8, will continue to attend study visits and be followed per protocol. Subjects who are ongoing in the study after that date and who do not yet meet established treatment discontinuation criteria, as outlined in Section 5.8, may continue to receive study treatment per protocol, provided the investigator feels such treatment is in the best interest of the subject.

Table 2 Trial Treatment for MK-1248 Monotherapy (Arm 1)

Drug	Dose	Dose Frequency	Route of Administration	Regimen	Use
Treatment during Part A : Dose escalation					
MK-1248	0.12 mg 0.6 mg 3 mg 10 mg	Q3 weeks	IV infusion	Day 1 of each 21 day cycle	Experimental
Treatment during Part B : 3+3					
MK-1248	30 mg 60 mg 120 mg 170 mg 240 mg 330 mg 460 mg 650 mg 900 mg	Q3 weeks	IV infusion	Day 1 of each 21 day cycle	Experimental

Note: Dose levels shown in Table 2 are proposed dose levels. Actual doses tested in the trial will depend on whether or not safety observations trigger the switch to 40 % dose level increases before the 120 mg dose.

Table 3 Trial Treatment for MK-1248 and Pembrolizumab Combination (Arm 2)

Drug	Dose	Dose Frequency	Route of Administration	Regimen	Use
Treatment during Part D: 3+3					
MK-1248	0.12 mg 0.6 mg 3 mg 10 mg 30 mg 60 mg 120 mg 170 mg 240 mg 330 mg 460 mg 650 mg 900 mg	Q3 weeks	IV infusion	Day 1 of each 21 day cycle	Experimental
Pembrolizumab	200 mg	Q3 weeks	IV infusion	Day 1 of each 21 day cycle	Experimental

Note: Dose levels shown in Table 3 are proposed dose levels. Actual doses of MK-1248 tested in the trial will depend on whether or not safety observations trigger the switch to 40 % dose level increases before the 120 mg dose.

In Arm 2, pembrolizumab will be administered first, then after a 30-minute observation period MK-1248 will be administered.

Based on preliminary safety information from the ongoing study, the Sponsor recommends that all subjects be prophylactically pre-medicated, 1.5 hours (± 30 minutes) before infusion with MK-1248, with the following:

(1) Dexamethasone, 8 mg intravenously;

(2) Acetaminophen, 1000 mg orally; and

(3) Loratadine, 10 mg orally.

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

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

5.2.1 Dose Selection/Modification

5.2.1.1 Dose Selection (Preparation)

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

Details on preparation of administration of MK-1248 and pembrolizumab are provided in the Procedure Manual.

5.2.1.2 Dose Escalation

In Arm 1 (MK-1248 monotherapy), dose escalation will begin with 0.12 mg in cohorts of 2 subjects each, and will proceed based on safety events to a dose of 10 mg. Starting at a 30 mg dose (or at a lower dose as described in Section 5.2.1.3) in Part B, dose escalation will continue with a 3+3 design to identify a preliminary maximum tolerated dose (MTD). In Part C, dose confirmation will refine the estimate of the tolerability of the MTD (or maximum administered dose), using a toxicity probability interval [1].

Enrollment to Arm 2, (MK-1248 in combination with pembrolizumab) will begin once 2 subjects complete 1 cycle of MK-1248 monotherapy at the ≥3 mg dose level in Part A, and will follow a 3+3 design to identify a preliminary MTD in Part D. The starting dose of MK-1248 will be 0.12 mg. Doses of MK-1248 will be escalated as described in Table 3 and the dose of pembrolizumab will be fixed at 200 mg. Dose confirmation in Part E will refine the estimate of tolerability of the MTD using a toxicity probability interval [1].

5.2.1.3 Accelerated Dose Escalation (MK-1248 Monotherapy)

During the accelerated dose escalation stage (Part A), each cohort will enroll two subjects and dose escalation will proceed as designated in Table 2 and Table 3, until a DLT is observed or until the dose level of 10 mg is safely administered. At least 2 days of observation will occur between each of the first 2 subjects at each dose level.

If a DLT is observed during a 2-subject cohort, an additional subject will be enrolled at this dose level for a total of 3 subjects, and the rules of 3+3 dose escalation described in Section 5.2.1.4 will apply:

- If the new subject does not develop a DLT (for a total of 1/3 subjects with a DLT at that dose level), three more subjects will be enrolled at this dose level and the rules of 3+3 design (Section 5.2.1.4) will be followed for a cohort of 6 subjects. The 3+3 dose escalation design will be followed from then on with 40% increments in the dose level.
- If the new subject develops a DLT (for a total of 2/3 subjects with a DLT at this dose level), the dose escalation stage of the trial will be terminated. The third subject will be enrolled in the dose directly below the current dose and the 3+3 dose escalation design will be followed from then on with 40% increments in the dose level.

See Section 5.2.2 for definition of DLTs.

Starting with the 30 mg dose, 3 subjects will be enrolled to each dose level.

5.2.1.4 3+3 Dose Escalation (MK-1248 Monotherapy and MK-1248 plus Pembrolizumab Combination)

During MK-1248 monotherapy (Arm 1), once the 10 mg dose is safely administered, starting with the next dose the study will proceed to 3 subjects enrolled at each dose level and dose escalation continuing according to Table 2. During 3+3 dose escalation, at least 2 days of observation will occur between each of the first 3 subjects at each dose level.

For MK-1248, intermediate lower dose levels, not specified in Table 2 and Table 3 may be investigated. This escalation schedule may be adjusted downward based on PD, PK, and safety data emerging throughout the Phase 1 study.

The rules for the preliminary MK-1248 dose finding during MK-1248 monotherapy (Arm 1) and during MK-1248 plus pembrolizumab combination treatment (Arm 2) using the 3+3 design are as follows (all dose adjustments are made only to MK-1248):

An initial cohort of 3 subjects is enrolled.

- If 0/3 subjects develops a DLT, escalation to the next dose of MK-1248 will occur.
- If 1/3 subjects develops a DLT, another 3 subjects will be enrolled at this dose level.
    - If 0 of the 3 new subjects develops a DLT (for a total of 1/6 subjects with a DLT at this dose level), escalation to the next dose level will occur.
    - If ≥1 of the 3 new subjects develop a DLT (for a total of ≥2/6 subjects with a DLT at this dose level), the dose escalation stage of the trial will be terminated. If the dose directly below the current dose had been studied in at least 3 subjects, the dose directly below the current dose will be considered the preliminary MTD, and the study will proceed to the confirmation stage. If the dose directly below the current dose had been studied in <3 subjects, more subjects to a total of 3 will be enrolled at the dose directly below the current dose before proceeding to the confirmation stage.
- If ≥2/3 subjects develop a DLT, the dose escalation stage of the trial will be terminated. If the dose directly below the current dose had been studied in at least 3 subjects, the dose directly below the current dose will be considered the preliminary MTD, and the study will proceed to the confirmation stage. If the dose directly below the current dose had been studied in <3 subjects, more subjects to a total of 3 will be enrolled at the dose directly below the current dose before proceeding to the confirmation stage.

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

If the highest candidate dose of MK-1248 is studied during dose escalation, and 0/3 subjects or <2/6 subjects develop a DLT at that dose, then dose escalation will terminate with this finding and this dose level may be taken to the confirmation stage.

5.2.1.5 Dose Confirmation

The objective of dose confirmation in Part C and Part E is to refine the estimate of the MK-1248 MTD based on TPI design [1] with target toxicity rate ≤30%. Dose confirmation involves the expansion of at least 1 dose level studied in the dose escalation stage of the study.

The toxicity probability interval (TPI) design [1] will be used at the dose confirmation stage. Based on the observed DLTs, the approach recommends actions of escalating, staying at, or de-escalating the dose level as presented in Table 4.

Dose confirmation will begin with expansion of the preliminary MTD/MAD identified in the dose escalation stage described above. The dose confirmation part will continue until 14 subjects are studied at the selected dose (combined from dose escalation and dose confirmation) with ≤5 of 14 subjects experiencing a DLT. As subjects become evaluable for DLT assessment, the number of subjects who are evaluable for DLT versus the number of subjects who developed a DLT will be continuously assessed and de-escalation and re-escalation to eligible doses of MK-1248 will occur as shown in Table 4

The 200 mg dose of pembrolizumab will not be adjusted.

Table 4 Dose Confirmation Rules

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

E = Escalate to the next higher dose
S = Stay at the current dose
D = De-escalate to the next lower dose
DU = The current dose is unacceptably toxic
Target toxicity rate = 30%
a=1; b=1; k1=1; k2=1.5; pow=1 per [1].

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

If enrollment expands to 14 subjects for a dose level, and ≤5 of the 14 subjects develop a DLT, then the dose confirmation will stop. If enrollment expands to 14 subjects for a dose level and >5/14 subjects develop a DLT, then the next lower dose may be expanded to further explore the dose-response relationship. Note that while 30% has been the target toxicity rate used to generate the guidelines in Table 4 the observed rate of subjects with DLT at the MTD may be slightly above or below 30%.

5.2.2 Definition of Dose Limiting Toxicity

DLT's will be defined from toxicities observed during the first cycle of treatment (21 days) for each dose level. See Section 5.2.4 for rules on replacement of subjects in the DLT period.

The occurrence of any of the following toxicities during Cycle 1, if assessed by the Investigator to be possibly, probably or definitely related to study drug (MK-1248 in Arm 1 or the MK-1248 with pembrolizumab combination in Arm 2), will be considered a DLT:

1. Grade 4 non-hematological toxicity (not laboratory)
2. Grade 4 hematological toxicity lasting ≥7 days, except thrombocytopenia
    a. Grade 4 thrombocytopenia of any duration
    b. Grade 3 thrombocytopenia is a DLT if associated with bleeding:
3. Any Grade 3 non-hematological toxicity (not laboratory), with the exception of Grade 3 nausea, vomiting or diarrhea, which will not be considered a DLT unless lasting more than 3 days despite optimal supportive care
4. Any Grade 3 or Grade 4 non-hematological laboratory abnormality, if
    - medical intervention is required, or
    - the abnormality leads to hospitalization, or
    - the abnormality persists for >1 week
5. Febrile neutropenia Grade 3 or Grade 4
6. Any drug-related AE which caused subject to discontinue treatment during Cycle 1
7. Grade 5 toxicity
8. Any treatment-related toxicity which causes a greater than 2 week delay in initiation of Cycle 2

5.2.3 Guidelines for Dose Modification due to Adverse Events

5.2.3.1 Dose Modification and Toxicity Management for Adverse Events Associated with MK-1248 and/or Pembrolizumab

The Common Terminology Criteria for Adverse Events version 4.0 (CTCAE 4.0) must be used to grade the severity of adverse events.

The Investigator may attribute each toxicity event to MK-1248 alone, pembrolizumab alone, or to the combination of both treatments and modify the dose as appropriate. If a dose reduction for toxicity occurs with any agent, the dose may not be re-escalated. Dose modifications are always based on the previous cycle. Reduction or holding of 1 agent and not the other agent is appropriate if, in the opinion of the Investigator, the toxicity is clearly related to one of the study drugs. For subject convenience in Arm 2, if 1 drug is delayed, the second drug can be delayed until both can be administered. If, in the opinion of the Investigator, the toxicity is related to the combination of 2 agents, both drugs should be held according to the recommended dose modification guidelines.

Subjects may have 1 dose modification to MK-1248 throughout the course of the study, as described in Table 5. If further toxicity occurs or the criteria for resuming treatment are not met, the subject must be discontinued from the agent. If a subject experiences several toxicities and there are conflicting recommendations, follow the most conservative dose adjustment recommended (dose reduction appropriate to the most severe toxicity).

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

Adverse events (both non-serious and serious) associated with MK-1248 and pembrolizumab exposure may represent an immunologic etiology. These adverse events may occur shortly after the first dose to several months after the last dose of treatment.

MK-1248 will be withheld for Grade 3 thrombocytopenia associated with bleeding, Grades 3 and 4 febrile neutropenia, Grade 4 hematological toxicities lasting ≥7 days, Grade 4 thrombocytopenia of any duration, Grade ≥3 non-hematological toxicities including laboratory abnormalities, and severe or life-threatening AEs as per Table 5.

Pembrolizumab treatment interruption/discontinuation and toxicity management guidelines are described in Section 5.2.3.2 and Section 5.2.3.3.

Table 5 MK-1248 Dose Modification and Treatment Discontinuation Guidelines for Drug-Related Adverse Events

Toxicity	Hold Treatment	Criteria for Restarting Treatment	Dose/Schedule for Restarting Treatment	Criteria for Discontinuation after Consultation with Sponsor
Hematological toxicities:				
• Any Grade 1, 2, or 3 hematological toxicity except Grade 3 thrombocytopenia associated with bleeding and Grade 3 febrile neutropenia	No	N/A	N/A	N/A
• Grade 3 thrombocytopenia associated with bleeding • Grade 3 febrile neutropenia • Grade 4 hematological toxicities lasting ≥7 days • Grade 4 thrombocytopenia of any duration • Grade 4 febrile neutropenia	Yes	Toxicity resolves to Grade 0-1, or to baseline	The dose may be reduced by one dose level upon discussion with Study Team. Intervals between treatments remain unchanged	Toxicity does not resolve within 12 weeks of last dose. *Permanent discontinuation should be considered for any severe or life-threatening event*
Non-hematological toxicities:				
• Any Grade 1 non-hematological toxicity • Grade 2 alopecia • Grade 2 fatigue	No	N/A	N/A	N/A
• Any Grade 2 non-hematological toxicity except Grade 2 alopecia and Grade 2 fatigue	Consider holding for persistent symptoms	Toxicity resolves to Grade 0-1 or baseline	Clinical AE resolves within 3 weeks: treat at same dose and schedule Clinical AE does not resolve within 3 weeks: The dose may be reduced by one dose level upon discussion with Study Team. Intervals between treatments remain unchanged	Toxicity does not resolve within 12 weeks of last dose.
• Any Grade 3 or 4 non-hematological toxicity	Yes	Toxicity resolves to Grade 0-1 or baseline	The dose may be reduced by one dose level upon discussion with Study Team. Intervals between treatments remain unchanged	Toxicity does not resolve within 12 weeks of last dose. *Permanent discontinuation should be considered for any severe or life-threatening event*

In case toxicity does not resolve to Grade 0-1 within 12 weeks after last infusion, trial treatment should be discontinued after consultation with the Sponsor.

With Investigator and Sponsor agreement, subjects with a laboratory adverse event still at Grade 2 after 12 weeks may continue treatment in the trial only if asymptomatic and controlled.

After any Grade 4 drug-related adverse event, subjects should not restart trial treatment without consultation with the Sponsor; the toxicity must have resolved to Grade 0-1 or baseline prior to restarting.

5.2.3.2 Dose Interruption/Discontinuation and Toxicity Management Guidelines for Immune-Related Adverse Events Associated with Pembrolizumab

Adverse events associated with pembrolizumab exposure may represent an immunologic etiology. These irAEs may occur anywhere from shortly after the first dose to several months after the last dose of pembrolizumab treatment and may affect more than one body system simultaneously. 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 dose interruptions and administration of corticosteroids and/or other supportive care. For suspected irAEs, ensure adequate evaluation to confirm etiology and/or exclude other causes. Additional procedures or tests such as bronchoscopy, endoscopy, and/or skin biopsy may be included as part of the evaluation. Dose interruption/discontinuation and toxicity management guidelines for irAEs associated with pembrolizumab are provided in Table 6.

Table 6 Pembrolizumab Dose Interruption/Treatment Discontinuation and Toxicity Management Guidelines for Immune-Related Adverse Events

General instructions:

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

Immune-related AE	Toxicity grade or condition (CTCAEv4.0)	Action taken with pembrolizumab	irAE management with corticosteroid and/or other therapy	Monitor guideline 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
	Grade 3 or 4, or recurrent Grade 2	Permanently discontinue		
Diarrhea / Colitis	Grade 2 or 3	Withhold	• Administer corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper	• Monitor 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 suspicious for 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 by IV infusion
	Grade 4	Permanently discontinue		

Immune-related AE	Toxicity grade or condition (CTCAEv4.0)	Action taken with pembrolizumab	irAE management with corticosteroid and/or other therapy	Monitor guideline 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 liver function tests (consider weekly or more frequently) until liver enzyme values return to baseline or are stable
	Grade 3 or 4	Permanently discontinue	• Administer corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper	
Type 1 diabetes mellitus (T1DM) or Hyperglycemia	Newly onset T1DM or Grade 3 or 4 hyperglycemia associated with evidence of β-cell failure	Withhold	• Initiate insulin replacement therapy for 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 discontinue1		
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 discontinue1		
Hypothyroidism	Grades 2-4	Continue	• Initiate thyroid replacement hormones (eg, levothyroxine or liothyroinine) per standard of care	• Monitor for signs and symptoms of thyroid disorders
Nephritis and Renal dysfunction	Grade 2	Withhold	• Administer corticosteroids (prednisone 1-2 mg/kg or equivalent) followed by taper	• Monitor changes of renal function
	Grade 3 or 4	Permanently discontinue		
Myocarditis	Grade 1 or 2	Withhold	• Based on severity of AE, administer corticosteroids	• Ensure adequate evaluation to confirm etiology and/or exclude other causes
	Grade 3 or 4	Permanently discontinue		

Immune-related AE	Toxicity grade or condition (CTCAEv4.0)	Action taken with pembrolizumab	irAE management with corticosteroid and/or other therapy	Monitor guideline and follow-up
All other immune-related AEs	Intolerable/ persistent Grade 2	Withhold	• Based on type and severity of AE, administer corticosteroids	• Ensure adequate evaluation to confirm etiology and/or exclude other causes
	Grade 3	Withhold or permanently discontinue based on the type of event. Events that require discontinuation include but are not limited to: Gullain-Barre Syndrome, encephalitis		
	Grade 4 or recurrent Grade 3	Permanently discontinue		
1. The decision to withhold or permanently discontinue pembrolizumab is at the discretion of the investigator or treating physician. **NOTE:** For participants with Grade 3 or 4 immune-related endocrinopathy where pembrolizumab is withheld, pembrolizumab may be resumed when AE resolves to Grade ≤2 and is controlled with hormonal replacement therapy, or metabolic control is achieved (in case of T1DM).				

5.2.3.3 Toxicity Management of Infusion Reactions Related to Pembrolizumab

Pembrolizumab may cause severe or life-threatening infusion reactions including severe hypersensitivity or anaphylaxis. Signs and symptoms usually develop during or shortly after drug infusion and generally resolve completely within 24 hours of completion of the infusion. Toxicity management guidelines for pembrolizumab-associated infusion reactions are provided in Table 7.

Table 7 Pembrolizumab 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/hr to 50 mL/hr). 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 hous (± 30 minutes) prior to infusion of pembrolizumab 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		

5.2.4 Replacement of Subjects During DLT Evaluation Period

In order to determine safety, all subjects selected must meet the criteria for evaluability for Cycle 1. Subjects are considered non-evaluable for DLT assessment and will be replaced if:

- They are enrolled but not treated
- They discontinue from the trial prior to completing all the safety evaluations for reasons other than treatment-related adverse events
- They receive less than 90% of the total MK-1248 or pembrolizumab infusion in Cycle 1 (e.g., because the infusion had to be discontinued due to an infusion reaction) and did not experience a DLT

Non-evaluable subjects will not be counted toward the cohort total for DLT evaluation.

If a subject experiences a DLT in Cycle 1, study treatment may be discontinued following discussion between the sponsor and Investigator. However, if the subject is deriving clinical

benefit from the study treatment, the subject may be allowed to continue after discussion between the sponsor and the Investigator.

5.2.5 Timing of Dose Administration

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

In Arm 2, pembrolizumab will be administered first on Day 1 of each cycle, with administration of MK-1248 occurring approximately 30 minutes after completion of the pembrolizumab administration.

Based on preliminary safety information from the ongoing study, the Sponsor recommends that all subjects be prophylactically pre-medicated, 1.5 hours (± 30 minutes) before infusion with MK-1248, with the following:

(1) Dexamethasone, 8 mg intravenously;

(2) Acetaminophen, 1000 mg orally; and

(3) Loratadine, 10 mg orally.

5.2.6 Trial Blinding/Masking

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

5.3 Randomization or Treatment Allocation

Treatment allocation by non-random assignment to Arm 1 or Arm 2 will occur centrally using an IVRS/IWRS. Allocation to a treatment arm will take into consideration whether or not a treatment arm is open to allocation based on minimizing enrollment time, ensuring minimum number of days between each study-wide allocated subject for a given dose, and sequencing Arm 2 relative to the study-wide results of Arm 1.

Note: Enrollment into this study has been prematurely discontinued due to program prioritization and not related to any safety concerns. The cut-off date for enrollment is 31-Mar-2017. Subjects who are ongoing in the study after that date and who do not yet meet established protocol discontinuation criteria, as outlined in Section 5.8, will continue to attend study visits and be followed per protocol. Subjects who are ongoing in the study after that date and who do not yet meet established treatment discontinuation criteria, as outlined in Section 5.8, may continue to receive study treatment per protocol, provided the investigator feels such treatment is in the best interest of the subject.

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)

5.5.1 Acceptable Concomitant Medication

Drugs specifically prohibited in the exclusion criteria are not allowed during the ongoing trial. Listed below are some specific restrictions for concomitant therapy use during the course of the trial. If there is a clinical indication for one of these or other medications specifically prohibited during the trial, discontinuation from trial therapy may be required. The investigator should discuss any questions regarding this with the Sponsor. The final decision on any supportive therapy rests with the investigator and/or the subject's primary physician. However, the decision to continue the subject on trial therapy requires the mutual agreement of the investigator, the Sponsor and the subject. All treatments that the investigator considers necessary for a subject's welfare may be administered at the discretion of the investigator in keeping with the community standards of medical care. All concomitant medication will be recorded on the case report form (CRF) including all prescription, over-the-counter (OTC), herbal supplements, and IV medications and fluids. If changes occur during the trial period, documentation of drug dosage, frequency, route, and date will also be included on the CRF.

Palliative and supportive care is permitted during the course of the trial for underlying medical conditions and management of symptoms. Surgery or radiotherapy for tumor control is not permitted during the study; however, radiotherapy or procedures for symptom management is allowed.

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

5.5.2 Prohibited Concomitant Medications

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

- Immunotherapy not specified in this protocol.
- Antineoplastic systemic chemotherapy or biological therapy.
- Investigational agents not specified in this protocol.
- Radiation therapy; radiotherapy for symptom management is allowed.
- Live vaccines within 30 days prior to the first dose of 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, BCG, and typhoid vaccine. Seasonal influenza vaccines for injection are generally killed virus vaccines and are allowed. However, intranasal influenza vaccines (e.g. FluMist®) are live attenuated vaccines, and are not allowed.

- Glucocorticoids for any purpose other than to modulate symptoms from an event of clinical interest. Chronic systemic replacement doses of steroids are allowed. Inhaled steroids for management of asthma are allowed.

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

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

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

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-1248 and/or pembrolizumab, 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.

5.7 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-1248 and pembrolizumab may have adverse effects on a fetus in utero. Furthermore, it is not known if either drug has transient adverse effects on the composition of sperm. Non-pregnant, non-breast-feeding women may be enrolled if they are considered highly unlikely to conceive. Highly unlikely to conceive is defined as 1) surgically sterilized, or 2) postmenopausal (a woman who is ≥45 years of age and has not had menses for greater than 1 year will be considered postmenopausal), or 3) not heterosexually active for the duration of the study. The 2 birth control methods can be either 2 barrier methods or a barrier method plus a hormonal method to prevent pregnancy.

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

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

5.7.3 Use in Pregnancy

If a subject inadvertently becomes pregnant while on treatment with MK-1248 or pembrolizumab, the subject will immediately be removed from the study. The site will contact the subject at least monthly and document the subject's status until the pregnancy has been completed or terminated. The outcome of the pregnancy will be reported to the SPONSOR without delay and within 24 hours if the outcome is a serious adverse experience (e.g., death, abortion, congenital anomaly, or other disabling or life-threatening complication to the mother or newborn). The study investigator will make every effort to obtain permission to follow the outcome of the pregnancy and report the condition of the fetus or newborn to the SPONSOR. If a male subject impregnates his female partner the study personnel at the site must be informed immediately and the pregnancy reported to the SPONSOR and followed as described above and in Section 7.2.2.

5.7.4 Use in Nursing Women

It is unknown whether MK-1248 or pembrolizumab is excreted in human milk. Since many drugs are excreted in human milk, and because of the potential for serious adverse reactions in the nursing infant, subjects who are breast-feeding are not eligible for enrollment.

5.8 Subject Withdrawal/Discontinuation Criteria

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

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

Note: Subjects who discontinue treatment for reasons other than PD will have post-treatment follow-up for disease status until PD, initiating a non-study cancer treatment, withdrawing consent, or becoming lost to follow-up.

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

- The subject or legal representative (such as a parent or legal guardian) withdraws consent.
- Confirmed disease progression

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

- The subject withdraws consent for treatment
- Confirmed disease progression
- Unacceptable adverse events (See Dose Modification Section 5.2.3)
- Intercurrent illness that prevents further administration of treatment
- Investigator's decision to withdraw subject
- Subject has confirmed positive serum pregnancy test
- Noncompliance with study treatment or procedure requirements
- Administrative reasons
- Completed treatment as defined in this protocol

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5.9 Subject Replacement Strategy

A subject who discontinues from the trial will not be replaced except as described in Section 5.2.4 Replacement of Subjects During DLT Evaluation Period.

5.10 Beginning and End of the Trial

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

5.11 Clinical Criteria for Early Trial Termination

There are no pre-specified criteria for terminating the trial early.

6.0 TRIAL FLOW CHART

Note: Enrollment into this study has been prematurely discontinued due to program prioritization and not related to any safety concerns. The cut-off date for enrollment is 31-Mar-2017. Subjects who are ongoing in the study after that date and who do not yet meet established protocol discontinuation criteria, as outlined in Section 5.8, will continue to attend study visits and be followed per protocol. Subjects who are ongoing in the study after that date and who do not yet meet established treatment discontinuation criteria, as outlined in Section 5.8, may continue to receive study treatment per protocol, provided the investigator feels such treatment is in the best interest of the subject.

	Screening Phase	Treatment Phase Cycle = 21 days															End of Treatment	Post Treatment Phase		
Treatment Cycle/Title	Screening (Visit 1)	Cycle 1						Cycles 2-4[1]						Cycles 5 and 6 (Arm 2 only)[1]	Cycle 7 and Beyond (Arm 2 only)[1]	Discon	Safety Follow-up	Follow-up	
Cycle Day		1	2	3	5	8	15	1	2	3	5	8	15	9 weeks after 1st dose	1	1		30 days after last dose	3 and 6 months after last dose	Every 9 weeks until PD
Scheduling Window (Days)	-28 to -1				+/- 3	+/- 3	+/- 3				+/- 3	+/- 3	+/- 3	+/- 7				+/- 7	+/- 7	+/- 7
Administrative Procedures																				
Informed Consent[2]	X																			
Informed Consent for Future Biomedical Research[3]	X																			
Inclusion/Exclusion Criteria	X																			
Subject Identification Card	X																			
Demographics and Medical History	X																			
Concomitant Medication Review	X	X	X			X	X	X	X			X	X		X	X	X	X		
Prior Oncology Treatment	X																			

	Screening Phase	Treatment Phase Cycle = 21 days															End of Treatment	Post Treatment Phase		
Treatment Cycle/Title	Screening (Visit 1)	Cycle 1						Cycles 2-4[1]							Cycles 5 and 6 (Arm 2 only)[1]	Cycle 7 and Beyond (Arm 2 only)[1]	Discon	Safety Follow-up	Follow-up	
Cycle Day		1	2	3	5	8	15	1	2	3	5	8	15	9 weeks after 1st dose	1	1		30 days after last dose	3 and 6 months after last dose	Every 9 weeks until PD
Scheduling Window (Days)	-28 to -1				+/- 3	+/- 3	+/- 3				+/- 3	+/- 3	+/- 3	+/- 7				+/- 7	+/- 7	+/- 7
History																				
MK-1248 Drug Administration (Arms 1 & 2)[4]		X						X												
Pembrolizumab Drug Administration (Arm 2 only)[5]		X						X							X	X				
Clinical Procedures/Assessments																				
Adverse Events Monitoring	X	X	X	X		X	X	X	X	X		X	X		X	X				
Full Physical Examination	X	X[6]						X[6]							X[6]	X[6]	X	X		X
Height	X																			
Weight	X	X						X							X	X	X	X		
Vital Signs (temperature, pulse, respiratory rate, blood pressure)[7]	X	X	X	X		X	X	X	X	X		X	X		X	X	X	X		
12-Lead Electrocardiogram[8]	X	X[6]						X[6]												
ECOG Performance Status	X	X[6]						X[6]							X[6]	X[6]	X	X		
Tumor Imaging and irRECIST Response Assessment[9]	X													X	X	X				X
Survival Status[10]		←																		→

	Screening Phase	Treatment Phase Cycle = 21 days															End of Treatment	Post Treatment Phase		
Treatment Cycle/Title	Screening (Visit 1)	Cycle 1						Cycles 2-4[1]							Cycles 5 and 6 (Arm 2 only)[1]	Cycle 7 and Beyond (Arm 2 only)[1]	Discon	Safety Follow-up	Follow-up	
Cycle Day		1	2	3	5	8	15	1	2	3	5	8	15	9 weeks after 1st dose	1	1		30 days after last dose	3 and 6 months after last dose	Every 9 weeks until PD
Scheduling Window (Days)	-28 to -1				+/- 3	+/- 3	+/- 3				+/- 3	+/- 3	+/- 3	+/- 7				+/- 7	+/- 7	+/- 7
Laboratory Procedures/Assessments –Analysis by Local Lab																				
CBC with differential	X[11]	X[6, 12]	X			X	X	X[6,12]				X	X		X[6, 12]	X[6, 12]	X	X		
C Reactive Protein	X[11]	X[6, 12]	X			X	X	X[6, 12]				X	X		X[6, 12]					
PT/INR and aPTT	X[11]																			
Chemistry Panel	X[11]	X[6, 12]	X			X	X	X[6, 12]				X	X		X[6, 12]	X[6, 12]	X	X		
LDH, GGT	X[11]	X[6]						X[6]							X[6]					
Pregnancy Test – Urine or Serum β-hCG, if applicable[13]	X	X[13]																		
Immunoglobulins (IgA, IgG, IgM)		X[6]						X[6]							X[6]					
Urinalysis	X[11]																			
Thyroid Function (T4, T3, TSH)[14]		X[6]						X[6]							X[6]	X[6]		X		
HIV, Hepatitis B and C[15]	X																			

	Screening Phase	Treatment Phase Cycle = 21 days															End of Treatment	Post Treatment Phase		
Treatment Cycle/Title	Screening (Visit 1)	Cycle 1						Cycles 2-4[1]							Cycles 5 and 6 (Arm 2 only)[1]	Cycle 7 and Beyond (Arm 2 only)[1]	Discon	Safety Follow-up	Follow-up	
Cycle Day		1	2	3	5	8	15	1	2	3	5	8	15	9 weeks after 1st dose	1	1		30 days after last dose	3 and 6 months after last dose	Every 9 weeks until PD
Scheduling Window (Days)	-28 to -1				+/- 3	+/- 3	+/- 3				+/- 3	+/- 3	+/- 3	+/- 7				+/- 7	+/- 7	+/- 7
Laboratory Procedures/Assessments-Analysis to be Performed by Central Lab																				
Humoral Immunity Assays[16]		X[6]						X							X					
Cytokine Panel[17]		X[6]	X	X				X	X	X					X					
Anti-MK-1248 Antibodies (Arms 1 & 2)[18]		X[6]	X	X		X	X	X	X	X		X	X		X			X	X	
Pharmacokinetics for MK-1248 (Arms 1 & 2)[19]		X[6]	X	X	X (require for 4 lowest dose levels in Arm 1)	X	X	X	X	X	X (require for 4 lowest dose levels in Arm 1)	X	X		X			X	X	
Anti-MK-3475 Antibodies (Arm 2 only)[20]		X	X	X		X	X	X	X	X		X	X		X	X		X	X	
Pembrolizumab/MK-3475 PK (Arm 2 only)[21]		X	X	X		X	X	X	X	X		X	X		X	X		X	X	
Blood for DNA Correlative Studies[22]		X						X												

	Screening Phase	Treatment Phase Cycle = 21 days															End of Treatment	Post Treatment Phase		
Treatment Cycle/Title	Screening (Visit 1)	Cycle 1						Cycles 2-4[1]							Cycles 5 and 6 (Arm 2 only)[1]	Cycle 7 and Beyond (Arm 2 only)[1]	Discon	Safety Follow-up	Follow-up	
Cycle Day		1	2	3	5	8	15	1	2	3	5	8	15	9 weeks after 1st dose	1	1		30 days after last dose	3 and 6 months after last dose	Every 9 weeks until PD
Scheduling Window (Days)	-28 to -1				+/- 3	+/- 3	+/- 3				+/- 3	+/- 3	+/- 3	+/- 7				+/- 7	+/- 7	+/- 7
Blood for RNA Correlative Studies [22]		X						X												
Blood for Genetic Analysis [23]		X																		
Tumor Tissue Collection[24]	X																			
Post Treatment Tumor Biopsy[25]						X														
Pharmacodynamic (receptor availability flow cytometry assay (Arms 1 & 2)[26]	X	X[6]	X	X (require for MK-1248 dose levels <30mg)	X (require for 4 lowest dose levels in Arm 1)	X	X	X	X	X require for MK-1248 dose levels <30mg)	X (require for 4 lowest dose levels in Arm 1	X	X		X					

1. Trial treatment may be administered up to 3 days before or 5 days after the scheduled Day 1 of each cycle, beginning in Cycle 3. Cycle 2 Day 1 may be administered up to 5 days after the scheduled Day 1.
2. Written consent must be obtained prior to performing any protocol specific procedure. Tests performed prior to the subject signing consent as part of routine clinical management are acceptable in lieu of a screening test if performed within the specified time frame.
3. Signing the informed consent for future biomedical research (FBR) is optional, and may be signed at any time during the subject's participation in the trial. Detailed instructions for the collection and management of FBR specimens are provided in the Procedure Manual.
4. The Sponsor recommends that all subjects be prophylactically pre-medicated with 8 mg dexamethasone, intravenously, 1000 mg acetaminophen, orally, and 10 mg loratadine, orally, 1.5 hours (±30 minutes) before infusion with MK-1248.
5. In the Arm 2, pembrolizumab is administered first, then following a 30-minute interval, MK-1248 will be administered.

6. These samples and procedures required predose Day 1 may be performed up to 72 hours prior to dosing.
7. Vital signs (VS) to include temperature, pulse, respiratory rate and blood pressure. On Day 1 of Cycles 1-4 in Arm 1 and Arm 2, collect prior to dosing, at 2-hr, 4-hr and 6-hr after start of the MK-1248 infusion. In Arm 2, beginning with Cycle 5, collect VS prior to pembrolizumab dosing on Day 1 of each cycle.
8. 12-lead ECG should be performed at screening for all subjects and repeated in Arm 1 prior to and within 30 minutes after the end of the MK-1248 infusion in Cycles 1-4.
9. Tumor imaging (CT scan or MRI) should be performed within 28 days of enrollment. Tumor imaging and response assessment to be performed 9 weeks after first dose, than every 9 weeks until disease progression. Imaging assessments should be repeated every 9 weeks and follow calendar days and should not be adjusted for delays in Cycle starts or extensions of dosing frequencies. The same imaging technique should be used on a subject throughout the trial. Scans used for tumor measurements may be requested for central review.
10. Upon Sponsor request, participants may be contacted for survival status at any time during the course of the study.
11. Laboratory tests at Screening are to be performed within 7 days prior to the first dose of study treatment.
12. In Arm 1 and Arm 2, on Day 1 in cycles 1-4, CBC with differential, CRP and chemistry profile should be drawn prior to dosing and repeated 4 hours after the start of the MK-1248 infusion, with results of the CBC and chemistry profile reviewed by the PI or appropriate designee before the subject is discharged from the clinic. In Arm 2, beginning with Cycle 5, CBC with differential, CRP and chemistry profile should be drawn prior to dosing.
13. For women of reproductive potential, a urine pregnancy test will be performed at Screening and within 24 hours prior to the first dose of study treatment. If a urine pregnancy test cannot be confirmed as negative, a serum pregnancy test is required.
14. Thyroid function testing is to be performed starting in Cycle 1 and then every other cycle and at the Post treatment safety follow-up visit
15. Include HCV, RNA (qualitative) or Hepatitis C antibody, HBsAg, and HIV type 1 and type 2 (e.g., HIV-1/-2 antibody screening test and evaluation of HIV viral load as needed).
16. Collect humoral immunity assays prior to dosing in Cycles 1-4 in Arm 1 and Cycles 1-6 in Arm 2 (specific assays designated in procedures manual).
17. For Arm 1, collect cytokine panels for cycles 1-4 on day 1 predose, 1 hour and 4 hours post infusion, and on day 2 and day 3. For Arm 2, collect cytokine panels for cycles 1-4 on day 1 predose, 1 hour and 4 hours post infusion, and on day 2 and day 3. For Cycles 5 and 6, collect samples on day 1 Predose, 1hour and 4 hour post infusion.
18. MK-1248 Anti-drug antibody (ADA) will be drawn in Arm 1, predose MK-1248 on Day 1, Day 2, Day 3, Day 8 and Day 15 of Cycles 1-4, and at the Safety visit 30 days post discontinuation and at 3 months and 6 months after the last dose . In Arm 2 MK-1248 ADA will be obtained predose MK-1248 on Day 1, on Day 2, Day 3, Day 8 and Day 15 of Cycles 1-4, predose pembrolizumab Cycles 5, and 6, and at the Safety visit 30 days post discontinuation and at 3 months and 6 months after the last dose .
19. MK-1248 Pharmacokinetic (PK) samples will be drawn in each cycle on Day 1 predose MK-1248, at the end of the MK-1248 infusion (+ 10 minutes), 2h after the start of the MK-1248 infusion (+/- 10 minutes), and on Day 2, Day 3, Day 5, Day 8, and Day 15 and at the Safety visit 30 days post discon and at 3 months and 6 months after the last dose for subjects treated at the 4 lowest dose levels in Arm 1. Starting at the 30 mg dose in Arm 1 and all dose levels in Arm 2, PK samples will be drawn in each cycle on Day 1 predose MK-1248, at the end of MK-1248 infusion (+ 10 minutes), 2h after the start of the MK-1248 infusion (+/- 10 minutes), on Day 2, Day 3, Day 8, and Day 15 in Cycles 1-4 and the Safety visit 30 days post discon and at 3 months and 6 months after the last dose. In addition, in Arm 2, MK-1248 PK will be drawn predose pembrolizumab in Cycles 5, and 6. If the sample day falls on a weekend or holiday, please consult the sponsor for alternate sample collection times.
20. Pembrolizumab Anti-drug antibody (ADA) will be drawn in Arm 2 at the following timepoints: predose pembrolizumab on Day 1, on Day 2, Day 3, Day 8 and Day 15 in Cycles 1-4, predose in Cycles 5, 6, 8 and every 4 cycles thereafter, and at the Safety visit 30 days post discontinuation and at 3 months and 6 months after the last dose.
21. Pembrolizumab Pharmacokinetic (PK) samples will be drawn in Arm 2, Cycles 1-4 Day 1 predose pembrolizumab, at the end of the Pembrolizumab infusion (+10 minutes) at the end of MK-1248 infusion (+ 10 minutes), 2h after the start of the MK-1248 infusion (+/- 10 minutes), and on Day 2, Day 3, Day 8, and Day 15, predose in Cycles 5, 6, 8 and every 4 cycles thereafter, at the Safety visit 30 days post discon and at 3 months and 6 months after the last dose.. If the sample day falls on a weekend or holiday, please consult the sponsor for alternate sample collection times.

22. Blood for correlative studies (RNA and DNA samples) will be drawn prior to dosing on Cycle 1 Day 1 and prior to dosing on Cycle 2 Day 1 or Cycle 1 Day 22 for subjects who do not receive a second dose of MK-1248. Detailed instructions for the collection and management of these samples are provided in the Procedure Manual.
23. This sample should be drawn for planned analysis of the association between genetic variants in DNA and drug response. If there is either a documented law or regulation prohibiting collection, or if the IRB/IEC does not approve the collection of the sample for these purposes, then this sample will not be collected at that site. If the sample is collected, leftover extracted DNA will be stored for future biomedical research if the subject signs the FBR consent. If the planned genetic analysis is not approved, but FBR is approved and consent is given, this sample will be collected for the purpose of FBR
24. Tumor tissue (archival or newly obtained biopsy) will be required at Screening in Parts B, C, D, and E. Leftover tissue may also be saved for future biomedical research if the subject signs the Future Biomedical Research consent.
25. Post treatment tumor biopsy is optional, but strongly encouraged in Parts B, C, D, and E, in Cycle 1 between Day 8 and Day 15. Leftover tissue may also be saved for future biomedical research if the subject signs the Future Biomedical Research consent.
26. In Arm 1, blood sample for pharmacodynamic (PD) will be drawn in Screening, in Cycles 1-4 on Day 1 pre-dose MK-1248, at the end of MK-1248 infusion (+ 10 minutes), 2h after the start of the MK-1248 infusion (+/- 10 minutes), on Day 2, Day 8, and Day 15; on Day 3 dose level <30 mg, Day 5 required for 4 lowest dose levels. In case of DLT, starting at the 5th dose level in Arm 1, PD samples will be drawn in Screening, in Cycles 1-4 on Day 1 pre-dose MK-1248, at the end of the MK-1248 infusion (+ 10 minutes), 2h after the start of the MK-1248 infusion (+/- 10 minutes), on Day 2, Day 3, Day 8, and Day 15. For all dose levels in Arm 2, PD samples will be drawn at screening , in Cycles 1-4 on Day 1 pre-dose pembrolizumab, at the end of the MK-1248 infusion (+ 10 minutes), 2h after the start of the MK-1248 infusion (+/- 10 minutes), on Day 2, Day 3, Day 8, and Day 15. In Arm 2, Day 5 will not be drawn for any dose levels. Day 3 will be drawn for MK-1248 doses <30 mg. In addition, in Arm 2 PD samples will be drawn pre-dose pembrolizumab in Cycles 5-6.

7.0 TRIAL PROCEDURES

7.1 Trial Procedures

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

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

7.1.1 Administrative Procedures

7.1.1.1 Informed Consent

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

7.1.1.1.1 General Informed Consent

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

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

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

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

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

7.1.1.1.2 Consent and Collection of Specimens for Future Biomedical Research

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

7.1.1.2 Inclusion/Exclusion Criteria

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

7.1.1.3 Subject Identification Card

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

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

7.1.1.4 Medical History

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

7.1.1.5 Disease Details

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

7.1.1.6 Prior Oncology Treatment History

The Investigator or qualified designee will record all prior cancer treatments including systemic treatments, radiation and surgeries.

7.1.1.7 Prior and Concomitant Medications Review

7.1.1.7.1 Prior Medications

The investigator or qualified designee will review prior medication use, including any protocol-specified washout requirement, and record prior medication taken by the subject within 30 days before starting the trial. Treatment for the disease for which the subject has

been enrolled in this trial will be recorded separately and should not be listed in prior medications.

7.1.1.7.2 Concomitant Medications

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

7.1.1.8 Assignment of Screening Number

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

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

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

7.1.1.9 Assignment of Randomization Number

All eligible subjects will be allocated, by non-random assignment, and will receive a randomization number. The randomization number identifies the subject for all procedures occurring after treatment allocation. While the subjects are being allocated to their treatment, and not 'randomized', this unique number is termed a randomization number throughout the protocol for operational purposes. Allocation of subjects between the two arms will be managed by the Sponsor through an IVRS. Once a randomization number is assigned to a subject, it can never be re-assigned to another subject.

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

7.1.1.10 Trial Compliance (Study Drug Administration)

Interruptions from the protocol specified treatment for $\geq$28 days require consultation between the investigator and the Sponsor and written documentation of the collaborative decision on subject management.

All doses of MK-1248 and pembrolizumab will be administered under the supervision of a qualified physician and/or designee experienced in the use of anticancer agents.

Instructions for preparing and administering study drugs will be provided in the Procedure Manual.

7.1.2 Clinical Procedures/Assessments

7.1.2.1 Adverse Event (AE) Monitoring

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

All AEs of unknown etiology associated with MK-1248 and pembrolizumab exposure should be evaluated to determine if it is possibly an event of clinical interest (ECI) of a potential immunologic etiology (irAE). See Section 5.2.3.2 regarding the identification, evaluation and management of AEs of a potential immunological etiology.

This is a dose escalation trial to establish the MTD of MK-1248 alone and in combination with pembrolizumab; therefore, each dose escalation will be based on the safety and tolerability experienced by subjects at each dose level. The safety and tolerability of each cohort for the DLT evaluation period will be reviewed prior to the start of the next cohort. The Sponsor and the Principal Investigators or Sub-Investigators will review the safety and tolerability of each study treatment, the appropriateness of dose escalation, when each cohort is completed and the next cohort is opened for enrollment. Frequency of these communications will depend on the enrollment of each cohort, as well as any potential new information regarding a safety concern in this trial or other relevant trials.

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

7.1.2.2 Full Physical Examination

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

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

7.1.2.3 Vital Signs and Weight

Vital signs should include temperature, pulse, respiratory rate, blood pressure, and weight at the frequency defined in the Study Flow Chart (Section 6.0).

Height will be obtained at Screening only.

7.1.2.4 Electrocardiogram (ECG)

A standard 12-lead ECG will be performed using local standard procedure at Screening, with any clinically significant abnormal findings recorded as medical history.

Additional timepoints for ECGs are according to the Study Flow Chart (Section 6.0). Clinically significant abnormal findings seen on all ECGs performed after Screening should be recorded as AEs.

7.1.2.5 Eastern Cooperative Oncology Group (ECOG) Performance Status

The investigator or qualified designee will assess the ECOG performance status as the timepoints specified in the Study Flow Chart (Section 6.0).

7.1.2.6 Tumor Imaging

The initial CT scan or MRI for tumor imaging must be performed within 28 days prior to enrollment, and the site study team must confirm the subject has measurable disease as defined by RECIST version 1.1 to confirm eligibility.

Tumor imaging performed should be repeated every 9 weeks from the first dose of treatment until confirmed disease progression, the start of new anti-cancer therapy, withdrawal of consent, death, or end of the study, whichever is earlier.

The same imaging technique should be performed at each timepoint.

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

7.1.2.7 Response Assessment

7.1.2.7.1 Immune-related RECIST (irRECIST)

RECIST 1.1 will be adapted to account for the unique tumor response characteristics seen with treatment with pembrolizumab and MK-2148. Immunotherapeutic agents such as pembrolizumab may produce antitumor effects by potentiating endogenous cancer-specific immune responses. The response patterns seen with such an approach may extend beyond the typical time course of responses seen with cytotoxic agents, and can manifest a clinical response after an initial increase in tumor burden or even the appearance of new lesions. Standard RECIST may not provide an accurate response assessment of immunotherapeutic agents such as pembrolizumab and MK-1248. Immune-related RECIST (irRECIST) is RECIST 1.1 adapted as described below to account for the unique tumor response seen with immuno-therapeutics. irRECIST will be used by site investigators to assess tumor response and progression, and make treatment decisions.

Therefore, RECIST 1.1 will be used with the following adaptations:

If radiologic imaging by local radiology shows initial PD, tumor assessment should be repeated ≥4 weeks later in order to confirm PD with the option of continuing treatment per below while awaiting radiologic confirmation of progression.

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

If repeat imaging confirms PD due to any of the scenarios list below, subjects will be discontinued from study therapy and the initial date of Progression recorded as the PD date.

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

Scenarios where PD is confirmed at repeat imaging:

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

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

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

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

NOTE: In subjects who discontinue study therapy without documented disease progression, every effort should be made to continue monitoring their disease status by radiologic imaging every 9 weeks (± 7 days) until (1) the start of new anti-cancer treatment, (2) disease progression (3) death, or (4) the end of the study, whichever is earlier.

Confirmation of partial response (PR) and complete response (CR) is required at least 4 weeks after the initial response assessment of PR and CR.

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.

7.1.3.1 Laboratory Safety Evaluations (Hematology, Chemistry and Urinalysis)

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

Table 8 Laboratory Tests

Hematology	Chemistry	Urinalysis	Other
Hematocrit	Albumin	Blood	
Hemoglobin	Alkaline phosphatase	Glucose	Serum β-human chorionic gonadotropin (β-hCG)
Platelet count	Alanine aminotransferase (ALT)	Protein	Hepatitis HBsAg
WBC (total and differential)	Aspartate aminotransferase (AST)	Specific gravity	Hepatitis C (HCV RNA) or Hepatitis C antibody
RBC	Bicarbonate or carbon diaoxide (CO_2)	Microscopic exam, if abnormal results are noted	HIV
PT or INR	Calcium	Urine pregnancy test, if required	IgA, IgG, IgM
aPTT	Chloride		Free thyroxine (T4)
	Creatinine		Thyroid Stimulating Hormone (TSH)
	Glucose		Total Triiodothyronine (T3)
	Gamma Glutamyl transpeptidase (GGT)		C reactive protein (CRP)
	Lactate dehydrogenase (LDH)		
	Phosphorus		
	Potassium		
	Sodium		
	Total Bilirubin		
	Direct Bilirubin, if total bilirubin is elevated above the upper limit of normal		
	Total protein		
	Blood Urea Nitrogen		
	Uric Acid		

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

7.1.3.2 Blood for Correlative DNA/RNA

Blood for correlative studies (RNA and a separate DNA sample) will be obtained as indicated in Section 6.0.

Sample collection, storage and shipment instructions for correlative study samples will be provided in the Procedure Manual.

7.1.4 Pharmacokinetic/Pharmacodynamic Evaluations

7.1.4.1 Blood Collection for MK-1248 and Pembrolizumab PK

To evaluate the exposure of MK-1248 and pembrolizumab in this indication, sample collections for analysis of PK are currently planned as shown in the Trial Flow Chart. Blood samples for PK collected may be stored. Analysis will be performed only if required. If ongoing PK sampling is deemed to be unnecessary by the Sponsor, it may be reduced or discontinued.

7.1.4.2 Blood Collection for Anti-MK-1248 Antibodies and Anti-Pembrolizumab Antibodies (ADA)

To evaluate the immunogenicity of MK-1248 and pembrolizumab in this indication, sample collections for analysis of ADAs are currently planned as shown in the Trial Flow Chart. Blood samples for ADA collected may be stored. Analysis will be performed only if required. If ongoing ADA sampling is deemed to be unnecessary by the Sponsor, it may be reduced or discontinued.

7.1.4.3 Blood for Receptor Availability Assay (PD)

Sample collection, storage and shipment instructions for PD blood samples will be provided in the Procedure Manual.

The timepoints for PD sampling are described in Section 6.0-Trial Flow Chart. If the sample day falls on a holiday or weekend, please consult the sponsor for alternate collection day.

Once the PD Receptor Availability Assay indicates saturation of the receptor, then the SPONSOR may elect to not collect samples for this PD assay at higher doses. In this case, the SPONSOR will notify study sties by administrative memo that this sample will no longer be collected. Decision to stop collection of blood for the receptor Availability Assay will be made independently for Arms 1 and 2.

7.1.4.4 Tumor Tissue Collection

All subjects will be required to provide a tumor sample (archival or newly obtained sample) at Screening in Parts B, C, D, and E. Samples will be sent to a central lab.

Submission of formalin-fixed paraffin embedded tumor tissue sample blocks are preferred; if submitting unstained slides, the slides should be freshly cut and submitted to the testing laboratory within 14 days from site slide sectioning date otherwise a new specimen will be requested.

Post treatment tumor biopsy is optional, but strongly encouraged in Parts B, C, D, and E, in Cycle 1 between Day 8 and Day 15. Leftover tissue may also be saved for future biomedical research if the subject signs the Future Biomedical Research consent.

If the subject signs the Future Biomedical Research (FBR) consent, any leftover tissue that would ordinarily be discarded at the end of the main study will be retained for FBR. Details regarding time points for collection of tumor tissue are outlined in the Study Flow Chart – Section 6.0.

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

7.1.5 Planned Genetic Analysis Sample Collection

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

7.1.6 Future Biomedical Research

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

- Leftover tumor for future research
- Leftover main study DNA from Blood for Genetic Analysis stored for future research

7.1.7 Other Procedures

7.1.7.1 Withdrawal/Discontinuation

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

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

7.1.7.1.1 Withdrawal From Future Biomedical Research

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

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

7.1.7.2 Blinding/Unblinding

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

7.1.7.3 Calibration of Critical Equipment

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

Critical Equipment for this trial includes:

- Laboratory equipment as required for inclusion labs and trial assessments
- Imaging equipment as required for study objectives
- ECG equipment as required for trial assessments
- Infusion pump and/or syringe pump used to administer study treatment

7.1.8 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.

7.1.8.1 Screening

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

Screening procedures may be repeated after consultation with the Sponsor.

7.1.8.2 Treatment Period

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

After a screening phase of up to 28 days, eligible subject will be assigned to one of 2 Arms and a dose level of MK-1248 by IVRS. In Arms 1 and 2, MK-1248 treatment will be administered on Day 1 of each 21-day cycle for up to a maximum of 4 cycles. In Arm 2, pembrolizumab will be administered on Day 1 of each 21 day cycle for up to 24 months of treatment.

Subjects will be followed until confirmed disease progression, unacceptable adverse event(s), intercurrent illness that prevents further administration of treatment, investigator's decision

to withdraw the subject, subject withdraws consent, pregnancy of the subject, noncompliance with study treatment or procedure requirements, or administrative reasons.

7.1.8.3 Post-Treatment Visits

7.1.8.3.1 Safety Follow-Up Visit

The mandatory Safety Follow-Up Visit should be conducted approximately 30 days after the last dose of study treatment or before the initiation of a new antineoplastic treatment, whichever is earlier. Subjects with an AE of Grade >1 will be further followed until the resolution of the AE to Grade 0-1 or until beginning of a new antineoplastic therapy, whichever is earlier.

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

7.1.8.3.2 Follow-Up Visits

Subjects who complete treatment or who discontinue study treatment for a reason other than disease progression, will move into the Follow-Up Phase and should be assessed every 9 weeks (± 7 days) by radiologic imaging to monitor disease status. Every effort should be made to collect information regarding disease status until the start of new anti-neoplastic therapy, disease progression, death, or end of the study.

7.1.8.4 Survival Status

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

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

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

For purposes of this trial, an overdose will be defined as any dose exceeding the prescribed dose for MK-1248 by 20%, or a pembrolizumab dose of ≥1000mg (≥5x the indicated dose). No specific information is available on the treatment of overdose of MK-1248 or pembrolizumab. In the event of overdose, MK-1248 or pembrolizumab should be discontinued and the subject should be observed closely for signs of toxicity. Appropriate supportive treatment should be provided if clinically indicated.

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

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

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

7.2.2 Reporting of Pregnancy and Lactation to the Sponsor

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

Pregnancies and lactations that occur after the consent form is signed but before randomization/treatment allocation must be reported by the investigator if they cause the

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

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

7.2.3 Immediate Reporting of Adverse Events to the Sponsor

7.2.3.1 Serious Adverse Events

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

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

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

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

Refer to Table 9 for additional details regarding each of the above criteria.

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

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

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

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

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

7.2.3.2 Events of Clinical Interest

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

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

For the time period beginning at randomization/treatment allocation through 90 days following cessation of treatment, or 30 days following cessation of treatment if the subject initiates new anticancer therapy, whichever is earlier, any ECI, or follow up to an ECI, whether or not related to the Sponsor’s product, must be reported within 24 hours to the Sponsor, either by electronic media or paper. Electronic reporting procedures can be found in the EDC data entry guidelines. Paper reporting procedures can be found in the Investigator Trial File Binder (or equivalent).

Events of clinical interest for this trial include:

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

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

7.2.4 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 9 Evaluating Adverse Events

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

V4.0 CTCAE Grading	**Grade 1**	**Mild; asymptomatic or mid symptoms; clinical or diagnostic observations only; intervention not indicated.**
	Grade 2	**Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL.**
	Grade 3	**Severe or medically significant but not immediately life-threatening; hospitalization or prolongation or hospitalization indicated; disabling; limiting self-care ADL.**
	Grade 4	**Life threatening consequences; urgent intervention indicated.**
	Grade 5	**Death related to AE**
Seriousness	A serious adverse event is any adverse event occurring at any dose or during any use of Sponsor's product that:	
	†**Results in death**; or	
	†**Is life threatening; or** places the subject, in the view of the investigator, at immediate risk of death from the event as it occurred (Note: This does not include an adverse event that, had it occurred in a more severe form, might have caused death.); or	
	†**Results in a persistent or significant disability/incapacity** (substantial disruption of one's ability to conduct normal life functions); or	
	†**Results in or prolongs an existing inpatient hospitalization** (hospitalization is defined as an inpatient admission, regardless of length of stay, even if the hospitalization is a precautionary measure for continued observation. (Note: Hospitalization for an elective procedure to treat a pre-existing condition that has not worsened is not a serious adverse event. A pre-existing condition is a clinical condition that is diagnosed prior to the use of a Merck product and is documented in the patient's medical history.); or	
	†**Is a congenital anomaly/birth defect** (in offspring of subject taking the product regardless of time to diagnosis);or	
	Is a cancer (although not serious per ICH definition, is reportable to the Sponsor within 24 hours to meet certain local requirements); **or**	
	Is associated with 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.

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8.0 STATISTICAL ANALYSIS PLAN

8.1 Statistical Analysis Plan Summary

This section contains a brief summary of the statistical analyses for this trial. Full details are provided in the remainder of Section 8.

Study Design Overview	Phase 1 Trial of Single Agent MK-1248 and MK-1248 in combination with Pembrolizumab in Subjects With Advanced Solid Tumors
Analysis Populations	Safety: All Subjects as Treated (ASaT) Efficacy (exploratory): Single Agent MK-1248 Full Analysis Set (FAS1), MK-1248 in combination with Pembrolizumab Full Analysis Set (FAS2)
Primary Endpoint(s)	Safety: DLT
Key Secondary Endpoints	PK parameters of single agent MK-1248 and MK-1248 in combination with pembrolizumab and PK parameters of pembrolizumab for subjects treated with MK-1248 in combination with pembrolizumab; target engagement as measured by modulation in peripheral blood GITR receptor availability alone and in combination with pembrolizumab
Statistical Methods for Key Efficacy/Immunogenicity/ Pharmacokinetic Analyses	Serum concentrations of MK-1248 in the MK-1248 monotherapy arm and serum concentrations of MK-1248 and pembrolizumab in the MK-1248 and pembrolizumab combination arm will be summarized by planned visit and time for each dose separately; PK parameters will be summarized by dose
Treatment Assignment	Subjects are allocated to increasing doses of single agent MK-1248 and MK-1248 co-administered with pembrolizumab without randomization centrally through IVRS; the study is open-label
Statistical Methods for Key Safety Analyses	Summary statistics (counts, percentage, mean, standard deviation, etc.) will be provided for the safety endpoints as appropriate. The estimate of the DLT rate among subjects treated with the recommended MK-1248 Phase 2 dose and the 95% Bayesian Probability Interval (PI) for the estimate will be provided.
Interim Analyses	Study has no interim analyses
Multiplicity	No multiplicity adjustment is planned in this Phase 1/1b study.
Sample Size and Power	The sample size of the dose acceleration, dose escalation, and dose confirmation (Parts A-E) depends on the observed DLT profiles of MK-1248 monotherapy and MK-1248 co-administered with pembrolizumab. The sample size of 96 subjects that will be obtained if no DLTs are observed will be used for study planning purposes. In certain low probability scenarios, more than 96 subjects will be needed.

8.2 Responsibility for Analyses/In-House Blinding

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

This trial is conducted as an open-label trial, i.e., subjects, investigators, and SPONSOR personnel will be aware of subject treatment assignments after each subject is enrolled and treatment is assigned. Allocation to treatment will not be randomized.

The database will be locked for analysis when all subjects who have not discontinued due to progression, death or withdrawal of consent are at least 6 months after their first dose.

8.3 Hypotheses/Estimation

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

8.4 Analysis Endpoints

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

8.4.1 Efficacy/Immunogenicity/Pharmacokinetics Endpoints

Efficacy endpoints and their definitions are presented in Section 8.4.3.

8.4.2 Safety Endpoints

The primary safety endpoint is DLT. Safety will be monitored by cumulative data reviews throughout the trial. The toxicities and grades experienced by subjects who have received study treatment, including adverse events (AEs), serious adverse events (SAEs) and events of clinical interest (ECIs) will be summarized. Other safety measures evaluated in all parts of the study include laboratory safety assessments, ECGs, vital signs, and physical examinations.

8.4.3 Derivations of Efficacy/Immunogenicity/Pharmacokinetics Endpoints

Exploratory efficacy endpoints and their definitions are presented below.

Objective Response Rate (ORR): is defined as the percentage of subjects who have achieved confirmed complete response (CR) or partial response (PR) according to irRECIST by the investigator review. Subjects with missing outcome on objective response will be considered non-responders.

Disease Control Rate (DCR): is defined as the percentage of subjects who have achieved stable disease for at least 8 weeks or confirmed complete response (CR) or confirmed partial response (PR) according to irRECIST by the investigator review. Subjects with missing response will be considered not to have achieved DCR.

Duration of Response (DOR): is defined as the time interval between the date of the first confirmed response (CR/PR) (the response prior to confirmation) and the date of first documented disease progression based upon irRECIST by the investigator review. Response duration will be only determined for confirmed responses.

Best Overall Response per irRECIST [Appendix 12.6]: the best response attained during the study with 4 categories based upon irRECIST by the investigator review: Complete Response (CR), Partial Response (PR), Stable Disease (SD), and Progressive Disease (PD). Categories of CR and PR need to be confirmed in this endpoint.

Progression-free Survival (PFS): is defined as the time from the start of treatment to progressive disease (PD) or death, whichever occurs earlier, based upon irRECIST by the investigator review. Subjects without documented PD/death will be censored at the last disease assessment date.

Best Target Lesion Response - maximum percent reduction in tumor line length over target lesions by the investigator review.

Time to Confirmed Response - defined only for subjects with confirmed response by the investigator review - the time interval between the start of treatment allocation and the date of the first confirmed response (CR/PR) (the response prior to confirmation).

Additional supportive analyses of these endpoints based on RECIST criteria and, if needed, central review might be conducted.

PK endpoints- serum concentrations of MK-1248 and pembrolizumab and derived PK parameters.

Target engagement endpoints – to be used in descriptive analyses

Biomarker endpoints– to be used in descriptive analyses

8.4.4 Derivations of Safety Endpoints

Description of safety measures is provided in Section 7.

8.5 Analysis Populations

8.5.1 Safety Analysis Populations

The All-Subjects-as-Treated (ASaT) population will be used for the analysis of safety data in this study. The ASaT population consists of all 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. However, in the MK-1248 and pembrolizumab combination arm (i.e. Arm 2), if some subjects received only pembrolizumab, but did not receive any dose of MK-1248, these subjects will be included in the ASaT population, but their safety data will be presented separately. 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 (subjects evaluable for DLT as described in Section 5.2.4) will be used.

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 Efficacy Analysis Populations

The full analysis set populations FAS1 and FAS2 are defined as all subjects with a baseline scan with measurable disease by investigator assessment who were administered MK-1248 (Arm 1; FAS1) or MK-1248 and pembrolizumab (Arm 2; FAS2). These populations will be used for exploratory analyses of efficacy.

Analysis of response duration is based on all confirmed responders.

8.6 Statistical Methods

8.6.1 Statistical Methods for Efficacy Analyses

This section describes the statistical methods that address the exploratory efficacy objectives.

For the subset of FAS1 subjects treated with the RP2D dose of MK-1248 and the subset of FAS2 subjects treated with the RP2D for combination of MK-1248 with pembrolizumab, the estimates of the ORR and DCR and the 95% confidence intervals for the estimates based on the Clopper-Pearson method [48] will be provided. For PFS, DOR, and time to confirmed response Kaplan-Meier plots will be provided. Graphic displays will be provided for the best target lesion response DOR.

The ORR, DCR, BOR, DOR, PFS, best target lesion response, and time to confirmed response in subjects treated with doses below the RP2 doses will be listed along with baseline characteristics.

For PFS, subjects without documented PD/death will be censored at the last disease assessment date or, if they started new anti-cancer treatment, at the last disease assessment before initiation of the new anticancer treatment.

Descriptive statistics will be provided for other exploratory efficacy parameters.

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.

DLTs will be listed. DLTs and adverse experiences will be summarized as counts and frequencies for each MK-1248 (Arm 1) or MK-1248 in combination with pembrolizumab dose level that had at least three subjects treated and listed for other dose levels. The estimate of the DLT rate among subjects treated with the RP2D and the 95% Bayesian probability interval for the estimate will be provided.

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

Immune-related AEs (irAEs) will be summarized in separate tables from other AEs. Any AE of unknown etiology associated with MK-1248 or MK-1248 in combination with pembrolizumab exposure will be evaluated to determine if it is possibly an AE of a potentially immunologic etiology).

In addition, the broad clinical and laboratory AE categories consisting of the percentage of subjects with any AE, a drug related AE, a serious AE, an AE which is both drug-related and

serious, and who discontinued due to an AE will be summarized for dose levels with at least 3 subjects treated and listed for other doses. Percentages of subjects in these categories among subjects treated with RP2D and 95% confidence intervals for the estimated percentages calculated using the Clopper-Pearson method [48] will be provided.

8.6.3 Summaries of Baseline Characteristics, Demographics, and Other Analyses

8.6.3.1 Demographic and Baseline Characteristics

The number and percentage of subjects screened, randomized/allocated, the primary reasons for screening failure, and the primary reason for discontinuation will be displayed. Demographic variables, baseline characteristics, primary and secondary diagnoses, and prior and concomitant therapies will be summarized either by descriptive statistics or categorical tables for ASaT population (by Arm), the set of subjects treated with the MK-1248 Recommended Phase 2 Dose (RP2D), and the set of subjects treated with the RP2D for combination of MK-1248 with pembrolizumab.

8.6.3.2 Population PK Analyses

Serum concentrations of MK-1248 in the MK-1248 arm and serum concentrations of MK-1248 and pembrolizumab in the MK-1248 administered with pembrolizumab arm will be summarized by planned visit and time for each dose separately; PK parameters will be summarized by dose. Descriptive statistics will be provided for each dose with at least 3 subjects; for other doses, the results will be listed.

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

8.7 Interim Analyses

No interim analyses are planned for this study.

8.8 Multiplicity

There will be no multiplicity control in this study.

8.9 Sample Size and Power Calculations

8.9.1 Dose Escalation and Dose Confirmation

The primary purpose of the dose escalation and dose confirmation parts of the trial is to investigate the safety and tolerability of MK-1248 monotherapy and MK-1248 co-administered with pembrolizumab in adult subjects with advanced solid tumors (Parts A-E) and to establish RP2Ds for MK-1248 monotherapy and MK-1248 co-administered with pembrolizumab.

The final number of subjects enrolled in the dose escalation and confirmation parts of the study will depend on the empirical safety (DLT) observations, in particular, at what dose the 3+3 design is triggered and what dose is identified as the RP2D. Sample sizes for a few possible scenarios as well as the estimated time required to enroll all subjects and the time

required to determine the MTD are provided below. The time required to estimate the MTD is the time from the first subject's first dose to the end of the 3-week observation period following the first dose of the last subject enrolled in the dose confirmation part. The study duration is derived as the time from the first subject's first dose to the end of 2-year treatment period following the enrollment of the last Part E subject.

The enrollment time was conservatively estimated assuming that during dose acceleration part it will take 4 weeks to proceed from one dose to the next and during 3+3 parts and that during the dose confirmation a subject can be enrolled every week.

Scenario 1. No DLTs during Parts A-E. For MK-1248 monotherapy, in a scenario where no DLTs are encountered during the dose escalation and confirmation parts and thus Part B continues to the highest dose in Table 2, the sample size across Parts A-C is 46 subjects (8 subjects in Part A, 27 subjects across 9 doses in Part B, and 11 subjects on RP2D in Part C). For MK-1248 with pembrolizumab, in a scenario where Arm 2 starts at 0.12mg MK-1248 and 200 mg pembrolizumab and no DLTs are encountered during the dose escalation and confirmation parts so that Part D continues to the highest dose in Table 2, the sample size across Parts D and E is 50 subjects (39 subjects across 13 doses in Part D, and 11 subjects on RP2D in Part E). The total sample size across Parts A-E is 96 subjects.

It will take 16 weeks to enroll and observe for DLTs the 8 MK-1248 monotherapy subjects in Part A and proceed to Part B enrolment; it will take additional 88 weeks to enroll 88 subjects (38 in Parts B and C and 50 in Parts D and E). Thus, in this scenario the enrollment time across Parts A-E is 104 weeks and the time required to determine the two MTDs is 107 weeks. The study duration then is approximately 104 weeks + 2 years or 4.0 years.

If dose escalation stops at a dose below the highest dose for either arm, the study might require less than 96 subjects and the enrollment duration shorter than 120 weeks. For example, if, in absence of DLTs, it is decided based on >95% receptor occupancy in tissue samples for multiple consecutive dose levels to stop MK-1248 escalation at 330mg dose and not explore the top three MK-1248 doses in Parts B and D, the sample size across Parts A-E will be 96-18=78 subjects. The enrollment duration will be 104-18=86 weeks and the total study duration will be 86 weeks+2 years or 3.6 years.

Also, with no DLTs observed, it might be possible to enter Part C and Part E subjects faster than one subject every week which will shorten the study duration.

Scenario 2: Flat DLT dose response. Suppose no DLTs are observed in Part A, and dose escalation in Parts B and D continues to the highest dose with flat dose response so that in Arm 1, 4 dose levels are studied in 3 subjects each and 5 dose levels (including the top one) are studied in 6 subjects each in Part B, while in Arm 2, 6 dose levels are studied in 3 subjects each and 7 dose levels (including the top one) are studied in 6 subjects each in Part D. Also suppose that the top dose is confirmed as the RP2D dose without de-escalation in Parts C and E. Thus, the sample size in Arm 1 is 58 subjects (8 in Part A, 42 in Part B, and 8 in Part C) and the sample size in Arm 2 is 68 subjects (60 in Part D and 8 in Part E). Total sample size is 118 subjects.

It will take 16 weeks to enroll 8 MK-1248 monotherapy subjects in Part A and proceed to Part B enrolment; it will take additional 118 weeks to enroll 118 subjects (50 in Parts B and C, and 68 in Parts D and E). Thus, in this scenario the enrollment time across parts A-E is

134 weeks and the time required to determine the two MTDs is 137 weeks. The study duration then is approximately 137 weeks + 2 years or 4.6 years.

Any dose de-escalations in Part C will increase the sample size in this example.

Scenario 3. Early start of 40% dose increments for Arm 2. If in Arm 2, 40% increments in the 3+3 design doses are triggered at 3 mg dose and dose escalation continues in 18 steps to 915 mg dose, with 3 subjects per dose in 3+3 design and 11 subjects in Part C, the sample size of Arm 2 across Parts D and E is 65 (54 in Part D and 11 in Part E). Suppose that dose escalation in Arm 1 proceeds without DLTs as in Scenario 1, and thus, the sample size of Arm 1 across Parts A-C is 46 subjects (8 subjects in Part A, 27 subjects across 9 doses in Part B, and 11 subjects on RP2D in Part C). The total sample size across Parts A-E is 111 subjects.

It will take 16 weeks to enroll 8 MK-1248 monotherapy subjects in Part A and proceed to Part B enrolment; it will take additional 103 weeks to enroll 103 subjects (38 in Parts B and C and 65 in Parts D and E). Thus, in this scenario the enrollment time across Parts A-E is 135 weeks and the time required to determine the two MTDs is 122 weeks. The study duration then is approximately 125 weeks + 2 years or 4.3 years.

The plausible sample size of approximately 96 subjects and the enrollment time of 104 weeks (study duration of 4 years) that correspond to the first described scenario are used for operational purposes.

8.9.2 Precision of the DLT rate at RP2D

The TPI design [1] will be used at the dose confirmation stage. This design assumes the toxicity rate at each dose level follows a beta-binomial hierarchical model. Based on the distance between the toxicity rate of the current dose and a pre-specified targeted toxicity rate, it assigns the current dose level to one of three toxicity intervals (i.e. under-dosing interval, proper-dosing interval, and over-dosing interval), which recommend actions of escalating, staying, or de-escalating the dose level, respectively. One of its attractive properties is that all possible dose-escalation decisions for a given trial can be pre-calculated, and tabulated in a spreadsheet, thus allowing investigators to easily implement and monitor the trial without subsequent statistical input. The dose confirmation rules using TPI design for this trial are presented in Table 4, Subsection 5.2.1.5.

Since the TPI approach will be used during the dose confirmation Parts C and E, the estimated DLT rate, and its 95% Bayesian Probability Interval (PI) will be calculated from the posterior distribution of the DLT rate at RP2D using the model specified in the TPI approach. A uniform distribution between 0 and 1 is used as the prior when calculating the PIs in Table 10. If 14 subjects are finally dosed at RP2D during the dose confirmation stage, the estimated DLT rate and its 95% PI should be similar to one of the rows in Table 10.

Table 10 Precision of the estimated DLT rates at RP2D

Number of Subjects dosed at RP2D	Number of DLT Events	Estimated DLT Rate	Lower Bound of 95% PI	Upper Bound of 95% PI
14	2	0.143	0.027	0.373
14	3	0.214	0.068	0.460
14	4	0.286	0.106	0.533
14	5	0.357	0.158	0.609

8.10 Subgroup Analyses and Effect of Baseline Factors

No subgroup analyses will be performed.

8.11 Compliance (Medication Adherence)

Drug accountability data for trial treatment will be collected during the study. Percent compliance with drug administration will be calculated for each subject for MK-1248 and pembrolizumab separately.

For MK-1248 and pembrolizumab, percent compliance will be calculated as following:

$$\text{Percent Compliance} = \frac{\text{Number of Doses Taken}}{\text{Number of Doses that Should have been Taken}} \text{ x } 100.$$

For MK-1248, "Number of Doses that Should have been Taken" will be calculated as the minimum of the two numbers: 4 and (1 plus the number (integer) of 3-week intervals that fit between the date of the first dose and the date of the last dose of MK-1248).

For pembrolizumab, "Number of Doses that Should have been Taken" will be calculated as 1 plus the number (integer) of 3-week intervals that fit between the date of the first dose and the date of the last dose of pembrolizumab.

8.12 Extent of Exposure

A subject's extent of exposure to MK-1248 is defined as the total number of doses of MK-1248 the subject received. A subject's extent of exposure to pembrolizumab is defined as the total number of doses of pembrolizumab the subject received.

Extent of Exposure will be summarized for all MK-1248 and MK-1248 in combination with pembrolizumab dose levels with at least 3 subjects enrolled and listed for other dose levels.

9.0 LABELING, PACKAGING, STORAGE AND RETURN OF CLINICAL SUPPLIES

9.1 Investigational Product

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

Clinical Supplies will be provided by the Sponsor as summarized in Table 11.

Table 11 Product Descriptions

Product Name & Potency	Dosage Form
MK-1248 100 mg	Injection
MK-3475 100 mg	Injection

All other supplies not indicated in Table 11 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 will be responsible for recording the lot number, manufacturer and expiry date of any locally purchased product.

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-1248 and MK-3475/pembrolizumab as outlined. Each kit will contain one vial.

9.3 Clinical Supplies Disclosure

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

9.4 Storage and Handling Requirements

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

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

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

9.5 Discard/Destruction/Returns and Reconciliation

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

10.0 ADMINISTRATIVE AND REGULATORY DETAILS

10.1 Confidentiality

10.1.1 Confidentiality of Data

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

10.1.2 Confidentiality of Subject Records

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

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

10.1.3 Confidentiality of Investigator Information

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

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

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

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

10.1.4 Confidentiality of IRB/IEC Information

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

10.2 Compliance with Financial Disclosure Requirements

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

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

10.3 Compliance with Law, Audit and Debarment

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

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

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

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

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

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

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

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

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

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

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

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

10.4 Compliance with Trial Registration and Results Posting Requirements

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

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

10.5 Quality Management System

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

10.6 Data Management

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

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

10.7 Publications

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

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

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

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

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

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12.0 APPENDICES

12.1 Merck Code of Conduct for Clinical Trials

Merck*

Code of Conduct for Clinical Trials

I. Introduction

A. Purpose

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

B. Scope

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

II. Scientific Issues

A. Trial Conduct

1. Trial Design

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

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

2. Site Selection

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

3. Site Monitoring/Scientific Integrity

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

B. Publication and Authorship

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

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

III. Subject Protection

A. IRB/ERC review

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

B. Safety

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

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

C. Confidentiality

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

D. Genomic Research

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

IV. Financial Considerations

A. Payments to Investigators

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

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

B. Clinical Research Funding

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

C. Funding for Travel and Other Requests

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

V. Investigator Commitment

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

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

12.2 Collection and Management of Specimens for Future Biomedical Research

1. Definitions

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

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

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

d. DNA: Deoxyribonucleic acid.

e. RNA: Ribonucleic acid.

2. Scope of Future Biomedical Research

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

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

3. Summary of Procedures for Future Biomedical Research

a. Subjects for Enrollment

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

b. Informed Consent

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

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

c. eCRF Documentation for Future Biomedical Research Specimens

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

d. Future Biomedical Research Specimen Collections

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

4. Confidential Subject Information for Future Biomedical Research

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

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

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

5. Biorepository Specimen Usage

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

6. Withdrawal From Future Biomedical Research

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

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

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

7. Retention of Specimens

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

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

8. Data Security

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

9. Reporting of Future Biomedical Research Data to Subjects

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

If any exploratory results are definitively associated with clinical significance for subjects while the clinical trial is still ongoing, investigators will be contacted with information. After the clinical trial has completed, if any exploratory results are definitively associated with clinical significance, the Sponsor will endeavor to make such results available through appropriate mechanisms (e.g., scientific publications and/or presentations).

Subjects will not be identified by name in any published reports about this study or in any other scientific publication or presentation.

10. Future Biomedical Research Study Population

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

11. Risks Versus Benefits of Future Biomedical Research

For future biomedical research, risks to the subject have been minimized. Risks include those associated with venipuncture to obtain the whole blood specimen. This specimen will be obtained at the time of routine blood specimens drawn in the main trial.

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

12. Questions

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

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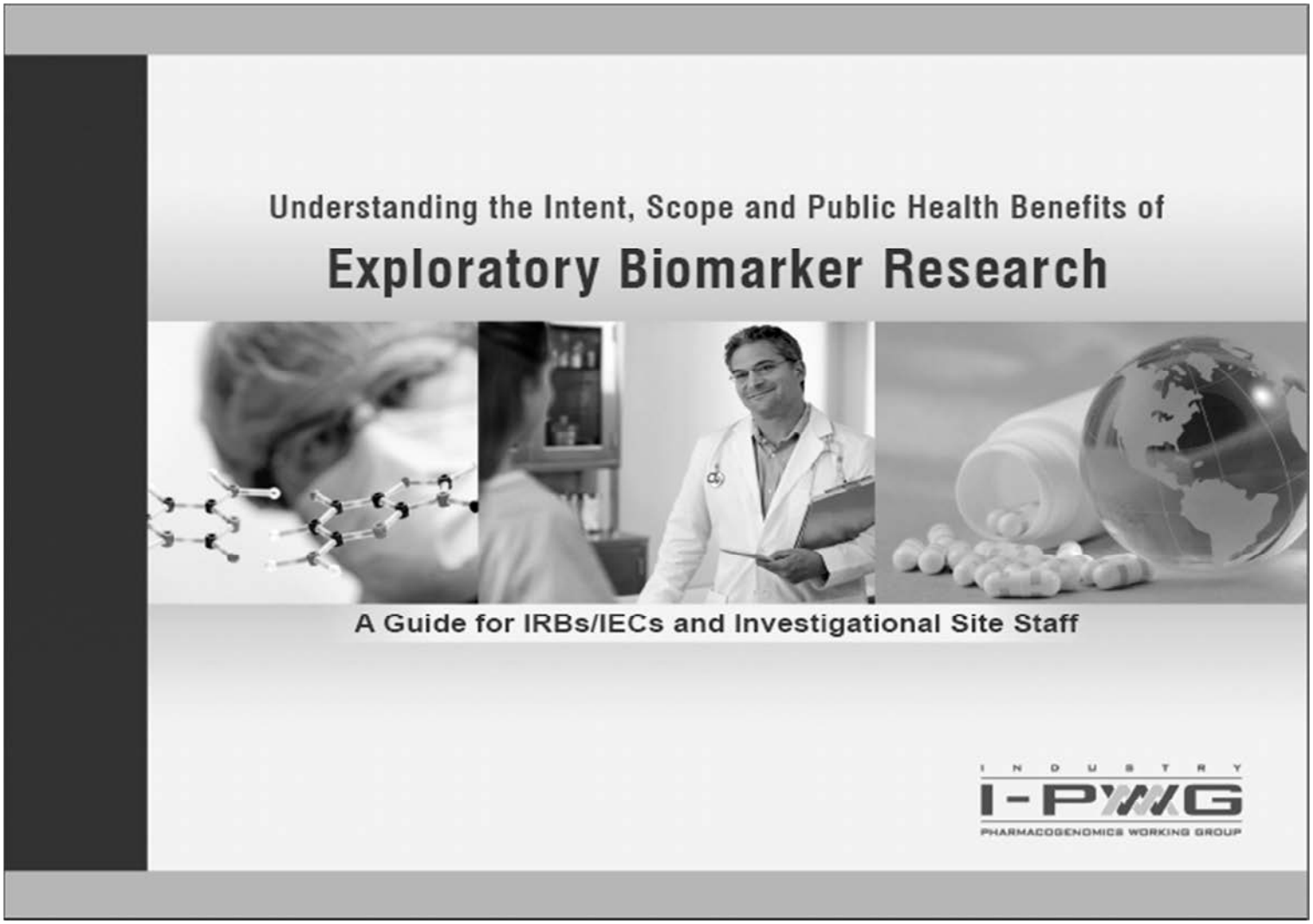
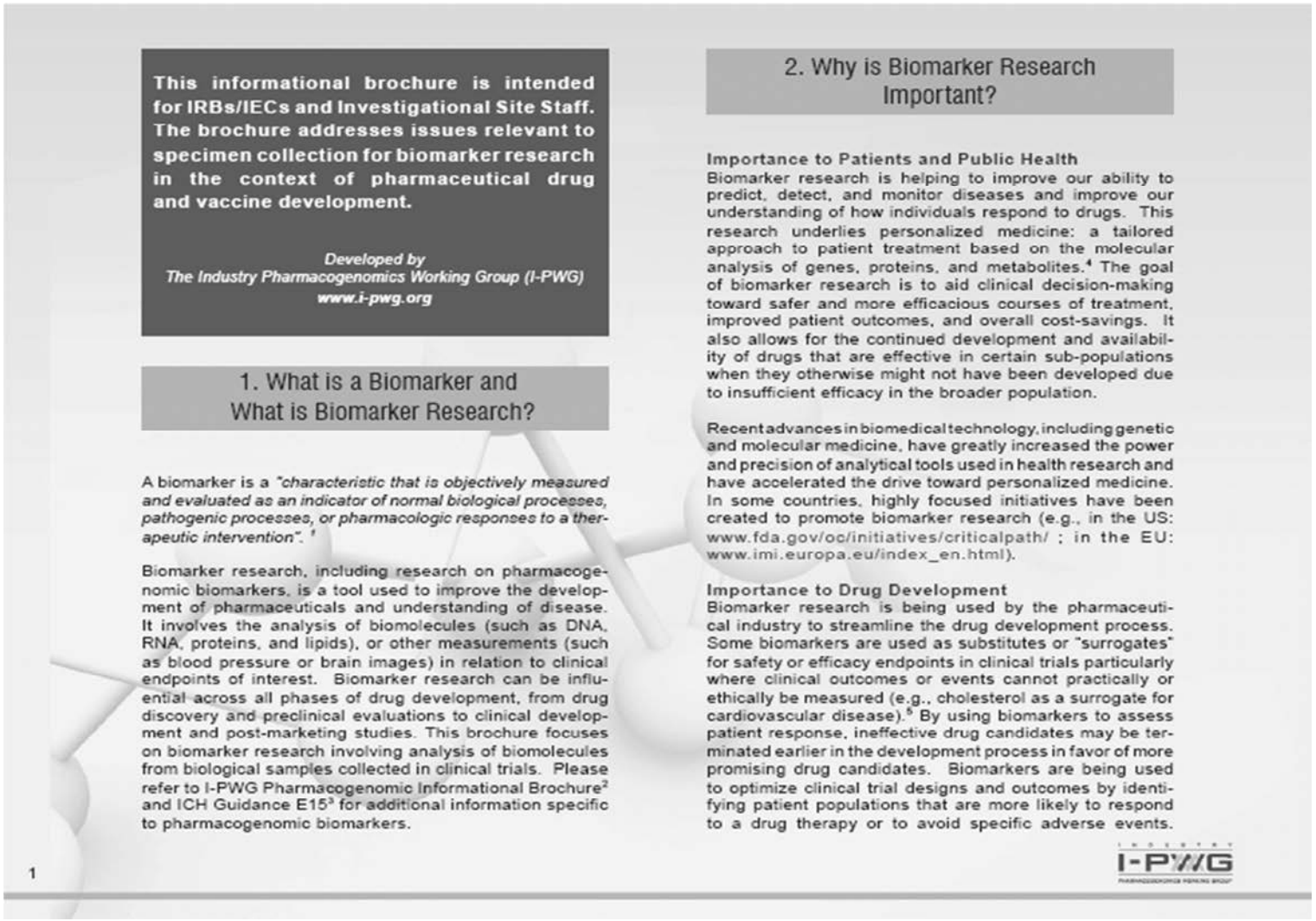
12.3 Understanding the Intent, Scope and Public Health Benefits of Exploratory Biomarker Research: A Guide for IRBs/IECs and Investigational Site Staff





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

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

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

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

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

2. Why is Biomarker Research Important?

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

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

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

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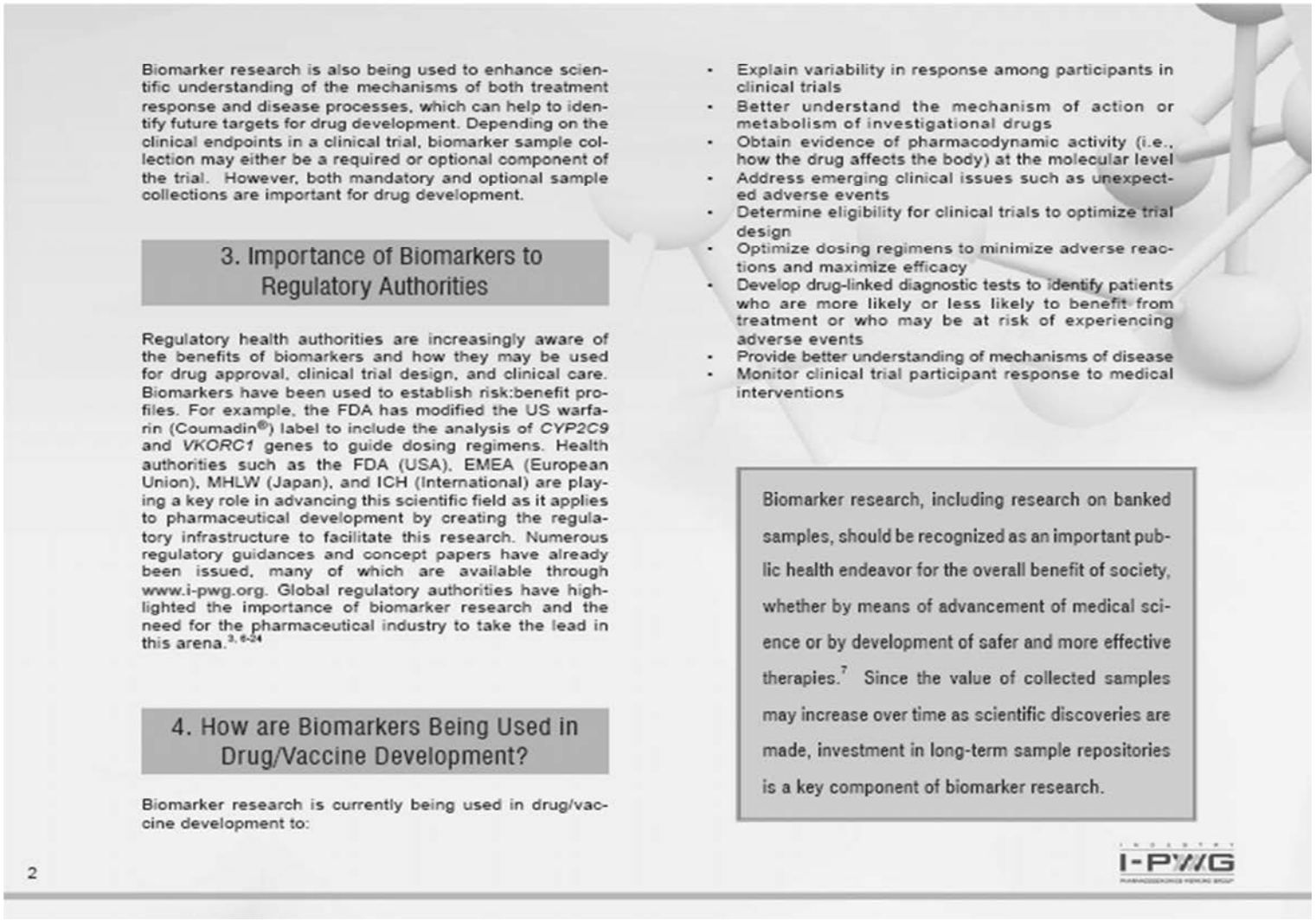
Biomarker research is also being used to enhance scientific understanding of the mechanisms of both treatment response and disease processes, which can help to identify future targets for drug development. Depending on the clinical endpoints in a clinical trial, biomarker sample collection may either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

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

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

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

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

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

6. Biomarker Samples from Clinical Trials: An Invaluable Resource

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

7. Informed Consent for Collection & Banking of Biomarker Samples

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

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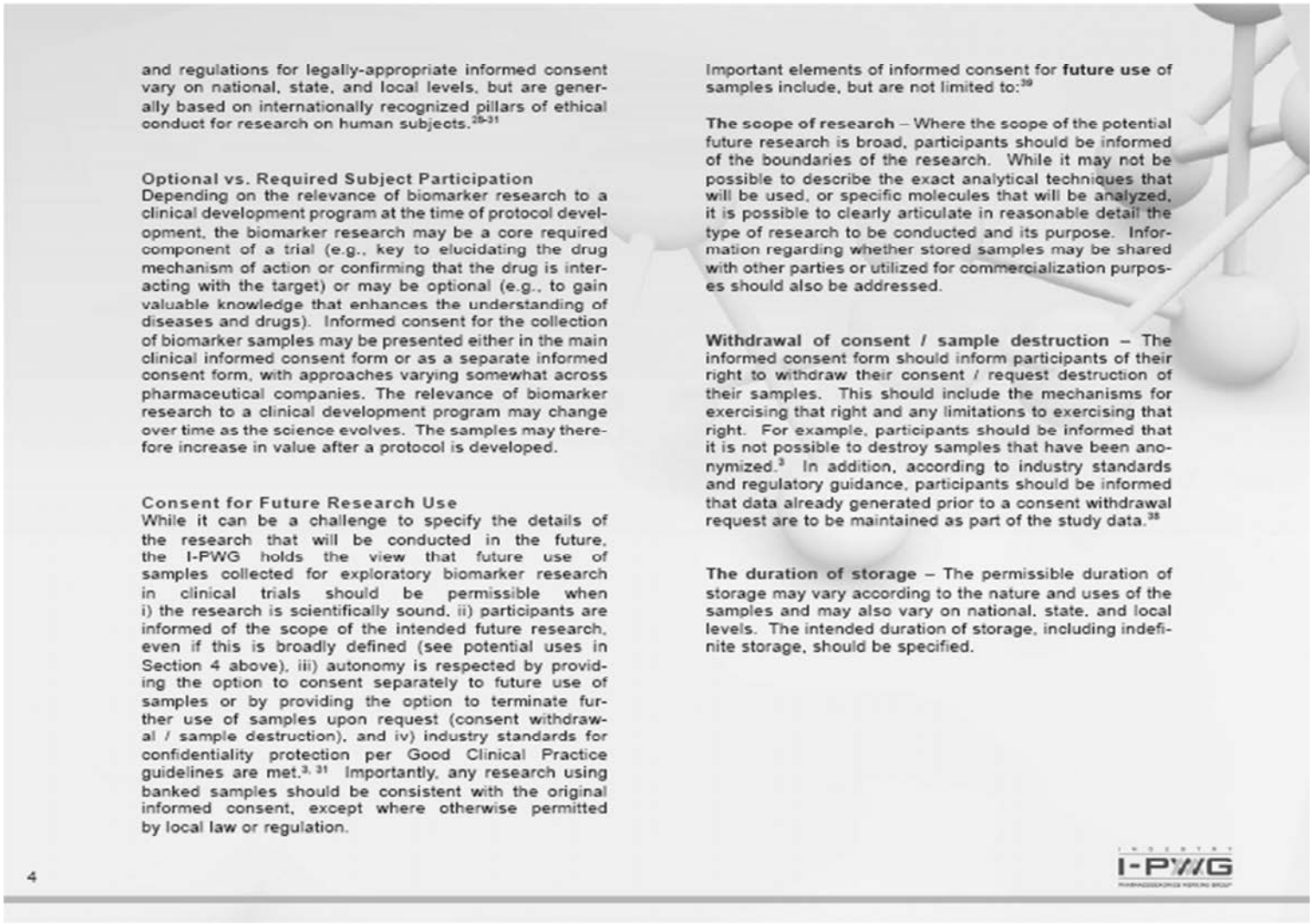

and regulations for legally-appropriate informed consent vary on national, state, and local levels, but are generally based on internationally recognized pillars of ethical conduct for research on human subjects.[28-31]

Optional vs. Required Subject Participation

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

Consent for Future Research Use

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

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

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

Withdrawal of consent / sample destruction – The informed consent form should inform participants of their right to withdraw their consent / request destruction of their samples. This should include the mechanisms for exercising that right and any limitations to exercising that right. For example, participants should be informed that it is not possible to destroy samples that have been anonymized.[3] In addition, according to industry standards and regulatory guidance, participants should be informed that data already generated prior to a consent withdrawal request are to be maintained as part of the study data.[35]

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

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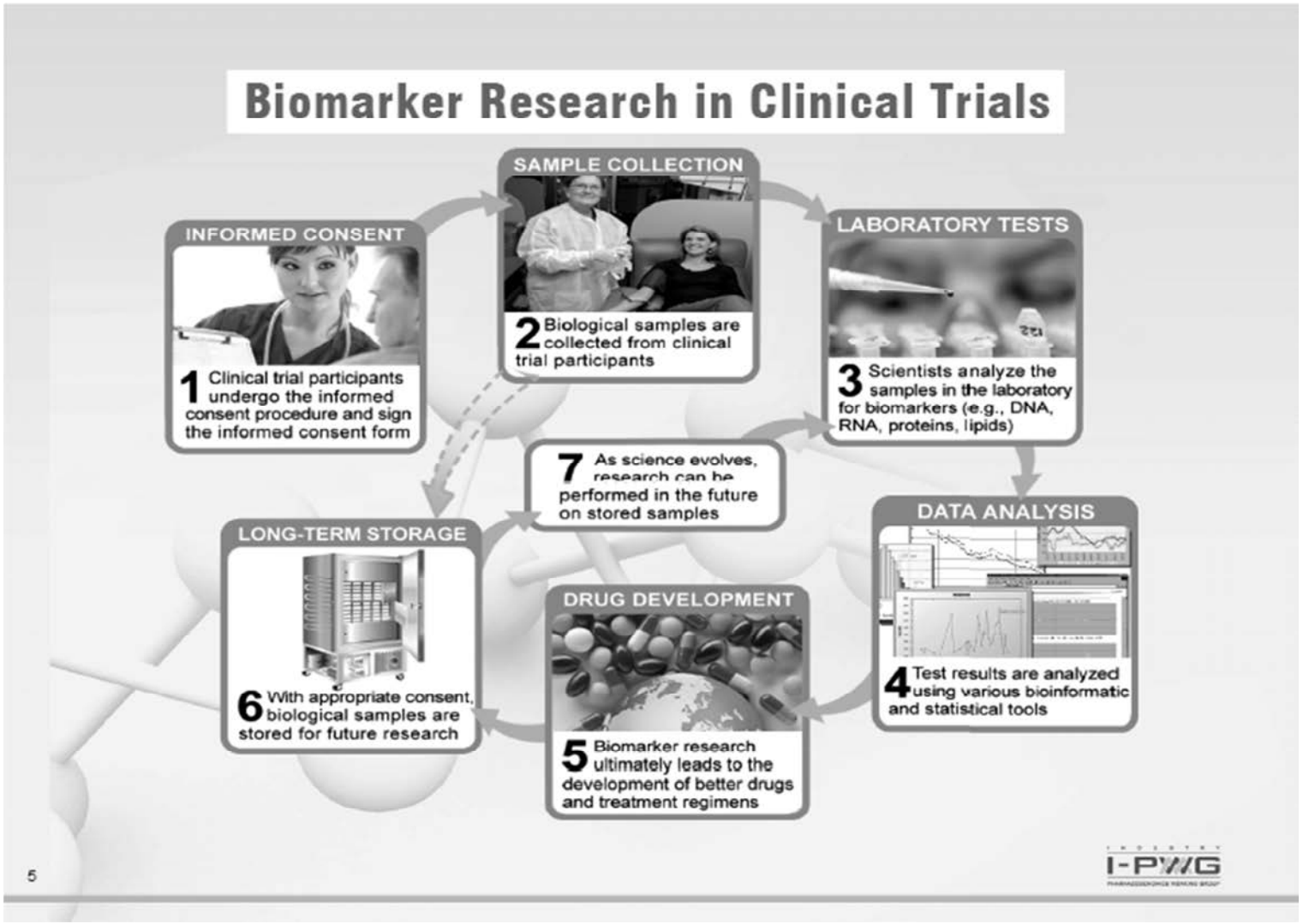
Biomarker Research in Clinical Trials
SAMPLE COLLECTION
2 Biological samples are collected from clinical trial participants
LABORATORY TESTS
3 Scientists analyze the samples in the laboratory for biomarkers (e.g., DNA, RNA, proteins, lipids)
INFORMED CONSENT
1 Clinical trial participants undergo the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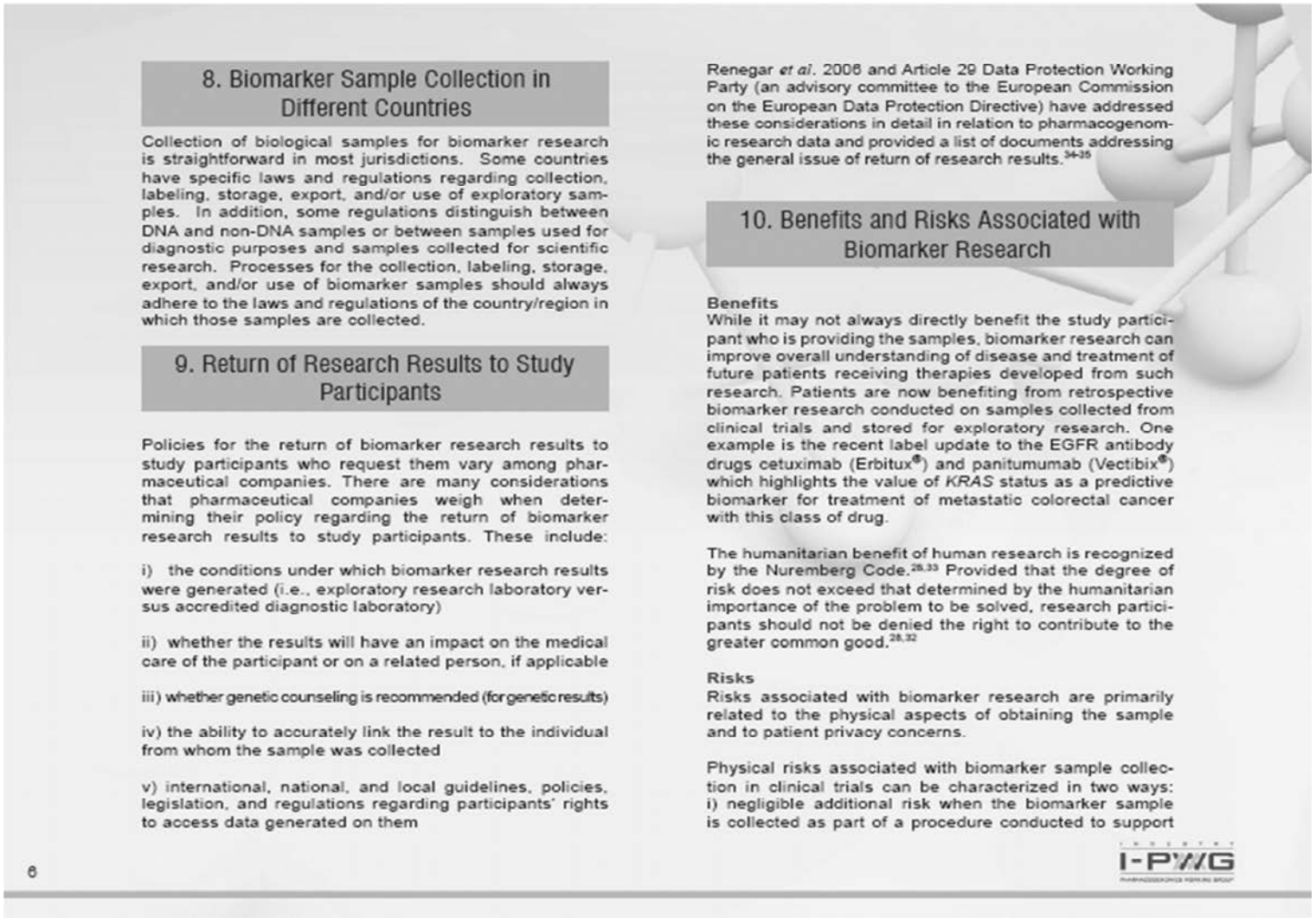

8. Biomarker Sample Collection in Different Countries

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

9. Return of Research Results to Study Participants

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

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

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

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

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

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

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

10. Benefits and Risks Associated with Biomarker Research

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

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

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

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

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

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

11. Privacy, Confidentiality, and Patient Rights

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

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

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

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

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

12.Where to Get More Information?

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

13. What is I-PWG?

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

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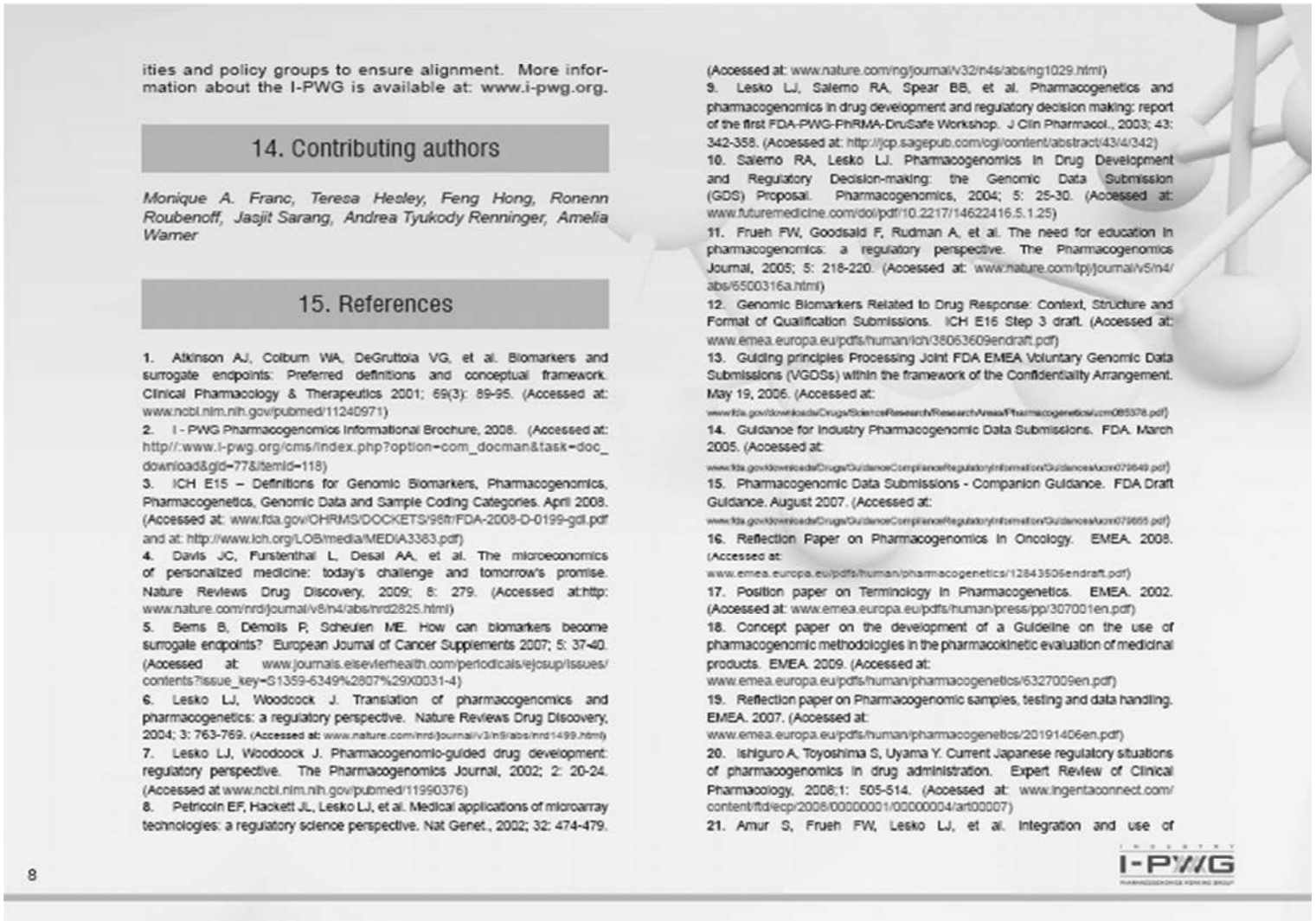

ities and policy groups to ensure alignment. More information about the I-PWG is available at: www.i-pwg.org.

14. Contributing authors

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

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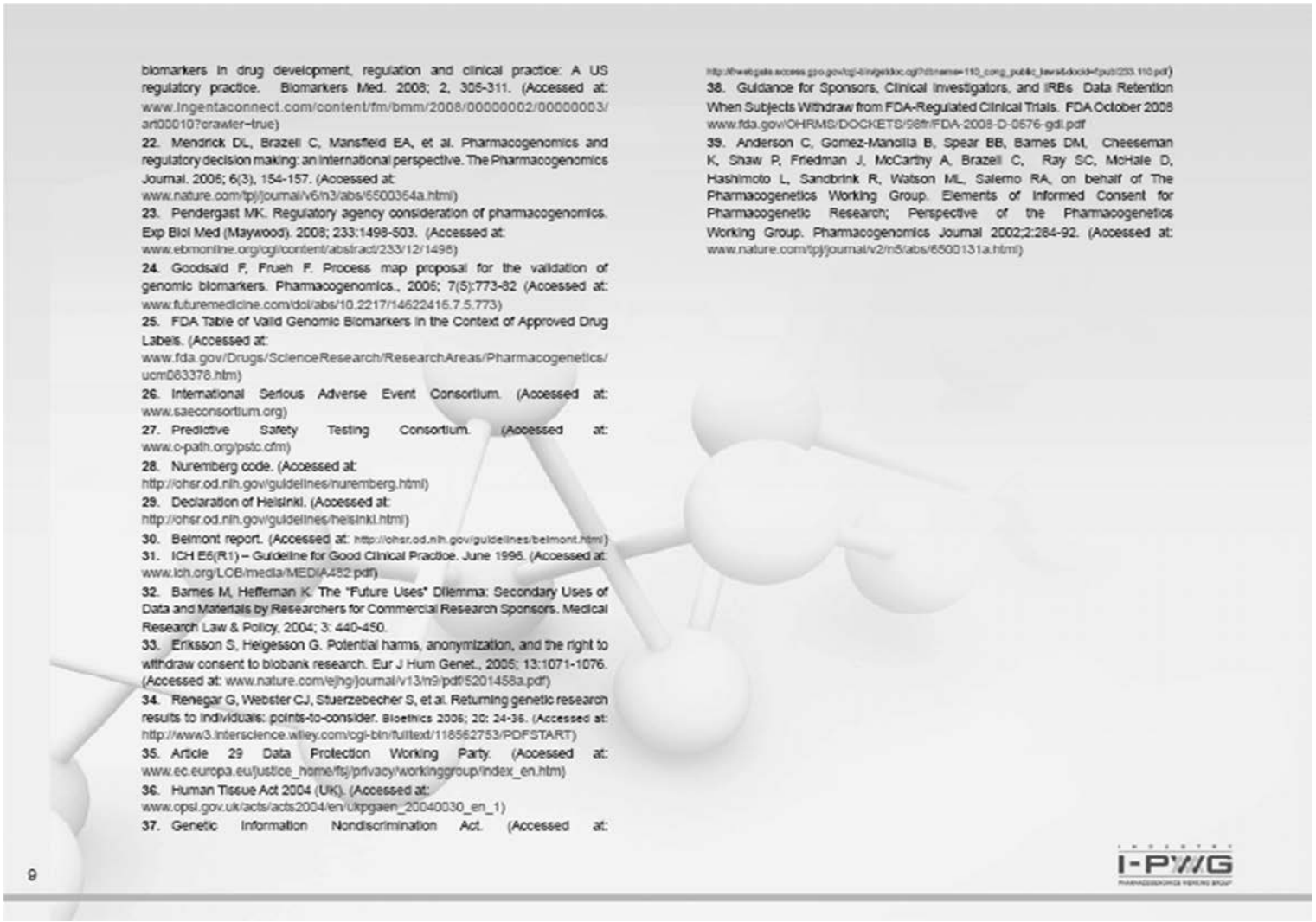

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12.4 ECOG Performance Status

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

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

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

13.0 SIGNATURES

13.1 Sponsor's Representative

TYPED NAME	
TITLE	
SIGNATURE	
DATE SIGNED	

13.2 Investigator

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

TYPED NAME	
TITLE	
SIGNATURE	
DATE SIGNED	