Official Protocol Title:	Phase 1 Trial of Single Agent MK-4166 and MK-4166 in Combination with Pembrolizumab in Subjects with Advanced Malignancies
NCT number:	NCT02132754
Document Date:	21-May-2019

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TITLE:

Phase 1 Trial of Single Agent MK-4166 and MK-4166 in Combination with Pembrolizumab in Subjects with Advanced Malignancies

IND NUMBER: 120143

EudraCT NUMBER: [Not Applicable]

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DOCUMENT HISTORY

Document	Date of Issue	Overall Rationale
4166-001-08	21-May-2019	Added language to allow ongoing study subjects to discontinue this study and transition into an extension study.
4166-001-07	06-Nov-2017	Added guidelines for dose interruption/treatment discontinuation and toxicity management in the event of myocarditis and intolerable or persistent Grade 2 drug-related toxicities
4166-001-06	02-Mar-2017	Expanded the dose confirmation phase of the study (Part E) to include all melanoma patients (treatment-naïve and pre-treated)
4166-001-05	17-Feb-2017	Removed the dose confirmation part (Part C) in the MK-4166 monotherapy arm; modified study design to increase the number of subjects in the dose confirmation part (Part E) in the MK-4166 plus pembrolizumab combination therapy arm and to limit enrollment in this part to subjects with advanced malignant melanoma
4166-001-04	21-Jul-2016	Exclusion criterion 10 modified to add language excluding subjects with a history of pneumonitis; added language to allow subjects with confirmed radiologic progression to continue study treatment, after consultation with the Sponsor, in circumstances in which the investigator believes that the subject is experiencing clinical benefit from treatment
4166-001-03	17-Apr-2015	Added combination treatment (MK-4166 + pembrolizumab) arm; changed RECIST to iRECIST; added requirement for baseline tumor sample beginning in Part B; updated SAP to comply with new template

Document	Date of Issue	Overall Rationale
4166-001-02	21-Oct-2014	Accommodation of FDA feedback
4166-001-01	09-Jun-2014	Accommodation of FDA feedback
4166-001-00	02-Apr-2014	First-in-human evaluation of MK-4166

SUMMARY OF CHANGES

PRIMARY REASON(S) FOR THIS AMENDMENT:

Section Number (s)	Section Title(s)	Description of Change (s)	Rationale
1.0; 2.1; 2.2; 5.8; 5.10; 7.1.5.3.2	Trial Summary; Trial Design; Trial Diagram; Subject Withdrawal/ Discontinuation Criteria; Beginning and End of the Trial; Follow-up Visits	Language was added to allow ongoing study subjects to discontinue this study and transition into an extension study to continue protocol-defined assessments and treatment.	This change will allow this study to be closed.

ADDITIONAL CHANGE(S) FOR THIS AMENDMENT:

No additional changes.

1.0 TRIAL SUMMARY

Abbreviated Title	Phase 1 Trial of MK-4166 Monotherapy and MK-4166 in Combination with Pembrolizumab in Subjects with Advanced Solid Tumors
Trial Phase	Phase 1
Clinical Indication	The 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: Treatment Arm 1: MK-4166 monotherapy Treatment Arm 2: MK-4166 in combination with pembrolizumab
Number of trial subjects	Approximately 92 subjects will be enrolled.
Estimated duration of trial	The sponsor estimates that the trial will require approximately 4.12 years (see Section 8.9.1 for assumptions) 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, eligible subjects will be allocated by non-random assignment to one of 2 treatment arms and receive treatment with MK-4166 alone or in combination with pembrolizumab. Study treatment in both arms will begin on Day 1 of each 21 day cycle. For subjects enrolled to Arm 1 and Arm 2, treatment with MK-4166 will end after 4 cycles of treatment; treatment with pembrolizumab in Arm 2 will continue for up to 24 months of treatment. Treatment in both Arms will continue until 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 trial treatment or procedure requirements, subject receives 4 cycles of treatment in Arm 1 or 24 months of study medication in Arm 2, 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 and events of clinical interest 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). Subjects who discontinue for reasons other than disease progression will have post-treatment follow-up for disease status until disease progression, initiating a non-study cancer treatment, withdrawing consent, or becoming lost to follow-up. Once subjects have achieved the study objectives or the study has ended, they will be discontinued from this study and will be enrolled into an extension study to continue protocol-defined assessments and treatment.

2.0 TRIAL DESIGN

2.1 Trial Design

This is a non-randomized, multi- site, 2-arm, open-label trial of MK-4166 monotherapy (Arm 1) and MK-4166 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 used (see Section 5.2.1.4). For dose confirmation in the combination arm only (Part E), the toxicity probability interval (TPI) design [1] will be used to refine the estimate of maximum tolerated dose ([MTD]; see Section 5.2.1.5). The study will not proceed with dose confirmation in the monotherapy arm.

In Arm 1, MK-4166 monotherapy, an accelerated dose escalation in single subject cohorts (Part A) will proceed based on safety events to a dose of 10 mg. Starting at a 30 mg dose (or earlier as described in Section 5.2.1.3), the study will continue with a 3+3 design to identify a preliminary MTD (Part B). During 3+3 dose escalation, an initial cohort of 3 subjects will be enrolled to each dose level. If none of the 3 subjects experience 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 >2/3 or >2/6 subjects at a dose level develop DLTs, dose escalation will be terminated. At least 2 days of observation will occur between each of the first 3 subjects at each dose level.

Arm 2, MK-4166 in combination with pembrolizumab, will follow a 3+3 design to identify a preliminary MTD (Part D). The starting dose of MK-4166 in Arm 2 will be 1.1 mg and will be escalated as shown in Table 3; a fixed dose of 200 mg of pembrolizumab will be administered. 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 1-week observation period between the first and second subjects 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 TPI design. Part E will enroll approximately 20 subjects with advanced malignant melanoma only. Doses of MK-4166 used in combination will be 1 to 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-4166 in combination may continue escalation up to that dose.

When both treatment arms are open for enrollment, 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). Once dose escalation (Parts A and B) is completed in Arm 1, only the combination therapy arm (Arm 2) of the study will be open for enrollment.

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 doses the 3+3 design is triggered, and what dose is identified as the recommended Phase 2 dose (RP2D). For example, for MK-4166 monotherapy, in a scenario where no DLTs are encountered during the dose escalation part and Part B continues to the highest dose in Table 2, the sample size across Parts A and B would be 36 subjects (9 subjects in Part A plus 27 subjects across 9 doses in Part B). For MK-4166 with pembrolizumab, in a scenario where Arm 2 starts at 1.1 mg MK-4166 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 3, the sample size across Parts D and E would be 56 subjects (36 subjects across 12 doses in Part D plus 20 subjects at the RP2D in Part E). In this scenario, the total sample size would be 92 subjects.

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

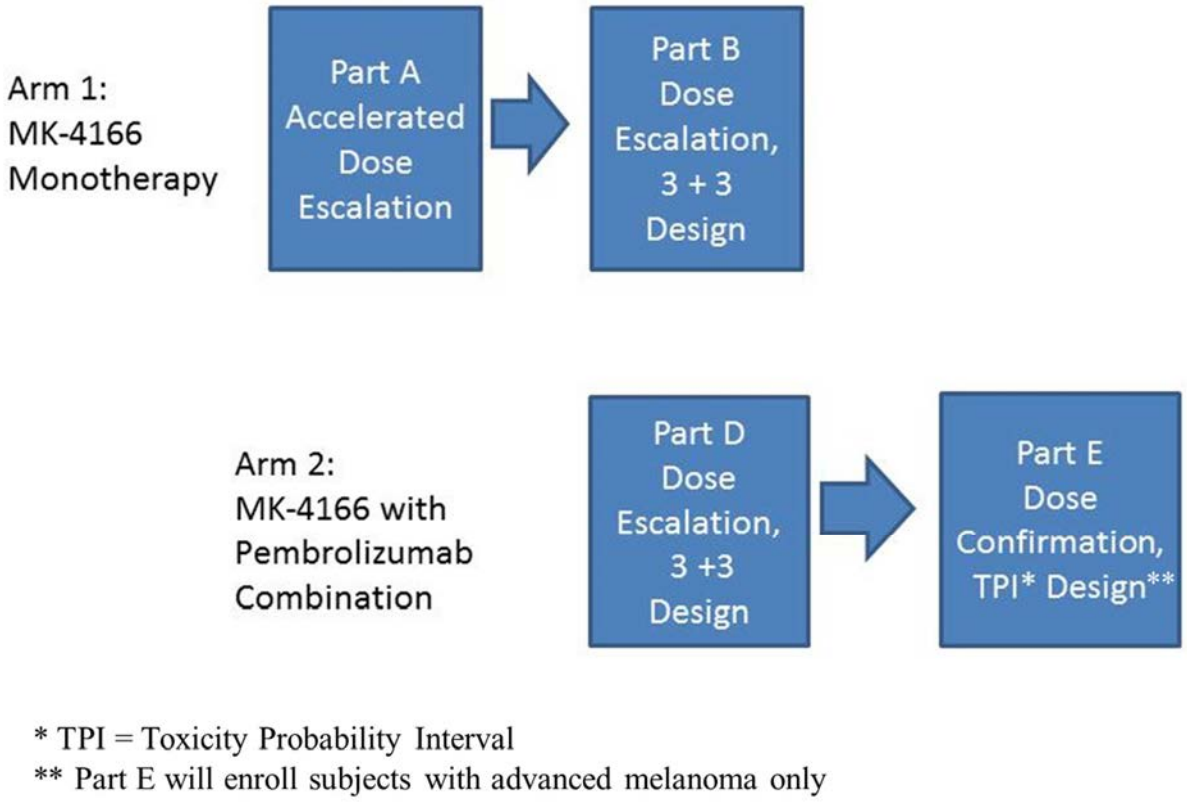
Adverse events (AEs) will be evaluated according to criteria outlined in the NCI Common Terminology Criteria for Adverse Events (CTCAE), version 4.

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.

Once subjects have achieved the study objectives or the study has ended, they will be discontinued from this study and will be enrolled into an extension study to continue protocol-defined assessments and treatment.

2.2 Trial Diagram

The trial design is depicted in Figure 1.



* TPI = Toxicity Probability Interval
** Part E will enroll subjects with advanced melanoma only

Figure 1 Trial Design

In Arm 1, an accelerated dose escalation in single subject cohorts will proceed based on safety events in Part A to a dose of 10 mg. Starting at a 30 mg dose (or earlier as described in Section 5.2.1.4) in Part B, the study will continue with a 3+3 design to identify a preliminary maximum tolerated dose (MTD). The study will not proceed with dose confirmation in Arm 1.

In Arm 2 Part D, treatment with the combination will begin with 1.1 mg of MK-4166. The dose of pembrolizumab in Arm 2 will be 200 mg IV every 3 weeks. Combination dose escalation will follow a 3+3 design to identify a preliminary MTD. The MK-4166 dose in the combination arm will not exceed the MTD for monotherapy. Dose confirmation in Part E will refine the estimate of tolerability of the MTD using a toxicity probability interval [1]. Part E will enroll approximately 20 subjects with advanced malignant melanoma.

Once subjects have achieved the study objectives or the study has ended, they will be discontinued from this study and will be enrolled into an extension study to continue protocol-defined assessments and treatment.

3.0 OBJECTIVE(S) & HYPOTHESIS(ES)

3.1 Primary Objective(s) & Hypothesis(es)

(1) **Objective:** To determine the safety and tolerability of single agent MK-4166 and to establish a maximum tolerated dose (MTD) or maximum administered dose (MAD) in subjects with advanced solid tumors. Note: The MTD or MAD established during dose escalation will not be confirmed.

(2) **Objective**: To establish the safety and tolerability of intravenous (IV) MK-4166 and to establish a maximum tolerated dose (MTD) or maximum administered dose (MAD) when given in combination with pembrolizumab.

3.2 Secondary Objective(s) & Hypothesis(es)

(1) **Objective**: To characterize the PK profile of single agent MK-4166.

(2) **Objective**: To characterize the PK profile of MK-4166 and pembrolizumab following administration of MK-4166 and pembrolizumab in combination.

(3) **Objective**: To evaluate target engagement as measured by modulation in peripheral blood GITR receptor availability.

3.3 Exploratory Objectives

(1) **Objective**: To evaluate the objective response rate (ORR), disease control rate (DCR), best overall response (BOR), best target lesion response, time to confirmed response, duration of response (DOR), and progression-free survival (PFS) of subjects with advanced solid tumors treated with MK-4166 as monotherapy or MK-4166 in combination with pembrolizumab, by irRECIST 1.1 as assessed by investigator review.

(2) **Objective:** To investigate the relationship between candidate efficacy biomarkers and anti-tumor activity of MK-4166 alone or in combination with pembrolizumab:

a. To evaluate the relationship between GITR expression levels in tumor samples and anti-tumor activity of MK-4166 alone or in combination with pembrolizumab.

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, T-cell immunophenotyping, ribonucleic acid [RNA] signature profiles, pharmacogenetic variation) that may correlate with tumor responses.

c. To evaluate differences in tumor tissue characteristics in biopsies taken post treatment with MK-4166 alone or in combination with pembrolizumab versus baseline.

(3) **Objective:** To examine concordance between archival tumor tissues, and newly obtained tumor tissues obtained during the trial period with respect to candidate efficacy biomarkers.

(4) **Objective**: To evaluate development of circulating anti-MK-4166 or anti-pembrolizumab antibodies.

4.0 BACKGROUND & RATIONALE

4.1 Background

Detailed background information on MK-4166 and pembrolizumab is available in the MK-4166 Investigator's Brochure (IB) and the Pembrolizumab IB.

4.1.1 Pharmaceutical and Therapeutic Background

4.1.1.1 MK-4166 Background

MK-4166 is a humanized IgG1 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 (Tregs) 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-4166 is a humanized agonistic mAb of the IgG1 isotype that targets human GITR and is intended for treatment of multiple human cancers. MK-4166 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 anti-tumor T-cell responses and induce tumor rejection in several 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™ (nivolumab) 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.

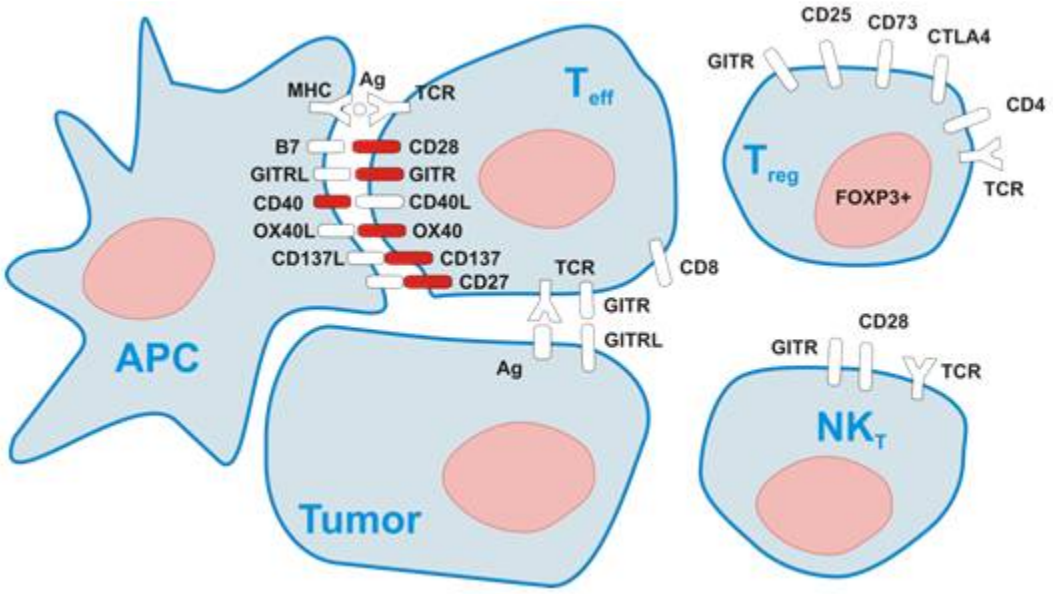


Figure 2 Schematic Diagram of Immune Stimulatory Targets

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-human (FIH) clinical studies [18], which urges caution for all ongoing and proposed agonist immunostimulatory antibodies.

Five agonist immunostimulatory molecules have entered investigational studies in humans. In early phase studies, the RP2D for CD40 agonists was established from the MTD where transaminitis was the main 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). TRX-518 (GITR, Inc.) is the only known anti-GITR mAb to enter clinical trials to date, other than MK-4166. It is under evaluation in a single dose escalation study in adults with biopsy proven unresectable Stage III or Stage IV melanoma and other solid tumor malignancies. The completion date for this 40-patient trial was expected in Dec 2014. TRX-518 is an agonist anti-hGITR mAb that contrasts with MK-4166 in that it contains a mutation in the Fc region of the molecule that abrogates binding to Fcγ receptors.

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 membersare 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, Tregs 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 Pre-clinical and Clinical Trials

4.1.2.1 MK-4166 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 murine 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}) (Teff:Treg ratio) and enhanced intra-tumor Teff 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 Tregs 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 Tregs 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 IgG2a; mDTA-1) revealed that administration of a single dose of mDTA-1 leads to complete regressions of established (84 to 117 mm^3 in volume) subcutaneous MC38, CT26, and CM3 tumors in a large proportion of animals. The maximal effective dose of mDTA-1 in these models is in the dose range of approximately 1 to 3 mg/kg (Figure 3).

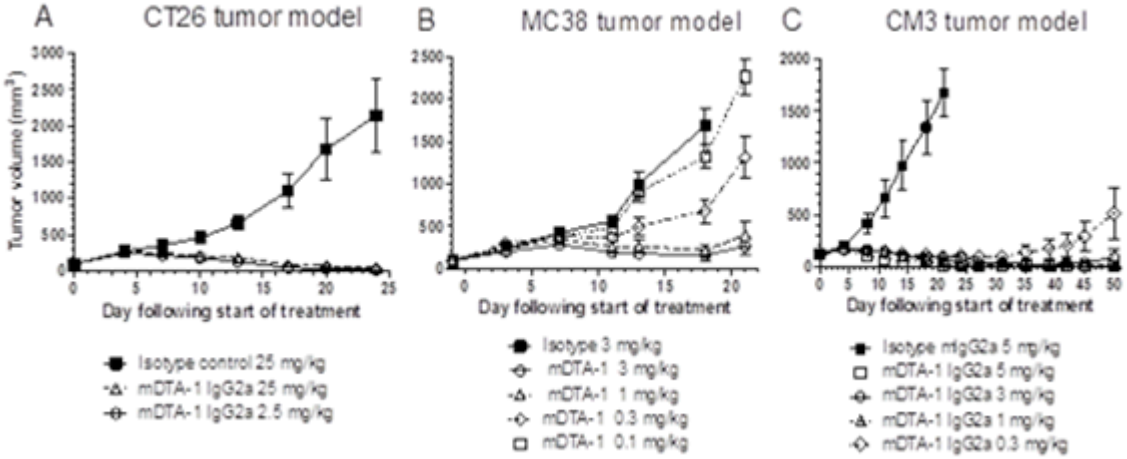


Figure 3 Efficacy of a Single Dose of mDTA-1 IgG2a in Established Syngeneic Mouse Tumor Model

The CT26 colon adenocarcinoma (panel A), MC38 colon adenocarcinoma (panel B), and CM3 melanoma (panel C) mouse tumor cell lines were implanted subcutaneously into immune-competent BALB/cAnN, C57BL/6J, and DBA/2J mice, respectively. Animals were randomized into treatment groups when the mean tumor volume reached 84 to 117 mm^3. Isotype control antibody mIgG2a or mDTA-1 IgG2a were administered as a single subcutaneous dose on Day 0. Tumors were measured twice weekly. Tumor volumes are presented as mean ± standard error of the mean. There were 6 to 12 animals in each group.

GITR stimulation induces humoral immune responses resulting in mechanism-based anti-drug antibody (ADA) formation in murine models, which is also seen in non-human primates (NHP) (details in Investigator Brochure). 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, IV bolus administration of mDTA-1 in the presence of pre-existing 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 administrations of mDTA-1 or in monkeys after multiple 30-minute IV infusions of MK-4166 (at dose levels of 0.03 to 200 mg/kg), suggesting that anti-GITR antibodies can be safely administered even in the presence of ADA.

4.1.2.2 Pembrolizumab Preclinical and Clinical Trials

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

that the mechanism of action involved local infiltration and activation of effector T-cell function in vivo [40]; [46]; [47]; [48]. Experiments have confirmed the in vivo efficacy of PD-1 blockade as a monotherapy as well as in combination with chemotherapy in syngeneic mouse tumor models (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-4166 with Pembrolizumab Combination Preclinical Trials

As MK-4166 acts to stimulate effector immune cells while pembrolizumab acts to prevent immune suppression in tumors, it is conceivable that a combination of MK-4166 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 MC38 and MB49 syngeneic mouse tumor models to assess the anti-tumor efficacy of treatment with mDTA-1 IgG2a (mouse surrogate for MK-4166) in combination with muDX400 (mouse surrogate for pembrolizumab). Due to the strong efficacy of monotherapy with mDTA-1 IgG2a or muDX400 in the standard established MC38 tumor model, an advanced MC38 tumor model with starting tumor volume 3 times larger than normal was used. mDTA-1 IgG2a or muDX400 were administered either as monotherapy or in combination twice with a 7-day interval at previously determined maximally effective monotherapeutic doses. Administration of mDTA-1 IgG2a in combination with muDX400 resulted in greater anti-tumor efficacy than administration of either antibody alone (Figure 4).

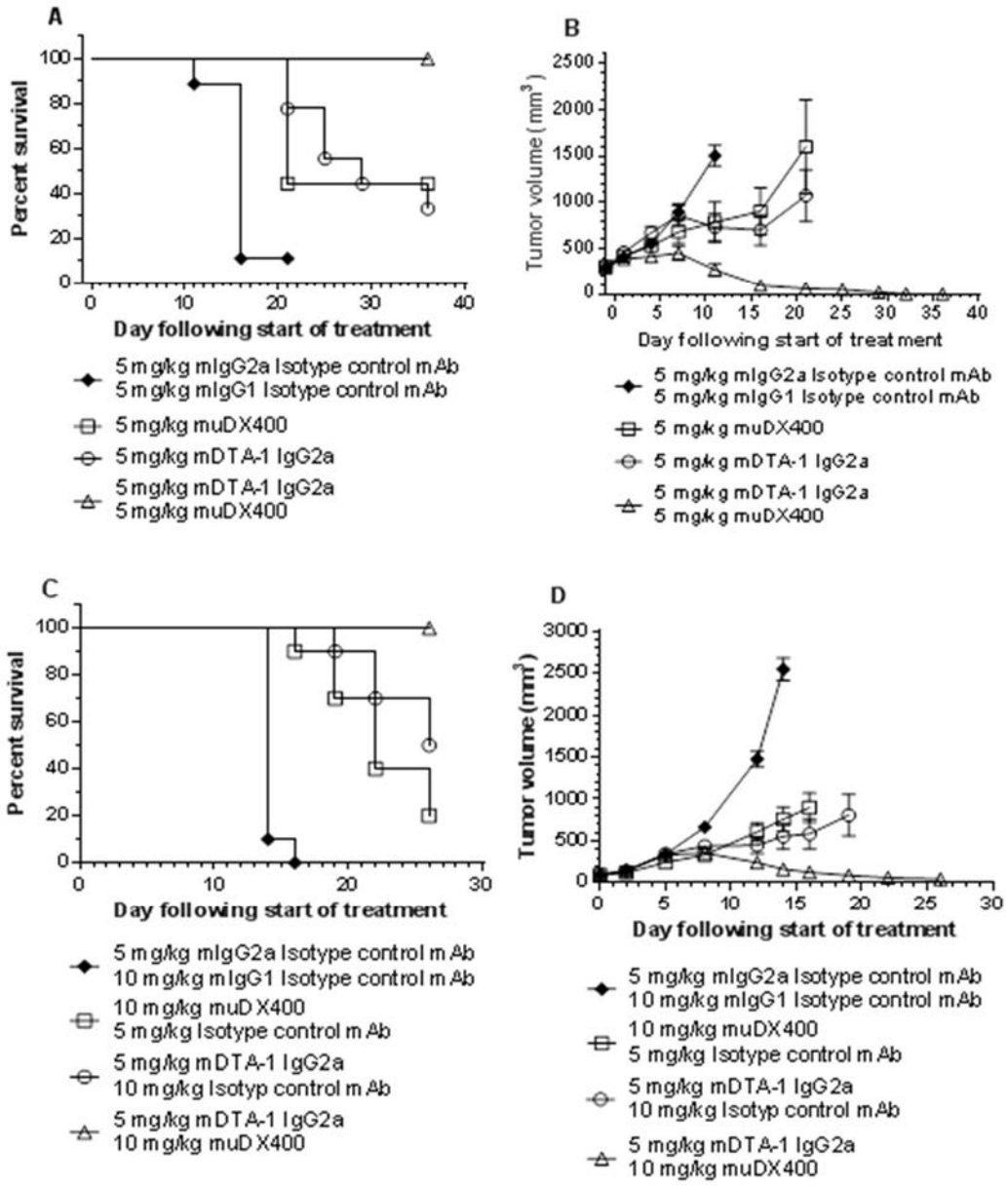


Figure 4 Efficacy of Combination Treatment with mDTA-1 IgG2a and xDX400 in Established Syngeneic Mouse Tumor Models

The MC38 colon adenocarcinoma (panels A and B) and MB49 bladder carcinoma (panels C and D) mouse tumor cell lines were implanted subcutaneously (SC) into immune-competent C57BL/6J mice. Animals were randomized into treatment groups when the mean tumor volume reached 300 mm3 (MC38) or 100 mm3 (MB49). mIgG2a isotype control monoclonal antibody (mAb) and mDTA-1 IgG2a were administered SC. mIgG1 isotype control mAb and muDX400 were administered intraperitoneally. All test and control articles were administered on Days 0 and 7. In panels A and C, animal survival curves are presented; (survival was defined as time to $\geq$2000 mm3 tumor volume). In panels B and D, mean group tumor volumes (± standard error of the mean) are presented.

4.1.3 Ongoing Clinical Trials

4.1.3.1 Ongoing Clinical Trials with MK-4166

This is the first clinical trial of MK-4166. As of 16-Jan-2017, data are available for a total of 73 subjects: 41 subjects treated with MK-4166 monotherapy and 32 subjects treated with MK-4166 in combination with pembrolizumab. Dose escalation has reached 480 mg in the monotherapy treatment arm and 240 mg in the combination treatment arm; dose escalation is continuing per protocol. Treatment has been generally well tolerated. A total of 2 (2.7%) subjects have discontinued study treatment due to AEs, one in each treatment arm. The most common AEs reported to date by preferred term have been fatigue (32 out of 73 [44%] subjects), nausea (16 out of 73 [22%] subjects), abdominal pain and malignant neoplasm progression (14 out of 73 [19%] subjects each), anaemia, decreased appetite, and dyspnoea (13 out of 73 [18%] subjects each), infusion related reaction and vomiting (12 out of 73 [16%] subjects each), and pruritus (11 out of 73 [15%] subjects each). In total, 1 DLT has been observed to date; this DLT was a Grade 3 Indiana Pouch perforation reported in a subject with metastatic urethral cancer. The subject received 30 mg MK-4166 monotherapy. The investigator determined the event to be possibly related to study treatment because of the low incidence of spontaneous perforation and no obvious explanation for the event.

4.1.3.2 Ongoing Pembrolizumab 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 hematologic malignancies. 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-4166 is being developed for treatment of solid tumors. This trial is the FIH trial designed to assess the safety, tolerability, pharmacokinetics, and pharmacodynamics of escalating doses of MK-4166 alone and in combination with pembrolizumab in subjects with advanced solid tumors that have failed standard therapy. The effect of MK-4166 on tumor size will also be explored. The trial will enroll subjects with solid tumors without regard to specific tumor type during dose escalation. Dose confirmation will proceed only in the combination therapy arm and will enroll subjects with advanced malignant melanoma.

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

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

4.2.2 Rationale for Dose Selection/Regimen

Since immunostimulatory agonists like MK-4166 are included in the group of compounds where there is potential for harm intrinsic to their mode of action, the starting dose of MK-4166 for this trial is based on the minimum anticipated biological effect level (MABEL).

4.2.2.1 Starting Dose for This Trial

Upon MK-4166 binding to the GITR receptor, the GITR receptor becomes internalized. Thus target engagement can be assessed by the disappearance of cell surface GITR receptors. This receptor availability assay was used to assess target engagement. Assuming that target binding is essential for drug effect [49], target engagement was used to predict the minimum level at which MK-4166 might exert a biological effect (MABEL) for the proposed FIH study.

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-4166 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 NKT cells is present in cynomolgus monkey blood, and a large but variable percentage of GITR-positive NK cells is present in human while none are present in cynomolgus monkey blood. Similar to studies in mice, non-linear PK properties were observed in cynomolgus monkeys at lower doses (0.0003 – 3 mg/kg). In line with changes in serum concentration-time profiles for MK-4166, 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-4166 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.

To select doses for the initial clinical study, GITR+ T-cells in blood were evaluated for MK-4166 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. To determine the MK-4166 starting dose, binding to blood at maximum serum concentrations (Cmax) was projected. Using conservative scaling assumptions, a dose of 0.000025 mg/kg was projected to correspond to 10% GITR engagement on peripheral blood $CD4^+CD95^+$ cells. This level of peripheral blood engagement represents less than 1% engagement of total body antigen pool since GITR is widely expressed in multiple tissue compartments. This dose was planned as the initial dose, as it reflected a balance between potential risk and benefit for subjects being administered the lowest doses of MK-4166.

A fixed dosing regimen was used for this FIH trial. Recent publications show that both body weight adjusted dosing and fixed dosing approaches can lead to similar variability in human exposure depending on how clearance and volume of distribution are related to body weight. [50]; [51]. In the absence of this information for MK-4166, a fixed dose approach has been chosen. A conservative initial fixed dose is proposed as 0.0015 mg determined based on a 60 kg patient receiving a dose of 0.000025 mg/kg. The effect of body weight on the pharmacokinetics (PK) of MK-4166 and GITR target engagement will be evaluated to inform whether future studies will continue with a fixed dose regimen or switch to weight based dosing.

MK-4166 will be administered as a 30-minute IV infusion (+10/-5 minutes). Additional information regarding drug preparation and administration can be found in the Procedures Manual.

As of 16-Jan-2017, data are available for a total of 73 subjects: 41 subjects treated with MK-4166 monotherapy and 32 subjects treated with MK-4166 in combination with pembrolizumab. In the monotherapy arm, dose escalation began at 0.0015 mg and has reached 480 mg. In the combination therapy arm, dose escalation began at 1.1 mg and has reached 240 mg. Dose escalation is continuing per protocol. Treatment has been generally well tolerated. A total of 2 (2.7%) subjects have discontinued study treatment due to AEs, one in each treatment arm. The most common AEs reported to date by preferred term have been fatigue (32 out of 73 [44%] subjects), nausea (16 out of 73 [22%] subjects), abdominal pain and malignant neoplasm progression (14 out of 73 [19%] subjects each), anaemia, decreased appetite, and dyspnoea (13 out of 73 [18%] subjects each), infusion related reaction and vomiting (12 out of 73 [16%] subjects each), and pruritus (11 out of 73 [15%] subjects each). In total, 1 DLT has been observed to date; this DLT was a Grade 3 Indiana Pouch perforation reported in a subject with metastatic urethral cancer. The subject received 30 mg MK-4166 monotherapy. The investigator determined the event to be possibly related to study treatment because of the low incidence of spontaneous perforation and no obvious explanation for the event. See the IB for pharmacokinetic and pharmacodynamics results to date.

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 to 330 mg for MK-4166. Although dose escalations will depend on safety evaluations, a potential dose of 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 monkeys) showed no adverse effects at doses where the Cmax and AUC values were 20-fold and 5-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-4166 Monotherapy

Maximal efficacy was achieved in mouse preclinical studies using single 1 to 3 mg/kg doses. In the rapidly progressing syngeneic tumor models, no improvement in efficacy was observed with weekly or every other week 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-4166 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, 3 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-4166 in Combination with Pembrolizumab

As described previously, the combination of MK-4166 and pembrolizumab showed greater efficacy in preclinical studies than either agent alone. Therefore, the combination of MK-4166 and pembrolizumab is planned for study in clinical trials to assess whether selected groups of cancer patients 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-4166 and pembrolizumab, and determine a maximum tolerated dose and recommended Phase 2 dose for MK-4166 when used in combination with pembrolizumab. In this trial, pembrolizumab will be administered at 200 mg every 3 weeks. This is the pembrolizumab regimen currently being studied in multiple registration trials. Similar to the preclinical studies, MK-4166 and pembrolizumab will be administered on the same day for the first 4 cycles in Arm 2 when both drugs are administered.

4.2.3 Rationale for Endpoints

4.2.3.1 Safety Endpoints

The primary safety endpoint of this trial is to characterize the safety and tolerability of single agent MK-4166 and MK-4166 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 experienced by subjects who have received MK-4166 alone and in combination with pembrolizumab, including serious adverse events (SAEs) and events of clinical interest (ECIs).

Safety will be assessed by reported adverse experiences using CTCAE, version 4. The attribution to drug, time-of onset, duration of event, its resolution, and any concomitant medications administered will be recorded. AEs will be analyzed including but not limited to

all AEs, SAEs, fatal AEs, and laboratory changes. Furthermore, the occurrence of specific immune-related adverse events (irAEs) will be collected.

4.2.3.2 Efficacy Endpoints

An exploratory endpoint for this trial is to evaluate the anti-tumor activity of MK-4166 and MK-4166 in combination with pembrolizumab in subjects with advanced solid malignancies. Tumor response will be accessed using irRECIST 1.1.

Immunotherapeutic agents such as MK-4166 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-4166 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.

4.2.3.3 Pharmacodynamic Endpoints

As a required first step in pharmacologic activity, receptor engagement is fundamental to dosing strategies. To evaluate GITR target engagement, a receptor availability (RA) assay that compares the availability of surface GITR pre- and post-administration of MK-4166 has been developed.

Additional exploratory analyses will be performed to assess the effect of MK-4166 on immune cells in tumor tissues and in the circulation and are discussed in the following sections.

4.2.3.3.1 Target Engagement: Receptor Availability on Peripheral Blood Lymphocytes

Due to GITR internalization upon binding by MK-4166, 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-4166 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.

4.2.3.3.2 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. ADA response at the beginning of each cycle will be determined to understand drug metabolism, exposure and safety.

4.2.3.3.3 Serum Cytokines of Systemic Immune Activation

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).

4.2.3.4 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:Treg 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 Treg 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.

In Arm 1 (Part B) 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 tumor biopsy for biomarker analysis before starting treatment. Subjects will also be asked to agree to an optional tumor biopsy for biomarker analysis after starting treatment.

Immune modulatory agents may alter populations of circulating immune cells in blood. To assess the effect of MK-4166 on these cell populations, peripheral blood samples will be obtained at designated times before and after MK-4166 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.

4.2.3.5 Future Biomedical Research

The Sponsor will conduct Future Biomedical Research on specimens routinely and specifically collected 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.

5.0 METHODOLOGY

5.1 Entry Criteria

5.1.1 Diagnosis/Condition for Entry into the Trial

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. Parts A, B, and D: Have a histologically- or cytologically-confirmed metastatic solid tumor for which there is no available therapy which may convey clinical benefit.

   Solid tumors of any type are eligible for enrollment during dose escalation. Tumor types of greatest interest include, but are not limited to, malignant melanoma, renal cell carcinoma, non-small cell lung cancer, ovarian carcinoma, and colorectal carcinoma.

   Part E: Have advanced malignant melanoma (treatment-naïve or pre-treated), excluding uveal melanoma.

2. Have measurable disease by RECIST 1.1 criteria (Appendix 12.6).

3. Be ≥18 years of age on day of signing informed consent.

4. Have a performance status of 0 or 1 on the Eastern Cooperative Oncology Group (ECOG) Performance Scale (Appendix 12.4).

5. Demonstrate adequate organ function as defined by the following table (Table 1). All screening labs should be performed within 7 days of treatment initiation.

Table 1 Adequate Organ Function Laboratory Values

System	Laboratory Value
Hematological	
Absolute neutrophil count	≥1,500/mcL
Platelets	≥100,00/mcL
Hemoglobin	≥9 g/dL or ≥5.6 mmol/L
Renal	
Serum Creatinine **or** Creatinine Clearance (CrCl) (measured or calculated)[a] **or** Glomerular Filtration Rate (GFR) in place of CrCl	≤1.5 X ULN **or** ≥60 mL/min for subject with creatinine levels >1.5 X ULN
Hepatic	
Total bilirubin (serum)	≤1.5 X ULN **or** Direct bilirubin ≤ULN for subjects with total bilirubin levels >1.5 X ULN
AST (SGOT) and ALT (SGPT)	≤2.5 X ULN
Coagulation	
International Normalized Ratio (INR) or Prothrombin Time (PT)	≤1.5 X ULN
Activated Partial Thromboplastin Time (aPTT)	≤1.5 X ULN
[a] Creatinine clearance should be calculated per institutional standard	

6. 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.

7. Female subjects of childbearing potential must have a negative urine or serum pregnancy test at Screening and again within 24 hours prior to receiving the first dose of study treatment. If the urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required. The serum pregnancy test must be negative for the subject to be eligible.

8. Female subjects of childbearing potential must 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 last dose of study medication. Subjects of childbearing potential are those who have not been surgically sterilized or have not been free of menses for >1 year. Male subjects must agree to use an adequate method of contraception during sexual contact with females of childbearing potential starting with the first dose of study medication through 180 days after the last dose of study therapy.

9. Submit an evaluable 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.

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 28 days of administration of MK-4166.

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

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

5. Has a history of a 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.

6. 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.

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

8. Has an active autoimmune disease or a documented history of autoimmune disease, except vitiligo or resolved childhood asthma/atopy.

9. Has an active infection requiring therapy.

10. Has current pneumonitis, or a history of (non-infectious) pneumonitis that required steroids.

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

12. Is positive for Human Immunodeficiency Virus (HIV), Hepatitis B, or Hepatitis C.

13. 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.

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

15. 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.

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

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

18. Has clinically significant heart disease.

19. Has had major surgery in the past 16 weeks.

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

21. Is or has an immediate family member (spouse or children) 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 treatments to be used in this trial are outlined below in Table 2 and Table 3.

In Arm 1, Part A, an accelerated dose escalation in single subject cohorts will proceed based on safety events to a dose of 10 mg. Starting at a 30 mg dose (or earlier as described in Section 5.2.1.4) in Part B, the study will continue with a 3+3 design to identify a preliminary MTD.

In Arm 2, Part D, treatment in the combination arm will follow a 3+3 design during dose escalation to identify a preliminary MTD. Dose confirmation in Part E will refine the estimate of tolerability of the MTD in subjects with advanced malignant melanoma using a toxicity probability interval [1].

When both treatment arms are open for enrollment, 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). Once dose escalation (Parts A and B) is completed in Arm 1, only the combination therapy arm (Arm 2) of the study will be open for enrollment.

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, dose escalation in that arm of the trial may be stopped at a level below the maximum dose planned in the absence of safety findings and an MTD would not be determined for the respective regimen. In this case an administrative letter will be used to document the preliminary completion of dose escalation and, in the combination arm, transition to the dose confirmation part (Part E).

Table 2 Trial Treatment for MK-4166 Monotherapy (Arm 1)

Treatment during Part A: Accelerated Dose Escalation					
Drug	Dose/Potency	Dose Frequency	Route of Administration	Regimen/Treatment Period	Use
MK-4166	0.0015 mg 0.0045 mg 0.014 mg 0.04 mg 0.12 mg 0.37 mg 1.1 mg 3.3 mg 10 mg	Every 21 days.	Intravenous over 30 minutes	Day 1 of each 21-day cycle for up to 4 cycles	Experimental
Treatment during Part B: Dose Finding					
Drug	Dose/Potency	Dose Frequency	Route of Administration	Regimen/Treatment Period	Use
MK-4166	30 mg 60 mg 120 mg 170 mg 240 mg 330 mg 460 mg 650 mg 900 mg	Every 21 days.	Intravenous over 30 minutes	Day 1 of each 21-day cycle for up to 4 cycles	Experimental
Note: Dose levels shown in Table 2 are proposed dose levels, with 3-fold increases between doses levels in Part A, and 100% increases at the 30 mg and 60 mg dose levels, followed by 40% increases at and after the 120 mg dose level in Part B. 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-4166 with Pembrolizumab Combination (Arm 2)

Drug	Dose	Dose Frequency	Route of Administration	Regimen	Use
Treatment during Part D: Dose Finding					
MK-4166	1.1 mg 3.3 mg 10 mg 30 mg 60 mg 120 mg 170 mg 240 mg 330 mg 460 mg 650 mg 900 mg	Every 21 days	Intravenous over 30 minutes	Day 1 of each 21-day cycle up to 4 cycles	Experimental
Pembrolizumab	200 mg	Every 21 days	Intravenous over 30 minutes	Day 1 of each 21 day cycle up to 24 months of treatment	Experimental
Note: Dose levels shown in Table 3 are proposed dose levels, actual doses of MK-4166 will depend on safety/tolerability experienced in the monotherapy arm. Doses of MK-4166 used in combination will be 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-4166 in combination may continue escalation to that dose. Combination dose escalation will follow 3 + 3 design to identify a preliminary maximum dose.					

In Arm 2, pembrolizumab will be administered first, than after a 30 minutes interval, MK-4166 will be administered.

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)

Details on dose calculation, preparation and administration of MK-4166 and pembrolizumab are provided in the Procedures Manual.

5.2.1.2 Dose Escalation

In Arm 1 (MK-4166 monotherapy), an accelerated dose escalation in single subject cohorts will proceed based on safety events in Part A to a dose of 10 mg. Beginning with the 30 mg dose (or earlier as described below), the study will continue with a 3+3 design to identify a preliminary MTD.

Enrollment to Arm 2, (MK-4166 with pembrolizumab) will begin at the 1.1 mg dose level. All dose levels in Part D will follow a 3+3 design. Doses of MK-4166 used in combination with pembrolizumab will be 1 to 2 dose levels behind the monotherapy dose, until the MTD in the monotherapy arm is determined. Once the MTD in the monotherapy arm is established, the dose of MK-4166 in the combination arm may continue escalation to that dose. However, the dose of MK-4166 used in combination with pembrolizumab would not exceed the MTD for monotherapy.

5.2.1.3 Accelerated Dose Escalation (MK-4166 Monotherapy)

During the accelerated dose escalation part (Part A), each cohort will enroll a single subject and dose escalation will proceed as designated in Table 2, until a DLT is observed, or a subject experiences a Grade 2 or greater possibly, probably or definitely drug-related adverse event, or until the dose level of 10 mg is safely administered.

If a subject experiences a DLT, the study will convert to a 3+3 design starting at that level with 40% dose increments. See Section 5.2.2 for definition of DLTs.

If a single subject at a given dose level experiences a Grade 2 or greater drug-related adverse event, this cohort will be expanded to 3 subjects. If no additional drug-related adverse events of Grade 2 or greater occur (1/3), accelerated dose escalation will continue. If an additional drug-related adverse event of Grade 2 or greater occurs at that dose level ($\geq$2/3), escalation will convert to the 3+3 design. This will signify the transition to Part B. Further dose escalations from that level will proceed in approximately 40% increments.

Starting with the 30 mg dose, 3 subjects will be enrolled to each dose level, and dose escalation will proceed as designated in Table 2.

5.2.1.4 3+3 Dose Escalation

In Arm 1, once the 10 mg dose is safely administered in Part A, the study will proceed to Part B starting at the 30 mg dose, with 3 subjects enrolled at each new dose level and dose escalation continuing according to Table 2. Arm 2 will start with 3+3 dose escalation according to Table 3.

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 1-week observation period between the first and second subject treated with the combination in the first cohort of Arm 2.

Dose escalation will increase in increments of approximately 40% after either the 120 mg dose is safely administered, or starting with any dose where a DLT or 2 >Grade 2 treatment-related toxicities are observed.

Intermediate lower dose levels, not specified in Table 2 or 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 applied for the preliminary dose finding using the 3+3 design are as follows:

An initial cohort of 3 subjects is enrolled.

- If 0/3 subjects develop a DLT, escalation to the next dose 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 develop 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 develops a DLT (for a total of 2/6 subjects with a DLT at this dose level), the dose escalation part 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. In the combination arm, the study will proceed to dose confirmation (Part E).
  - 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 part 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. In the combination arm, the study will proceed to dose confirmation (Part E). 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 declaring the preliminary MTD.
- If ≥2/3 subjects develop a DLT, the dose escalation part 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. In the combination arm, the study will proceed to dose confirmation (Part E). 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 declaring the preliminary MTD.

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 part of the study in the combination arm. 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.

If the highest candidate dose of MK-4166 in combination with pembrolizumab 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 will be taken to the confirmation part in the combination arm.

5.2.1.5 Dose Confirmation (Arm 2 only)

Dose confirmation will occur in the combination therapy arm (Arm 2) only and will be restricted to subjects with advanced malignant melanoma (Part E). The objective of dose confirmation is to refine the estimate of the MTD based on a TPI design [1] with a target toxicity rate ≤30%. Dose confirmation involves the expansion of at least 1 dose level studied in the dose escalation part of the study.

Dose confirmation will begin with expansion of the preliminary MTD/MAD identified in the dose escalation part described above (Part D). 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 continuously be assessed and de-escalation and re-escalation to eligible doses will occur as shown in Table 4. If the MTD is the MAD, future subjects would stay at the current dose level even if Table 4 indicated an escalation. Dose confirmation will end when 20 subjects have been treated at a given dose. 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%.

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**	**15**	**16**	**17**	**18**	**19**	**20**
0	**S**	**E**	**E**	**E**	**E**	**E**	**E**	**E**	**E**	**E**	**E**	**E**	**E**	**E**	**E**	**E**	**E**
1	**S**	**S**	**S**	**S**	**S**	**S**	**E**	**E**	**E**	**E**	**E**	**E**	**E**	**E**	**E**	**E**	**E**
2	**D**	**S**	**S**	**S**	**S**	**S**	**S**	**S**	**S**	**S**	**S**	**E**	**E**	**E**	**E**	**E**	**E**
3	**DU**	**D**	**D**	**S**	**S**	**S**	**S**	**S**	**S**	**S**	**S**	**S**	**S**	**S**	**S**	**S**	**E**
4	**DU**	**DU**	**DU**	**D**	**D**	**D**	**S**	**S**	**S**	**S**	**S**	**S**	**S**	**S**	**S**	**S**	**S**
5		**DU**	**DU**	**DU**	**DU**	**DU**	**D**	**D**	**S**	**S**	**S**	**S**	**S**	**S**	**S**	**S**	**S**
6			**DU**	**DU**	**DU**	**DU**	**DU**	**DU**	**D**	**D**	**D**	**S**	**S**	**S**	**S**	**S**	**S**
7				**DU**	**DU**	**DU**	**DU**	**DU**	**DU**	**DU**	**D**	**D**	**D**	**D**	**S**	**S**	**S**
8					**DU**	**DU**	**DU**	**DU**	**DU**	**DU**	**DU**	**DU**	**DU**	**D**	**D**	**D**	**D**
9						**DU**	**DU**	**DU**	**DU**	**DU**	**DU**	**DU**	**DU**	**DU**	**DU**	**DU**	**D**
10							**DU**	**DU**	**DU**	**DU**	**DU**	**DU**	**DU**	**DU**	**DU**	**DU**	**DU**
11								**DU**	**DU**	**DU**	**DU**	**DU**	**DU**	**DU**	**DU**	**DU**	**DU**
12									**DU**	**DU**	**DU**	**DU**	**DU**	**DU**	**DU**	**DU**	**DU**
13										**DU**	**DU**	**DU**	**DU**	**DU**	**DU**	**DU**	**DU**
14											**DU**	**DU**	**DU**	**DU**	**DU**	**DU**	**DU**
15												**DU**	**DU**	**DU**	**DU**	**DU**	**DU**
16													**DU**	**DU**	**DU**	**DU**	**DU**
17														**DU**	**DU**	**DU**	**DU**
18															**DU**	**DU**	**DU**
19																**DU**	**DU**
20																	**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.

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 MK-4166 in Arm 1 or the MK-4166 with pembrolizumab combination in Arm 2, will be considered a DLT:

1. Grade 4 non-hematologic toxicity (not laboratory)
2. Grade 4 hematologic 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. Grade 3 non-hematologic toxicity (not laboratory) lasting >3 days despite optimal supportive care. Grade 3 nausea, vomiting or diarrhea will be considered a DLT if lasting more than 3 days despite optimal supportive care.
4. Any Grade 3 or Grade 4 non-hematologic laboratory abnormality, if
    a. medical intervention is required, or
    b. the abnormality leads to hospitalization, or
    c. 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 >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-4166 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-4166 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-4166 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-4166 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-4166 will be withheld for Grade 4 hematologic toxicities, non-hematological toxicity ≥Grade 3 including laboratory abnormalities, and severe or life-threatening AEs as per Table 5 below. 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-4166 Dose Modification and Treatment Discontinuation Guidelines for Drug-Related Adverse Events

Toxicity	Grade	Hold Treatment	Criteria for Restarting Treatment	Dose/Schedule for Restarting Treatment	Criteria for Discontinuation after Consultation with Sponsor
Hematologic toxicity	1, 2, 3	No	N/A	N/A	N/A
	4	Yes	Toxicity resolves to Grade 0-1, or to baseline	No change in dose. May increase dosing interval by 1 week	Toxicity does not resolve within 12 weeks of last dose. *Permanent discontinuation should be considered for any severe or life-threatening event*
Non-hematologic toxicity Note: Exception to be treated similar to Grade 1 toxicity • Grade 2 alopecia • Grade 2 fatigue	1	No	N/A	N/A	N/A
	2	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: may increase the dose schedule by 1 week for each occurrence	Toxicity does not resolve within 12 weeks of last dose.
	3, 4	Yes	Toxicity resolves to Grade 0-1 or baseline	May increase the dose schedule by 1 week for each occurrence	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 in 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 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-4166 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, trial treatment may be discontinued following discussion between the Sponsor and Investigator. However, if the subject is deriving clinical benefit from the trial treatment, the subject may be allowed to continue after discussion between the Sponsor and Investigator.

5.2.5 Timing of Dose Administration

Trial treatment may be administered up to 3 days before or 5 days after the scheduled Day 1 of each cycle, beginning in Cycle 3. Cycle 2 Day 1 may be administered up to 5 days after the scheduled day 1. 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-4166 occurring approximately 30 minutes after completion of the pembrolizumab administration.

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 or Vaccine Allocation

Treatment allocation by non-random assignment to Arm 1 or Arm 2 will occur centrally using an interactive voice response system / integrated web response system (IVRS/IWRS).

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 trial 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 trial treatment and while participating in the trial. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, chickenpox, yellow fever, rabies, BCG, and typhoid 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-4166 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-4166 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, (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-4166 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-4166 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.

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.

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

- Confirmed disease progression per response assessment criteria (See Section 7.2.1.7)

A subject with confirmed radiologic progression may continue to receive study treatment, after consultation with the Sponsor, if the Investigator deems the subject is receiving clinical benefit or value from treatment. Subjects who continue to receive study treatment after confirmed radiologic progression will continue to be followed according to the procedures and assessments listed under Cycle 7 and beyond in the Trial Flow Chart (Section 6.0).

- Noncompliance with trial treatment or procedure requirements
- Investigator's decision to withdraw the subject
- Clinical progression
- Subject has a confirmed pregnancy test
- Unacceptable adverse events
- Intercurrent illness that prevents further administration of treatment
- Administrative reasons requiring cessation of treatment
- Lost to follow-up

Once subjects have achieved the study objectives or the study has ended, they will be discontinued from this study and will be enrolled into an extension study to continue protocol-defined assessments and treatment.

5.9 Subject Replacement Strategy

A subject who discontinues from the trial will not be replaced.

5.10 Beginning and End of the Trial

The study begins when the first subject signs the informed consent. The end of the study may be designated as the time point when all subjects have discontinued the study or are a minimum of 6 months post initial study medication administration.

By the end of the study, if there are still subjects ongoing 6 months post initial study medication administration, they will be discontinued and enrolled into a pembrolizumab extension study.

5.11 Clinical Criteria for Early Trial Termination

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

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

Ample notification will be provided in the event of Sponsor decision to no longer supply MK-4166 or pembrolizumab.

6.0 TRIAL FLOW CHART

	Screening Phase	Treatment Phase[1] Cycle = 21 days															End of Treatment	Post Treatment Phase		
Treatment Cycle/Title	Screening (Visit 1)	Cycle 1						Cycles 2-4							Cycles 5 and 6 (Arm 2 only)	Cycle 7 and Beyond (Arm 2 only)	Discon	Post Treatment Safety Follow-up	Follow-up Visits	
Cycle Day		1	2	3	5	8	15	1	2	3	5	8	15	9 wks from 1st dose	1	1	At time of discon	30 days post discon	3 mos and 6 mos after end of treatment	Every 9 weeks until PD
Scheduling Window (Days):	-28 to -1					± 3	± 3					± 3	± 3	± 7				± 7	± 7	± 7
Administrative Procedures																				
Informed Consent	X[2]																			
Informed Consent for Future Biomedical Research	X[3]																			
Inclusion/Exclusion Criteria	X																			
Subject Identification Card	X																			
Demographics and Medical History	X																			
Prior and Concomitant Medication Review[4]	X	X	X	X		X	X	X	X	X		X	X		X	X	X	X		
Prior Oncology Treatment History	X																			
MK-4166 Drug Administration (Arm 1 & 2)		X						X												
Pembrolizumab Drug Administration (Arm 2)[5]		X						X							X	X				

	Screening Phase	Treatment Phase[1] Cycle = 21 days															End of Treatment	Post Treatment Phase		
Treatment Cycle/Title	Screening (Visit 1)	Cycle 1						Cycles 2-4							Cycles 5 and 6 (Arm 2 only)	Cycle 7 and Beyond (Arm 2 only)	Discon	Post Treat-ment Safety Follow-up	Follow-up Visits	
Cycle Day		1	2	3	5	8	15	1	2	3	5	8	15	9 wks from 1st dose	1	1	At time of discon	30 days post discon	3 mos and 6 mos after end of treat-ment	Every 9 weeks until PD
Scheduling Window (Days):	-28 to -1					± 3	± 3					± 3	± 3	± 7				± 7	± 7	± 7
Clinical Procedures/Assessments																				
Adverse Events Monitoring[6]	X	X	X	X		X	X	X	X	X		X	X		X	X	X	X		X
Full Physical Examination	X	X[7]						X[7]							X	X	X	X		X
Vital signs and weight[8]	X	X	X	X		X	X	X	X	X		X	X		X	X	X	X		X
Height	X																			
12-Lead Electrocardiogram[9]	X	X[7]						X[7]										X		
ECOG Performance Status	X	X[7]						X[7]							X	X	X	X		
Tumor Imaging[10]	X													X	X	X				X
Response Assessment[11]														X						X
Survival Status[12]		←																		→
Laboratory Procedures/Assessments to be performed by local laboratory																				
CBC with Differential[13]	X[14]	X[7, 14]	X			X	X	X[7, 14]				X	X		X	X	X	X		
C reactive protein[13]	X[14]	X[7, 14]	X			X	X	X[7, 14]				X	X		X					
PT/INR and aPTT	X[14]																			
Chemistry Panel[13]	X[14]	X[7, 14]	X			X	X	X[7, 14]				X	X		X	X	X	X		
LDH, GGT	X[14]	X[7]						X[7]							X					
Pregnancy test –Urine or Serum β-HCG[15]	X	X																		
Urinalysis	X[14]																			
Immunoglobulins (IgA, IgG, IgM)		X[7]						X[7]							X					

	Screening Phase	Treatment Phase[1] Cycle = 21 days															End of Treatment	Post Treatment Phase		
Treatment Cycle/Title	Screening (Visit 1)	Cycle 1						Cycles 2-4							Cycles 5 and 6 (Arm 2 only)	Cycle 7 and Beyond (Arm 2 only)	Discon	Post Treat-ment Safety Follow-up	Follow-up Visits	
Cycle Day		1	2	3	5	8	15	1	2	3	5	8	15	9 wks from 1st dose	1	1	At time of discon	30 days post discon	3 mos and 6 mos after end of treat-ment	Every 9 weeks until PD
Scheduling Window (Days):	-28 to -1					± 3	± 3					± 3	± 3	± 7				± 7	± 7	± 7
Thyroid function (T4, T3, TSH)[16]		X[7]						X[7]							X	X		X		
HIV, Hepatitis B and C[17]	X																			
Laboratory Procedures/Assessments to be performed by a central laboratory																				
Humoral Immunity Assays[18]		X[7]						X[7]							X					
Cytokine Panel[19]		X[7]	X	X				X[7]	X	X					X					
Anti-MK-4166 Antibodies (Arms 1 & 2)[20]		X[7]	X	X		X	X	X	X	X		X	X		X					
Pharmacokinetics for MK-4166 (Arms 1 & 2)[21]		X[7]	X	X	X (require for 9 lowest dose levels in Arm 1)	X	X	X	X	X	X (require for 9 lowest dose levels in Arm 1)	X	X		X					
Anti-Pembrolizumab Antibodies (Arm 2 only)[22]		X	X	X		X	X	X	X	X		X	X		X	X				
Pharmacokinetics for Pembrolizumab (Arm 2 only)[23]		X	X	X		X	X	X	X	X		X	X		X	X				
Blood for T-cell Immunophenotyping[24]		X						X												

	Screening Phase	Treatment Phase[1] Cycle = 21 days															End of Treatment	Post Treatment Phase		
Treatment Cycle/Title	Screening (Visit 1)	Cycle 1						Cycles 2-4							Cycles 5 and 6 (Arm 2 only)	Cycle 7 and Beyond (Arm 2 only)	Discon	Post Treat-ment Safety Follow-up	Follow-up Visits	
Cycle Day		1	2	3	5	8	15	1	2	3	5	8	15	9 wks from 1st dose	1	1	At time of discon	30 days post discon	3 mos and 6 mos after end of treat-ment	Every 9 weeks until PD
Scheduling Window (Days):	-28 to -1					± 3	± 3					± 3	± 3	± 7				± 7	± 7	± 7
Blood for RNA Correlative Studies[25]		X[7]						X[7]												
Blood for DNA Correlative Studies[25]		X[7]						X[7]												
Blood (DNA) for Genetics[26]		X																		
Tumor tissue collection (Parts B, D, and E only)[27]		X																		
Post-treatment tumor biopsy(Parts B, D and E only)[28]						X														
Pharmacodynamics (receptor availability flow cytometry assay)[29] (Arms 1 & 2)	X	X[7]	X	X (require for MK-4166 dose levels < 30mg)	X (require for 9 lowest dose levels in Arm 1)	X	X	X	X	X require for MK-4166 dose levels < 30mg)	X (require for 9 lowest dose levels in Arm 1	X	X		X					

1. In general, assessments/procedures are to be performed on Day 1 and prior to dosing for each cycle, unless otherwise specified.
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 subjects participation in the trial. Detailed instructions for the collection and management of FBR specimens are provided in the Procedure Manual.
4. Prior medications-Record all medications taken within 28 days of the screening visit. Concomitant medication- Record all new medication started from the screening visit through the Safety Follow-up visit.
5. In the Arm 2, pembrolizumab is administered first, then following a 30-minute interval, MK-4166 will be administered.
6. Record all AEs occurring from signing of informed consent until 30 days after the last dose of MK-4166. Record all SAEs and ECIs through 90 days after last dose of treatment. Afterwards, report only SAEs and ECIs that are considered related to study treatment. See Section 7.2 for a full description of reporting requirements.
7. These samples and procedures required predose Day 1 may be performed up to 72 hours prior to dosing.
8. 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-4166 infusion. In Arm 2, beginning with Cycle 5, collect VS prior to pembrolizumab dosing on Day 1 of each cycle. Weight to be obtained Day 1 of each cycle. Height to be recorded at Screening only.
9. 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-4166 infusion in Cycles 1-4, and at the 30 days post discon visit.
10. Tumor imaging (CT scan or MRI) should be performed within 28 days of enrollment, 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.
11. Response evaluation will be according to irRECIST version 1.1. Response will be assessed locally at the study site 9 weeks after the 1st dose, than every 9 weeks until disease progression. Disease progression, partial response and complete response to be confirmed at least 4 weeks after initial determination. Scans used for tumor measurements may be requested for central review. The timing for imaging should follow calendar days and should not be adjusted for delays in Cycle starts or extension of cycle frequencies. The same imaging technique should be used on a subject throughout the trial.
12. Upon Sponsor request, participants may be contacted for survival status at any time during the course of the study.
13. In Arm 1 and Arm 2, on Day 1 in cycles 1-4, CBC with differential, CRP and chemistry panel should be drawn prior to dosing and repeated 4 hours after the start of the infusion, with results of the CBC and chemistry panel 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 panel should be drawn prior to dosing.
14. Laboratory tests at Screening are to be performed within 7 days prior to the first dose of study treatment.
15. For women of reproductive potential, a urine pregnancy test will be performed at Screening and within 24 hours of receiving the first dose of study medication. If urine pregnancy test cannot be confirmed as negative, a serum pregnancy test is required.
16. 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.
17. 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).
18. 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).
19. Collect cytokine panel on Day 1 predose, 1-hr, and 4-hr after the start of the infusion, and on Day 2, and Day 3 of Cycles 1-4 in Arm 1, and Cycles 1-6 in Arm 2. (Specific assays designated in procedures manual.)
20. MK-4166 anti-drug antibody (ADA) will be drawn in Arm 1, predose on Day 1, Day 2, Day 3, Day 8 and Day 15 of Cycles 1-4. In Arm 2, MK-4166 ADA will be obtained predose on Day 1, Day 2, Day 3, Day 8 and Day 15 of Cycles 1-4, and predose on Day 1 of Cycles 5 and 6.
21. MK-4166 pharmacokinetic (PK) samples will be drawn in each cycle on Day 1 predose, at the end of infusion (+ 10 minutes), 2h after the start of the infusion (+/- 10 minutes), and on Day 2, Day 3, Day 5, Day 8, and Day 15 for subjects treated at the 9 lowest dose levels in Arm 1. Starting at the 10th dose level in Arm 1 and all dose levels in Arm 2, PK samples will be drawn in each cycle on Day 1 predose, at the end of MK-4166 infusion (+ 10 minutes), 2h after the start of the MK-4166 infusion (+/- 10 minutes), on Day 2, Day 3, Day 8, and Day 15 of Cycles 1-4. In addition, in Arm 2, MK-4166 PK will be drawn predose in Cycles 5 and 6. If the sample day falls on a weekend or holiday, please consult the Sponsor for alternate sample collection times.
22. Pembrolizumab anti-drug antibody (ADA) will be drawn in Arm 2 only predose on Day 1, Day 2, Day 3, Day 8 and Day 15 in Cycles 1-4, predose in Cycles 5, 6, 8 and every 4 cycles thereafter.
23. Pembrolizumab pharmacokinetic (PK) samples will be drawn in Arm 2 only, Cycles 1-4 Day 1 predose, at the end of the pembrolizumab infusion (+10 minutes), at the end of MK-4166 infusion (+ 10 minutes), 2h after the start of the MK-4166 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. If the sample day falls on a weekend or holiday, please consult the Sponsor for alternate sample collection times.
24. Blood for T-cell immunophenotyping will be drawn prior to dosing on Day 1 of Cycles 1-4. Detailed instructions for the collection and management of these samples are provided in the Procedure Manual.

25. 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-4166. Detailed instructions for the collection and management of these samples are provided in the Procedure Manual.
26. Blood for genetics sample will be collected to explore host genetics and to identify genetic predictors which may have a role in therapeutic response to MK-4166. Detailed instructions for the collection and management of the genetics sample are provided in the Procedure Manual. Blood for genetics will be retained for Future Biomedical Research if the subject signs the Future Biomedical Research informed consent.
27. Tumor tissue (archival or newly obtained biopsy) will be required in Parts B, D, and E. Leftover tissue may also be saved for future biomedical research if the subject signs the Future Biomedical Research consent.
28. Tumor biopsy will be requested in Parts B, 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.
29. Blood sample for Pharmacodynamic (PD) will be drawn in Screening, in Cycles 1-4 on Day 1 pre-dose, at the end of MK-4166 infusion (+ 10 minutes), 2h after the start of the MK-4166 infusion (+/- 10 minutes), on Day 2, Day 3, Day 5, Day 8, and Day 15 for subjects treated at the 9 lowest dose levels in Arm 1. Starting at the 10^{th} dose level in Arm 1 and all dose levels in Arm 2, PD samples will be drawn in Screening, in Cycles 1-4 on Day 1 pre-dose, at the end of the MK-4166 infusion (+ 10 minutes), 2h after the start of the MK-4166 infusion (+/- 10 minutes), on Day 2, Day 3, Day 8, and Day 15. In addition, in Arm 2, PD samples will be drawn predose in Cycles 5-6. In both Arms, the following 2 timepoints -Day 1 2hr after start of infusion and Day 3 - PD samples will not be collected once the dose level off MK-4166 is $\geq$30 mg. If the sample day falls on a weekend or holiday, please consult the Sponsor for alternate sample collection times. If the data from the receptor availability assay indicates saturation of the receptor at a given dose, then the Sponsor may eliminate collection of blood for and assessment of this pharmacodynamic assay at higher doses. This will be indicated in an administrative memo.

7.0 TRIAL PROCEDURES

7.1 Trial Procedures

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

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

7.1.1 Administrative Procedures

7.1.1.1 Informed Consent

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

7.1.1.1.1 General Informed Consent

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

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

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

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

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

7.1.1.1.2 Consent and Collection of Specimens for Future Biomedical Research

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

7.1.1.2 Inclusion/Exclusion Criteria

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

7.1.1.3 Subject Identification Card

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

7.1.1.4 Medical History

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

7.1.1.5 Prior and Concomitant Medications Review

7.1.1.5.1 Prior Medications

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

7.1.1.5.2 Concomitant Medications

The investigator or qualified designee will record all 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.

7.1.1.6 Disease Details and Treatments

7.1.1.6.1 Disease Details

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

7.1.1.6.2 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 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.

7.1.1.8 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 in fact "randomized", this unique number is termed a randomization number throughout the protocol for operational purposes. Beginning with Amendment #3, the randomization number will be assigned by an IVRS at time of enrollment. Allocation of subjects between the 2 arms will be managed by the Sponsor through the 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.

In a situation where rerandomization of the subject is planned (eg, study extension periods), the rerandomization will be based on a new randomization schedule; however, each subject will retain his/her original treatment/randomization number. Only the study intervention regimen associated with the rerandomization period or phase may change.

7.1.1.9 Trial Compliance (Study Drug Administration)

All doses of MK-4166 and pembrolizumab will be administered under the supervision of a qualified physician and/or designee experienced in the use of anticancer agents.

The instructions for preparing and administering MK-4166 and pembrolizumab are provided in the Procedure Manual.

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

7.1.2 Clinical Procedures/Assessments

7.1.2.1 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. Toxicities will be characterized in terms of seriousness, causality, toxicity grade and action taken with regard to trial treatment.

All AEs of unknown etiology associated with MK-4166 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-4166 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 will review the safety and tolerability of each trial treatment, the appropriateness of dose escalation, when each cohort is completed and the next cohort is opened for enrollment. Frequency of these communications will depend on the enrollment of each cohort, as well as any potential new information regarding a safety concern in this trial or other relevant trials.

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

7.1.2.2 Full Physical 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 comes first.

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-4166. 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-4166. 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% 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. A subject with confirmed radiologic progression may continue to receive study treatment, after consultation with the Sponsor, if the Investigator deems the subject is receiving clinical benefit or value from treatment. Subjects who continue to receive study treatment after confirmed radiologic progression will continue to be followed according to the procedures and assessments listed under Cycle 7 and beyond in the Trial Flow Chart (Section 6.0).

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 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 occurs first.

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

7.1.2.8 Tumor Tissue Collection and Correlative Studies Blood Sampling

In Arm 1 (Part B) 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 tumor biopsy for biomarker analysis before starting treatment. Subjects will also be asked to agree to an optional tumor biopsy for biomarker analysis after starting treatment. Samples will be sent to a central laboratory.

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.

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.

Blood for correlative studies (RNA and a separate DNA sample) will be obtained prior to dosing in Cycle 1 and prior to dosing in Cycle 2, or Cycle 1 Day 22 for subjects who do not receive a second dose of MK-4166.

Sample collection, storage, and shipment instructions for archival tumor tissue samples, newly obtained biopsy specimens, and blood for correlative studies are provided in the Procedure Manual.

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 are provided 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	Serum β-human chorionic gonadotropin (β-hCG)
Hemoglobin	Alkaline phosphatase	Glucose	Hepatitis B (HBsAg)
Platelet count	Alanine aminotransferase (ALT)	Protein	Hepatitis C (HCV RNA) or Hepatitis C antibody
WBC (total and differential)	Aspartate aminotransferase (AST)	Specific gravity	HIV
Red Blood Cell Count	Carbon dioxide (CO_2 or Bicarbonate	Microscopic exam, if abnormal results are noted	PT (INR)
Absolute Neutrophil Count	Calcium	Urine pregnancy test	aPTT
Absolute lymphocyte count	Chloride		IgA
C reactive protein	Creatinine		IgG
	Glucose		IgM
	Lactate dehydrogenase (LDH)		Free thyroxine (T4)
	Phosphorus		Thyroid Stimulating Hormone (TSH)
	Potassium		Total Triiodothyronine (T3)
	Sodium		Anti-MK-4166 antibodies
	Total Bilirubin		Humoral Immunity Assay
	Direct Bilirubin, if total bilirubin is elevated above the upper limit of normal		Anti-MK-3475/pembrolizumab antibodies
	Total protein		Cytokines
	Blood Urea Nitrogen		
	Uric acid		
	Gamma Glutamyl transpeptidase (GGT)		

Laboratory tests for Screening should be performed within 7 days prior to the first dose of MK-4166 or pembrolizumab. After Cycle 1, pre-dose laboratory tests can be performed up to 72 hours prior to dosing. Results must be reviewed by the investigator of qualified designee and found to be acceptable prior to each dose of MK-4166 or pembrolizumab.

7.1.3.2 Pharmacokinetic/Pharmacodynamic Evaluations

7.1.3.2.1 Blood Collection for Serum MK-4166 and Pembrolizumab

To evaluate the exposure of MK-4166 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.

7.1.3.2.2 Blood Collection for Anti-MK-4166 Antibodies and Anti-Pembrolizumab Antibodies

To evaluate the immunogenicity of MK-4166 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.

7.1.3.2.3 Blood for Receptor Availability Assay

Sample collection, storage, and shipment instructions for receptor availability flow cytometry assay samples are provided in the Procedure Manual.

The timepoints for PD sampling are described in Section 6.0-Trial Flow Chart.

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 sites by administrative memo that this sample no longer will be collected. Decision to stop collection of blood for the receptor Availability Assay will be made independently for Arms 1 and 2.

7.1.3.3 Future Biomedical Research

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

- Leftover blood for genomics use
- Leftover archival tumor tissue or leftover newly obtained biopsy samples

7.1.4 Other Procedures

7.1.4.1 Withdrawal/Discontinuation

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

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

7.1.4.1.1 Withdrawal From Future Biomedical Research

Subjects may withdraw their consent for Future Biomedical Research and have their specimens and all derivatives destroyed. Subjects may withdraw consent at any time by contacting the

principal investigator for the main trial. If medical records for the main trial are still available, the investigator will contact the Sponsor using the designated mailbox (clinical.specimen.management@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.

7.1.4.2 Blinding/Unblinding

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

7.1.4.3 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 with the study documentation 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 syringe and/or pump – used to administer study treatment

7.1.5 Visit Requirements

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

7.1.5.1 Screening

Approximately 28 days prior to the first dose of treatment, 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.

Written consent must be obtained prior to performing any protocol specific procedure. Results of a test performed prior to the subject signing consent as part of routine clinical management are acceptable in lieu of a screening test if performed within the specified time frame. Screening procedures are to be completed within 28 days prior to the first dose of trial treatment except for the following:

- Screening laboratory tests are to be performed within 7 days prior to the first dose of trial treatment.

- For women of reproductive potential, a urine pregnancy test will be performed within 24 hours prior to first dose of trial treatment. If urine pregnancy results cannot be confirmed as negative, a serum pregnancy test, performed by the local study site laboratory, will be required.

7.1.5.2 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-4166 by the Sponsor. In Arms 1 and 2, MK-4166 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 trial treatment or procedure requirements, or administrative reasons requiring cessation of treatment.

7.1.5.3 Post-Treatment Visits

7.1.5.3.1 Safety Follow-up Visit

The mandatory Safety Follow-Up Visit should be conducted approximately 30 days after the last dose of trial treatment or before the initiation of a new antineoplastic treatment, whichever comes first. 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 occurs first.

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

7.1.5.3.2 Follow-up Visits

Subjects who complete treatment or who discontinue trial 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.

Once subjects have achieved the study objectives or the study has ended, they will be discontinued from this study and will be enrolled into an extension study to continue protocol-defined assessments and treatment.

7.1.5.4 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 the course of the use of the Sponsor's product in clinical trials or within the follow-up period specified by the protocol, or prescribed in clinical practice, from overdose (whether accidental or intentional), from abuse and from withdrawal.

Adverse events may also occur in screened subjects during any pre-allocation baseline period as a result of a protocol-specified intervention, including washout or discontinuation of usual therapy, diet, placebo treatment or a procedure.

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

All adverse events that occur after the consent form is signed but before randomization/treatment allocation must be reported by the investigator if they cause the subject to be excluded from the trial, or are the result of a protocol-specified intervention, including but not limited to washout or discontinuation of usual therapy, diet, placebo treatment or a procedure.

From the time of randomization/treatment allocation through 30 days following cessation of treatment, all adverse events must be reported by the investigator. Such events will be recorded at each examination on the Adverse Event case report forms/worksheets. The reporting timeframe for adverse events meeting any serious criteria is described in section 7.2.3.1. The investigator will make every attempt to follow all subjects with non-serious adverse events for outcome.

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

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

For purposes of this trial, an overdose will be defined as any dose exceeding the prescribed dose for MK-4166 by 20%, or a pembrolizumab dose of ≥1000mg (≥ 5x the indicated dose). No specific information is available on the treatment of overdose of MK-4166 or pembrolizumab. In the event of overdose, treatment should be discontinued and the subject should be observed closely for signs of toxicity. Appropriate supportive treatment should be provided if clinically indicated.

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

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

All reports of overdose with and without an adverse event must be reported within 24 hours to the Sponsor either by electronic media or paper. Sponsor Contact information 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 other than progression of the cancer under study (reference Section 7.2.3.3 for additional details), that occurs to any subject must be reported within 24 hours to the Sponsor if it causes the subject to be excluded from the trial, or is the result of a protocol-specified intervention, including but not limited to washout or discontinuation of usual therapy, diet, placebo treatment or a procedure.

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

Additionally, any serious adverse event, considered by an investigator who is a qualified physician to be related to the Sponsor's product that is brought to the attention of the investigator 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).

A separate guidance document has been provided entitled "MK-4166 and Pembrolizumab Events of Clinical Interest and Immune-Related Adverse Event Guidance Document." This document can be found in the administrative binder and provides guidance regarding identification, evaluation and management of ECIs and irAEs. Subjects should be assessed for possible ECIs prior to each dose. Laboratory results should be evaluated and subjects should be asked for signs and symptoms suggestive of an immune-related event. Subjects who develop an ECI thought to be immune-related should have additional testing to rule out other etiological causes. If laboratory results or symptoms indicated a possible immune-related ECI then additional testing should be performed to rule out other etiologic causes. If no other cause was found, then it is assumed to be immune-related.

7.2.4 Evaluating Adverse Events

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

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

Table 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 new **cancer;** (that is not a condition of the study) **or**	
	Is an overdose (whether accidental or intentional). Any adverse event associated with an overdose is considered a serious adverse event. 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 test drug	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 there is another obvious cause of the AE. (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.

8.0 STATISTICAL ANALYSIS PLAN

This section outlines the statistical analysis strategy and procedures for the study. Changes to analyses made after the protocol has been finalized, but prior to unblinding, will be documented in a supplemental SAP (sSAP) and referenced in the Clinical Study Report (CSR) for the study. Post hoc exploratory analyses will be clearly identified in the CSR.

8.1 Statistical Analysis Plan Summary

Key elements of the statistical analysis plan are summarized below; the comprehensive plan is provided in Section 8.2 to Section 8.12.

Study Design Overview	Phase 1 trial of single agent MK-4166 and MK-4166 in combination with pembrolizumab in subjects with advanced malignancies
Analysis Populations	Safety: All Subjects as Treated (ASaT) Efficacy (exploratory): Single agent MK-4166: Full Analysis Set (FAS1); MK-4166 in combination with pembrolizumab: Full Analysis Set (FAS2)
Primary Endpoint(s)	Safety: DLT
Key Secondary Endpoints	PK parameters of single agent MK-4166 and MK-4166 in combination with pembrolizumab
Statistical Methods for Key Efficacy/Immunogenicity/ Pharmacokinetic Analyses	Serum concentrations of MK-4166 in the MK-4166 Arm and serum concentrations of MK-4166 and pembrolizumab in the MK-4166 administered with pembrolizumab 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-4166 and MK-4166 co-administered with pembrolizumab without randomization; 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
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 of the study depends on the observed DLT profiles of MK-4166 monotherapy and MK-4166 co-administered with pembrolizumab. The sample size of 92 subjects will be used for study planning purposes.

8.2 Responsibility for Analyses/In-House Blinding

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

This trial is conducted as an open-label trial, 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 6 months after the enrollment of the last subject.

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 1.1 by the investigator review. Subjects with missing outcome on objective response will be considered non-responders. This endpoint is used to evaluate 2 primary efficacy hypotheses.

Disease Control Rate (DCR): is defined as the percentage of subjects who have achieved stable disease or confirmed complete response (CR) or confirmed partial response (PR) according to irRECIST 1.1 by the investigator review. Subjects with missing outcome on objective response will be considered non-responders.

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 1.1 by the investigator review. Response duration will be only determined for confirmed responses.

Best Overall Response per irRECIST 1.1 [Appendix 12.6]: the best response attained during the study with 4 categories based upon irRECIST 1.1 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 1.1 by the investigator review. Subjects without documented PD/death will be censored at the last disease assessment date.

Best Target Lesion Response: is defined as the maximum percent reduction in tumor line length over target lesions by the investigator review.

Time to Confirmed Response: is defined only for subjects with confirmed response by the investigator review as 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 1.1 criteria and, if needed, central review might be conducted.

PK endpoints: serum concentrations of MK-4166 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 7.0.

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 1 dose of study treatment. In case of treatment administration errors, subjects will be analyzed according to the treatment they actually received. For DLT evaluation, ASaT subjects that were observed for safety for 21 days after the first dose of assigned treatment or experienced a DLT prior to 21 days after the first dose of assigned treatment will be used.

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

8.5.2 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-4166 (Arm 1; FAS1) or MK-4166 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 at the RP2D or MTD for MK-4166 monotherapy and the subset of FAS2 subjects treated at the RP2D for combination MK-4166 plus pembrolizumab therapy, the estimates of the ORR and DCR and the 95% confidence intervals for the estimates based on the Clopper-Pearson method will be provided. For PFS, DOR, and time to confirmed response Kaplan-Meier plots will be provided. The waterfall plots will be provided for the best target lesion response and the swimmer plots will be provided for DOR.

The ORR, DCR, BOR, DOR, PFS, best target lesion response, and time to confirmed response in subjects treated with doses below the RP2D 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-4166 (Arm 1) or MK-4166 in combination with pembrolizumab dose level that had at least 3 subjects treated and listed for other dose levels. Laboratory assessments, vital signs, and other safety endpoints will be summarized as appropriate.

Immune-related ECIs (irECIs) that are designated as AEs of special interest will be summarized in separate tables from other AEs. Any AE of unknown etiology associated with MK-4166 or MK-4166 in combination with pembrolizumab exposure will be evaluated to determine if it is possibly an event of clinical interest (ECI) of a potentially immunologic etiology (irECI) (see Section 7.2.3.2).

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.

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 recommended MK-4166 Phase 2 dose or MTD, and the set of subjects treated with the recommended Phase 2 dose for combination of MK-4166 with pembrolizumab.

8.6.3.2 Population PK Analyses

Serum concentrations of MK-4166 in the MK-4166 Arm and serum concentrations of MK-4166 and pembrolizumab in the MK-4166 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-4166 monotherapy and MK-4166 co-administered with pembrolizumab in adult subjects with advanced solid tumors and to establish the MTD/RP2D for MK-4166 monotherapy and MK-4166 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 doses the 3+3 design is triggered, and what doses are identified as the RP2Ds. 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 in Part A to the end of the 2-year treatment period following enrollment of the last subject in Part E.

The enrollment time was conservatively estimated assuming that during dose acceleration a subject can be enrolled every 3 weeks and during the 3+3 parts and the dose confirmation a subject can be enrolled every week.

Scenario 1: No DLTs during Parts A, B, D, and E. For MK-4166 monotherapy, in a scenario where no DLTs are encountered during the dose escalation part and Part B continues to the highest dose in Table 2, the sample size across Parts A and B would be 36 subjects (9 subjects in Part A plus 27 subjects across 9 doses in Part B). For MK-4166 with pembrolizumab, in a scenario where Arm 2 starts at 1.1 mg MK-4166 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 3, the sample size across Parts D and E would be 56 subjects (36 subjects across 12 doses in Part D plus 20 subjects at the RP2D in Part E). In this scenario, the total sample size would be 92 subjects.

It would take 27 weeks to enroll 9 MK-4166 monotherapy subjects in Part A and proceed to Part B enrolment; it would take an additional 83 weeks to enroll 83 subjects (27 in Part B and 56 in Parts D and E). Thus, in this scenario the enrollment time would be 110 weeks and the time required to determine the 2 MTDs would be 113 weeks. The study duration then would be approximately 110 weeks + 2 years or 4.12 years. If dose escalation stops at a dose below the highest dose in either treatment arm, the study might require less than 92 subjects and the enrollment duration might be less than 110 weeks. Also, with no DLTs observed, it might be possible to enroll subjects faster than 1 subject every week during the 3+3 dose escalation parts (Parts B and D) and the dose confirmation part (Part E) which would 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 doses are given to 3 subjects each and 5 doses (including the highest one) are given to 6 subjects each in Part B, while in Arm 2, 6 doses are given to 3 subjects each and 6 doses (including the highest one) are given to 6 subjects each in Part D. Also suppose that the top dose is confirmed as the RP2D dose without de-escalation in Part E. Thus, the sample size in Arm 1 would be 51 subjects (9 subjects in Part A plus 42 subjects in Part B) and the sample size in Arm 2 would be 74 subjects (54 subjects in Part D plus 20 subjects in Part E). In this scenario, the total sample size would be 125 subjects.

It would take 27 weeks to enroll 9 MK-4166 monotherapy subjects in Part A and proceed to Part B enrolment; it would take an additional 116 weeks to enroll 116 subjects (42 in Part B

and 74 in Parts D and E). Thus, in this scenario the enrollment time would be 143 weeks and the time required to determine the 2 MTDs would be 146 weeks. The study duration then would be approximately 143 weeks + 2 years or 4.75 years.

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 the 1.1 mg dose and dose escalation continues in 21 steps to the 900 mg dose, with 3 subjects per dose in the 3+3 design, the sample size across Parts D and E in Arm 2 would be 83 subjects (63 subjects in Part D plus 20 subjects 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 is 36 subjects (9 subjects in Part A plus 27 subjects across 9 doses in Part B). In this scenario, the total sample size would be 119 subjects.

It would take 27 weeks to enroll 9 MK-4166 monotherapy subjects in Part A and proceed to Part B enrolment; it would take an additional 110 weeks to enroll 110 subjects (27 in Part B and 83 in Parts D and E). Thus, in this scenario the enrollment time would be 137 weeks and the time required to determine the 2 MTDs would be 140 weeks. The study duration then would be approximately 137 weeks + 2 years or 4.6 years.

The plausible sample size of approximately 92 subjects and the enrollment time of 110 weeks that correspond to the first described scenario are used for operational purposes.

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 may be calculated for each subject for MK-4166 and pembrolizumab separately.

8.12 Extent of Exposure

A subject's extent of exposure to MK-4166 is defined as the total number of doses of MK-4166 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-4166 and MK-4166 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 10.

Clinical supplies will be packaged to support enrollment and replacement subjects as required. When a replacement subject is required, the Sponsor or designee needs to be contacted prior to dosing the replacement supplies.

Table 10 Product Descriptions

Product Name & Potency	Dosage Form
MK-4166 100 mg	Injection
MK-3475 100 mg	Injection

All other supplies not indicated in Table 10 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-4166 as directed in the protocol. Each kit will contain 1 vial.

Sites will also receive open label vials of MK-3475.

9.3 Clinical Supplies Disclosure

The trial is open-label; therefore, the subject, the trial site personnel, the Sponsor and/or designee are not blinded. The product identification (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 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 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 discarding 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.

11.0 LIST OF REFERENCES

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

[2] Tone M, Tone Y, Adams E, Yates SF, Frewin MR, Cobbold SP, et al. Mouse glucocorticoid-induced tumor necrosis factor receptor ligand is costimulatory for T cells. Proc Natl Acad Sci U S A. 2003 Dec 9;100(25):15059-64.

[3] Nocentini G, Ronchetti S, Petrillo MG, Riccardi C. Pharmacological modulation of GITRL/GITR system: therapeutic perspectives. Br J Pharmacol 2012;165:2089-99.

[4] Miller AM, Lundberg K, Ozenci V, Banham AH, Hellstrom M, Egevad L, et al. CD4+CD25high T cells are enriched in the tumor and peripheral blood of prostate cancer patients. J Immunol 2006;177:7398-405.

[5] Pedroza-Gonzalez A, Verhoef C, Ijzermans JNM, Peppelenbosch MP, Kwekkeboom J, Verheij J, et al. Activated tumor-infiltrating CD4+ regulatory T cells restrain antitumor immunity in patients with primary or metastatic liver cancer. Hepatology 2013;57(1):183-94.

[6] Suvas S, Kim B, Sarangi PP, Tone M, Waldmann H, Rouse BT. In vivo kinetics of GITR and GITR ligand expression and their functional significance in regulating viral immunopathology. J Virol 2005;79(18):11935-42.

[7] Ronchetti S, Zollo O, Bruscoli S, Agostini M, Bianchini R, Nocentini G, et al. GITR, a member of the TNF receptor superfamily, is costimulatory to mouse T lymphocyte subpopulations. Eur J Immunol 2004;34:613-22.

[8] Kanamaru F, Youngnak P, Hashiguchi M, Nishioka T, Takahashi T, Sakaguchi S, et. al. Costimulation via glucocorticoid-induced TNF receptor in both conventional and CD25+ regulatory CD4+ T cells. J Immunol. 2004;172:7306-7314.

[9] Ronchetti S, Nocentini G, Bianchini R, Krausz LT, Migliorati G. Riccardi C. Glucocorticoid-induced TNFR-related protein lowers the threshold of CD28 costimulation in CD8+ T cells. J Immunol 2007;179:5916-26.

[10] Ponte JF, Ponath P, Gulati R, Slavonic M, Paglia M, O'Shea A, et al. Enhancement of humoral and cellular immunity with an anti-glucocorticoid-induced tumour necrosis factor receptor monoclonal antibody. Immunology. 2010 Jun;130(2):231-42.

[11] Stephens GL, McHugh RS, Whitters MJ, Young DA, Luxenberg D, Carreno BM, et al. Engagement of glucocorticoid-induced TNFR family-related receptor on effector T cells by its ligand mediates resistance to suppression by CD4+CD25+ T cells. J Immunol 2004;173:5008-20.

[12] Nocentini G, Ronchetti S, Cuzzocrea S, Riccardi C. GITR/GITRL: more than an effector T cell co-stimulatory system. Eur J Immunol 2007;37:1165-9.

[13] Shimizu J, Yamazaki S, Takahashi T, Ishida Y, Sakaguchi S. Stimulation of CD25(+)CD4(+) regulatory T cells through GITR breaks immunological self-tolerance. Nat Immunol. 2002 Feb;3(2):135-42.

[14] Mellman I, Coukos G, Dranoff G. Cancer immunotherapy comes of age. Nature 2011;480:480-9.

[15] Chen Y-L, Chen Y-S, Lin H-H, Chan C-W, Chen S-C, Chen C-H. Immunostimulatory flagellin from Burkholderia pseudomallei effects on an increase in the intracellular calcium concentration and up-regulation of TNF-alpha by mononuclear cells. Microbiol Immunol 2007;51(1):81-6.

[16] Hellstrom KE, Hellstrom I, Chen L. Can co-stimulated tumor immunity be therapeutically efficacious? Immunol Rev 1995;145:123-45.

[17] U.S. Prescribing Information: PROVENGE (sipuleucel-T) Suspension for Intravenous Infusion: 2011.

[18] Suntharalingam G, Perry MR, Ward S, Brett SJ, Castello-Cortes A, Brunner MD, et al. Cytokine storm in a phase 1 trial of the anti-CD28 monoclonal antibody TGN1412. N Engl J Med 2006;355(10):1018-28.

[19] Vonderheide RH, Dutcher JP, Anderson JE, Eckhardt SG, Stephans KF, Razvillas B, et al. Phase I study of recombinant human CD40 ligand in cancer patients. J Clin Oncol 2001;19(13):3280-7.

[20] Vonderheide RH, Flaherty KT, Khalil M, Stumacher MS, Bajor DL, Hutnick NA, et al. Clinical activity and immune modulation in cancer patients treated with CP-870,893, a novel CD40 agonist monoclonal antibody. J Clin Oncol 2007;25(7):876-83.

[21] Molckovsky A, Siu LL. First-in-class, first-in-human phase I results of targeted agents: highlights of the 2008 American society of clinical oncology meeting. J Hematol Oncol 2008;1:20.

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

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

[24] Al-Shibli K, Al-Saad S, Andersen S, Donnem T, Bremnes RM, Busund L-T. The prognistic value of intraepithelial and stromal CD3-, CD117- and CD138-positive cells in non-small cell lung carcinoma. APMIS 2010;118:371-82.

[25] Deschoolmeester V, Baay M, Van Marck E, Weyler J, Vermeulen P, Lardon F, et al. Tumor infiltrating lymphocytes: an intriguing player in the survival of colorectal cancer patients. BMC Immunol 2010;11:19.

[26] Diez M, Pollán M, Enriquez JM, Dominguez P, Santana A, Tobaruela E, et al. Histopathologic prognostic score in colorectal adenocarcinomas. Anticancer Res 1998;18(1B):689-94.

[27] Galon J, Costes A, Sanchez-Cabo F, Kirilovsky A, Mlecnik B, Lagorce-Pagès C, et al. Type, density, and location of immune cells within human colorectal tumors predict clinical outcome. Science 2006;313(5795):1960-4.

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

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

[30] Hodi FS, Dranoff G. The biologic importance of tumor-infiltrating lymphocytes. J Cutan Pathol 2010;37(Suppl 1):48-53.

[31] Kloor M. Lymphocyte infiltration and prognosis in colorectal cancer. Lancet Oncol. 2009 Sep;10(9):840-1.

[32] Hillen F, Baeten CIM, van de Winkel A, Creytens D, van der Schaft DWJ, Winnepenninckx V, et al. Leukocyte infiltration and tumor cell plasticity are parameters of aggressiveness in primary cutaneous melanoma. Cancer Immunol Immunother 2008;57(1):97-106.

[33] Lee HE, Chae SW, Lee YJ, Kim MA, Lee HS, Lee BL, et al. Prognostic implications of type and density of tumour-infiltrating lymphocytes in gastric cancer. Br J Cancer 2008;99(10):1704-11.

[34] Leffers N, Gooden MJM, de Jong RA, Hoogeboom B-N, ten Hoor KA, Hollema H, et al. Prognostic significance of tumor-infiltrating T-lymphocytes in primary and metastatic lesions of advanced stage ovarian cancer. Cancer Immunol Immunother 2009;58(3):449-59.

[35] Nishimura H, Honjo T, Minato N. Facilitation of beta selection and modification of positive selection in the thymus of PD-1-deficient mice. J Exp Med. 2000 Mar 6;191(5):891-8.

[36] Oble DA, Loewe R, Yu P, Mihm MC Jr. Focus on TILs: prognostic significance of tumor infiltrating lymphocytes in human melanoma. Cancer Immun. 2009 Apr 2;9:3.

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

[38] Suzuki H, Chikazawa N, Tasaka T, Wada J, Yamasaki A, Kitaura Y, et al. Intratumoral CD8+ T/FOXP3+ cell ratio is a predictive marker for survival in patients with colorectal cancer. Cancer Immunol Immunother 2010;59:653-61.

[39] Chew V, Tow C, Teo M, Wong HL, Chan J, Gehring A, et al. Inflammatory tumor microenvironment is associated with superior survival in hepatocellular carcinoma patients. J Hepatol 2010;52:370-9.

[40] Liotta F, Gacci M, Frosali F, Querci V, Vittori G, Lapini A, et al. Frequency of regulatory T cells in peripheral blood and in tumour-infiltrating lymphocytes correlates with poor prognosis in renal cell carcinoma. BJU Int 2011;107(9):1500-6.

[41] Ko K, Yamazaki S, Nakamura K, Nishioka T, Hirota K, Yamaguchi T, et al. Treatment of advanced tumors with agonistic anti-GITR mAb and its effects on tumor-infiltrating Foxp3+CD25+CD4+ regulatory T cells. J Exp Med. 2005 Oct 3;202(7):885-91.

[42] Cohen AD, Diab A, Perales MA, Wolchok JD, Rizzuto G, Merghoub T, et al. Agonist anti-GITR antibody enhances vaccine-induced CD8(+) T-cell responses and tumor immunity. Cancer Res. 2006 May 1;66(9):4904-12.

[43] Zhou P, L'italien L, Hodges D, Schebye XM. Pivotal roles of CD4+ effector T cells in mediating agonistic anti-GITR mAb-induced-immune activation and tumor immunity in CT26 tumors. J Immunol. 2007 Dec 1;179(11):7365-75.

[44] Cohen AD, Schaer DA, Liu C, Li Y, Hirschhorn-Cymmerman D, Kim SC, et al. Agonist anti-GITR monoclonal antibody induces melanoma tumor immunity in mice by altering regulatory T cell stability and intra-tumor accumulation. PLoS One. 2010 May 3;5(5):e10436.

[45] Murphy JT, Burey AP, Beebe AM, Gu D, Presta LG, Merghoub T, et al. Anaphylaxis caused by repetitive doses of a GITR agonist monoclonal antibody in mice. Blood. 2014 Apr 3;123(14):2172-80.

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

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

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

[49] Lowe PJ, Tannenbaum S, Wu K, Lloyd P, Sims J. On setting the first dose in man: quantitating biotherapeutic drug-target binding through pharmacokinetic and pharmacodynamic models. Basic Clin Pharmacol Toxicol 2009;106:195-209.

[50] Bai S, Jorga K, Xin Y, Jin D, Zheng Y, Damico-Beyer LA, et. al. A Guide to Rational Dosing of Monoclonal Antibodies. Clin Pharmacokinet. 2012;51(2):119-135.

[51] Wang DD, Zhang S, Zhao H, Men AY, Parivar K. Fixed dosing versus body size-based dosing of monoclonal antibodies in adult clinical trials. J Clin Pharmacol. 2009;49:1012-1024.

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 leftover DNA and leftover archival tumor tissue or leftover newly obtained biopsy specimen(s) collected in the current trial will be used to study various causes for how subjects may respond to a drug/vaccine. The leftover DNA and leftover archival tumor tissue or leftover newly obtained biopsy specimen(s) will be stored to provide a resource for future trials conducted by Merck 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 Merck or designees and research will be monitored and reviewed by a committee of our scientists and clinicians.

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. Information

contained on the consent form alone cannot be traced to any specimens, test results, or medical information once the specimens have been rendered de-identified.

Subjects are not required to participate in the Future Biomedical Research sub-trial in order to participate in the main trial. Subjects who decline to sign the Future Biomedical Research informed consent will not have the specimen collected nor will they be discontinued from the main trial.

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.

Each informed consent approved by an ethics committee is assigned a unique tracking number. The tracking number on this document will be used to assign specimen permissions for each specimen into the Entrusted Keyholder's Specimen Database.

c. eCRF Documentation for Future Biomedical Research Specimens

Documentation of both consent and acquisition of Future Biomedical Research specimens will be captured in the electronic Case Report Forms (eCRFs). Reconciliation of both forms will be performed to assure that only appropriately-consented specimens are used for this sub-trial's research purposes. Any specimens for which such an informed consent cannot be verified will be destroyed.

d. Future Biomedical Research Specimen Collections

Blood specimens for DNA or RNA isolation will usually be obtained at a time when the subject is having blood drawn for other trial purposes. Specimens like tissue and bone marrow will usually be obtained at a time when the subject is having such a procedure for clinical purposes.

Specimens will be collected and sent to the laboratory designated for the trial where they will be processed (e.g., DNA or RNA extraction, etc) following the Merck approved policies and procedures for specimen handling and preparation.

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, Merck has developed secure policies and procedures. All specimens will be de-identified 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.

This first code will be replaced with a second code at a Merck designated storage/lab facility. The second code is linked to the first code via a second key. The specimen is now double coded. Specimens with the second code are sometimes referred to as de-identified specimens. The use of the second code provides additional confidentiality and privacy protection for subjects over the use of a single code. Access to both keys would be needed to link any data or specimens back to the subject's identification.

The second code is stored separately from the first code and all associated personal specimen identifiers. A secure link, the second key, will be utilized to match the second code to the first code to allow clinical information collected during the course of the trial to be associated with the specimen. This second key will be transferred under secure procedures by the Merck designated facility to an Entrusted Keyholder at Merck. The second code will be logged into the primary biorepository database at Merck and, in this database, this identifier will not have identifying demographic data or identifying clinical information (i.e., race, sex, age, diagnosis, lab values) associated with it. The specimen will be stored in a designated biorepository site with secure policies and procedures for specimen storage and usage.

The second key can be utilized to reconstruct the link between the results of future biomedical research and the clinical information, at the time of analysis. This linkage would not be possible for the scientist conducting the analysis, but can only be done by the Merck Entrusted Keyholder under strict security policies and procedures. The Merck Entrusted Keyholder will link the information and then issue a de-identified data set for analysis. The only other circumstance by which future biomedical research data would be directly linked to the full clinical data set would be those situations mandated by regulatory authorities (e.g., EMEA, FDA), whereby this information would be directly transferred to the regulatory authority.

5. Biorepository Specimen Usage

Specimens obtained for the Merck Biorepository will be used for analyses using good scientific practices. However, exploratory analyses will not be conducted under the highly validated conditions usually associated with regulatory approval of diagnostics. The scope of research performed on these specimens is limited to the investigation of the variability in biomarkers that may correlate with a clinical phenotype in subjects.

Analyses utilizing the Future Biomedical Research specimens may be performed by Merck, or an additional third party (e.g., a university investigator) designated by Merck. The investigator conducting the analysis will be provided with double coded specimens. Re-association of analysis results with corresponding clinical data will only be conducted by the Merck Entrusted Keyholder. 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 the specific analysis is performed will be returned to the sponsor or destroyed and documentation of destruction will be reported to Merck.

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 Merck using the designated mailbox (clinical.specimen.management@merck.com) and a form will be provided by Merck 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 Merck 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 acquisition. 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 Merck 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 Merck policies and procedures and this destruction will be documented in the biorepository database.

8. Data Security

Separate databases for specimen information and for results from the Future Biomedical Research sub-trial will be maintained by Merck. This is done to separate the future exploratory test results (which include genetic data) from the clinical trial database thereby maintaining a separation of subject number and these results. The separate databases are accessible only to the authorized Sponsor 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 in international standards (e.g., ISO17799) to protect against unauthorized access. The Merck Entrusted Keyholder maintains control over access to all specimen data. These data are collected for future biomedical research purposes only as specified in this sub-trial will not be used for any other purpose.

9. Reporting of Future Biomedical Research Data to Subjects

There is no definitive requirement in either authoritative ethical guidelines or in relevant laws/regulations globally that research results have to be, in all circumstances, returned to the trial participant. Some guidelines advocate a proactive return of data in certain instances. No information obtained from exploratory laboratory studies will be reported to the subject or family, and this information will not be entered into the clinical database maintained by Merck on subjects. Principle reasons not to inform or return results to the subject include: lack of relevance to subject health, limitations of predictive capability, concerns of misinterpretation and absence of good clinical practice standards in exploratory research typically used for diagnostic testing.

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 as to how to offer clinical diagnostic testing (paid for by Merck) to subjects enrolled and will be advised that counseling should be made available for all who choose to participate in this diagnostic testing.

If any exploratory results are definitively associated with clinical significance after completion of a clinical trial, Merck will publish the results without revealing specific subject information, inform all trial sites who participated in the Merck clinical trial and post anonymized results on our website or other accredited website(s) that allow for public access (e.g., disease societies who have primary interest in the results) in order that physicians and patients may pursue clinical diagnostic testing if they wish to do so.

10. Gender, Ethnicity and Minorities

Although many diagnoses differ in terms of frequency by ethnic population and gender, every effort will be made to recruit all subjects diagnosed and treated on Merck clinical trials for future biomedical research. When trials with specimens are conducted and subjects identified to serve as controls, every effort will be made to group specimens from subjects and controls to represent the ethnic and gender population representative of the disease under current investigation.

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.

Merck 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.

It is necessary for subject-related data (i.e., ethnicity, diagnosis, drug therapy and dosage, age, toxicities, etc.) to be re-associated to double coded specimens at the time of data analysis. These subject data will be kept in a separate, secure Merck database, and all specimens will be stripped of subject identifiers. No information concerning results obtained from future biomedical research will be entered into clinical records, nor will it

be released to outside persons or agencies, in any way that could be tied to an individual subject.

12. Self-Reported Ethnicity

Subjects who participate in future biomedical research will be asked to provide self-reported ethnicity. Subjects who do not wish to provide this data may still participate in future biomedical research.

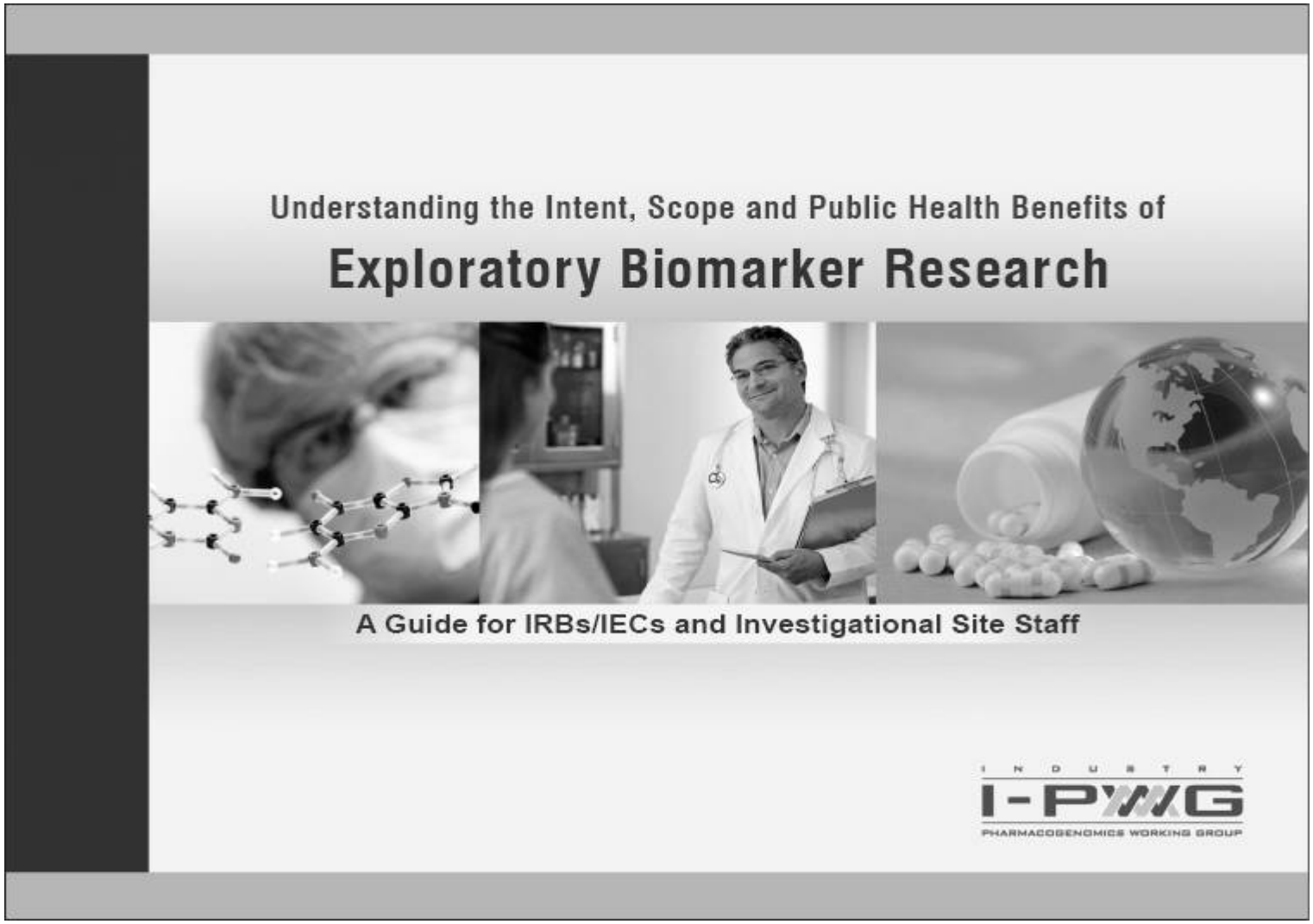
13. Questions

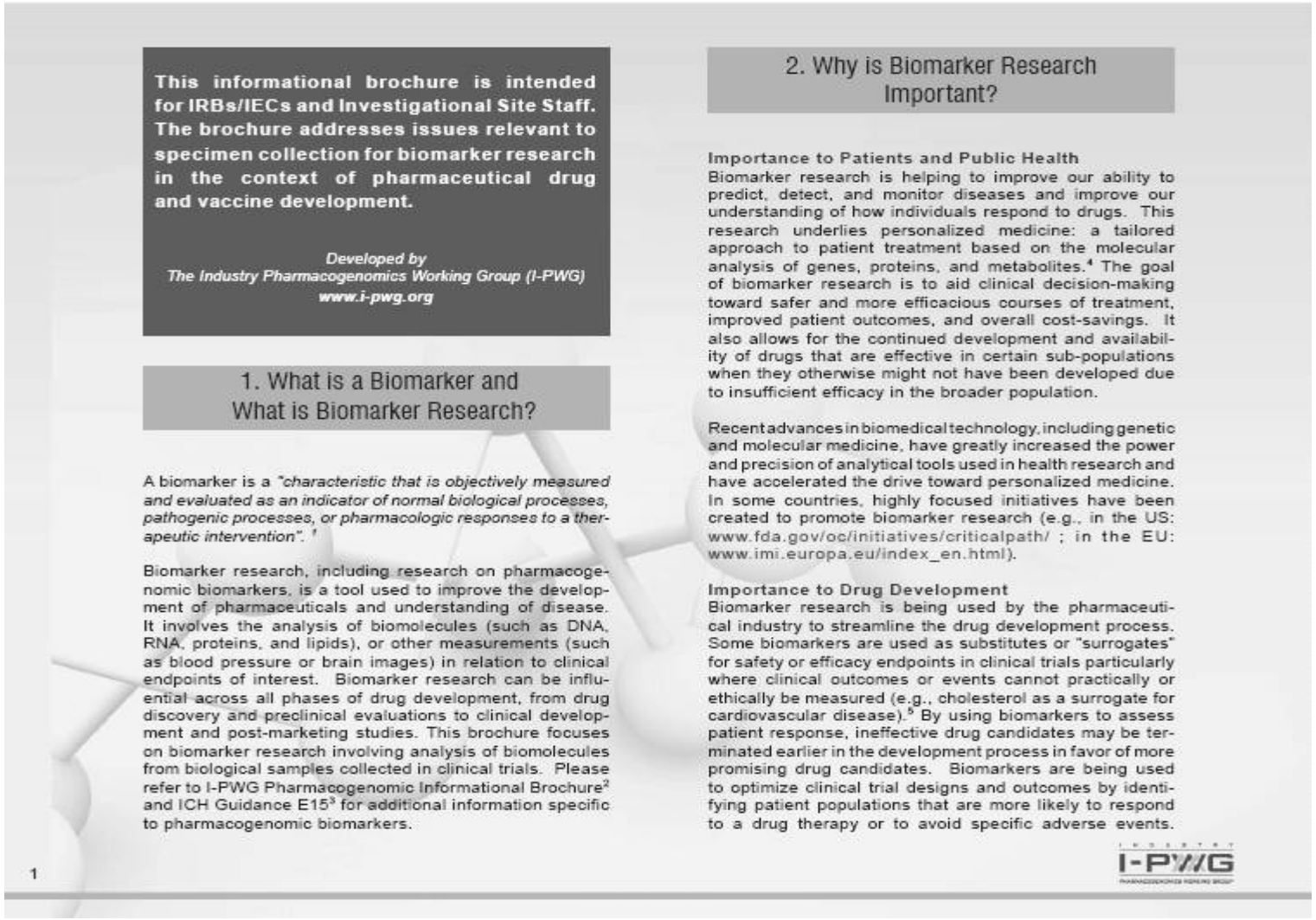
Any questions related to the future biomedical research should be e-mailed directly to clinical.specimen.management@merck.com.

14. References

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

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





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

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

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

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

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

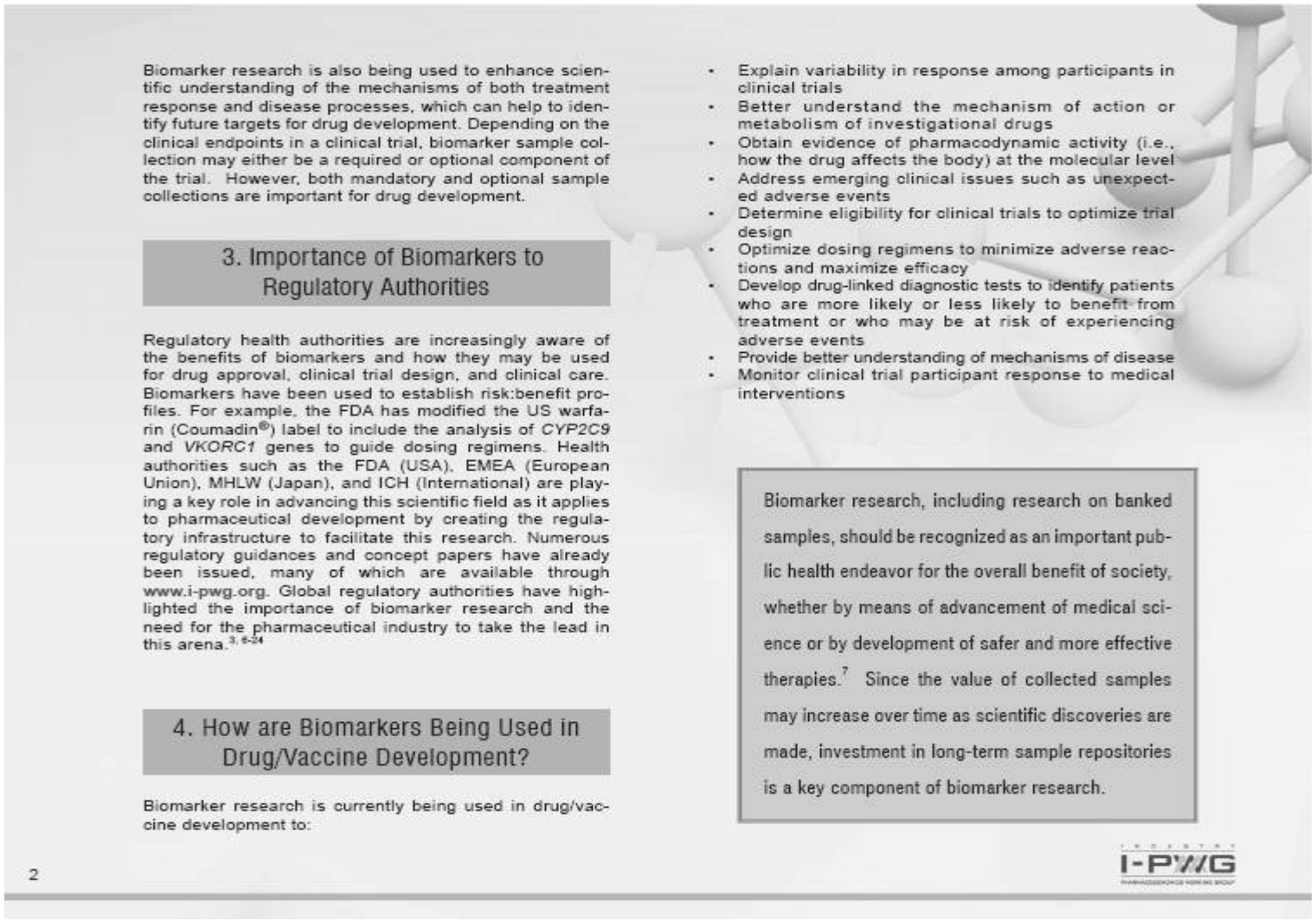
2. Why is Biomarker Research Important?

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

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

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

1


Biomarker research is also being used to enhance scientific understanding of the mechanisms of both treatment response and disease processes, which can help to identify future targets for drug development. Depending on the clinical endpoints in a clinical trial, biomarker sample collection may either be a required or optional component of the trial. However, both mandatory and optional sample collections are important for drug development.
3. Importance of Biomarkers to Regulatory Authorities
Regulatory health authorities are increasingly aware of the benefits of biomarkers and how they may be used for drug approval, clinical trial design, and clinical care. Biomarkers have been used to establish risk:benefit profiles. For example, the FDA has modified the US warfarin (Coumadin®) label to include the analysis of CYP2C9 and VKORC1 genes to guide dosing regimens. Health authorities such as the FDA (USA), EMEA (European Union), MHLW (Japan), and ICH (International) are playing a key role in advancing this scientific field as it applies to pharmaceutical development by creating the regulatory infrastructure to facilitate this research. Numerous regulatory guidances and concept papers have already been issued, many of which are available through www.i-pwg.org. Global regulatory authorities have highlighted the importance of biomarker research and the need for the pharmaceutical industry to take the lead in this arena.[3, 6-24]
4. How are Biomarkers Being Used in Drug/Vaccine Development?
Biomarker research is currently being used in drug/vaccine development to:
Explain variability in response among participants in clinical trials
Better understand the mechanism of action or metabolism of investigational drugs
Obtain evidence of pharmacodynamic activity (i.e., how the drug affects the body) at the molecular level
Address emerging clinical issues such as unexpected adverse events
Determine eligibility for clinical trials to optimize trial design
Optimize dosing regimens to minimize adverse reactions and maximize efficacy
Develop drug-linked diagnostic tests to identify patients who are more likely or less likely to benefit from treatment or who may be at risk of experiencing adverse events
Provide better understanding of mechanisms of disease
Monitor clinical trial participant response to medical interventions
Biomarker research, including research on banked samples, should be recognized as an important public health endeavor for the overall benefit of society, whether by means of advancement of medical science or by development of safer and more effective therapies.[7] Since the value of collected samples may increase over time as scientific discoveries are made, investment in long-term sample repositories is a key component of biomarker research.
I-PWG
2

5. Biomarkers are Already a Reality in Health Care

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

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

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

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

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

6. Biomarker Samples from Clinical Trials: An Invaluable Resource

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

7. Informed Consent for Collection & Banking of Biomarker Samples

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

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

Optional vs. Required Subject Participation

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

Consent for Future Research Use

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

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

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

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

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

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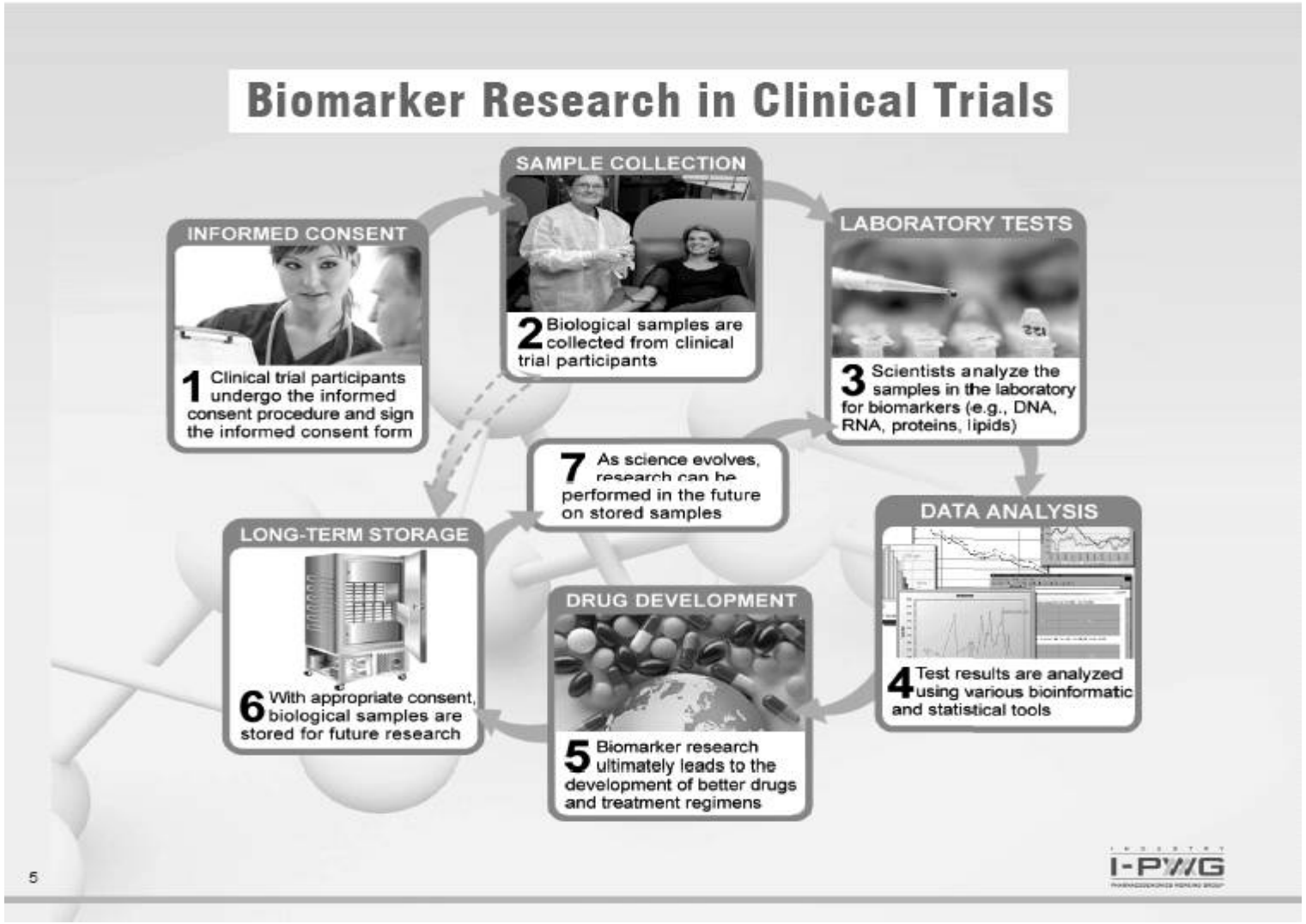
Biomarker Research in Clinical Trials
SAMPLE COLLECTION
2 Biological samples are collected from clinical trial participants
LABORATORY TESTS
3 Scientists analyze the samples in the laboratory for biomarkers (e.g., DNA, RNA, proteins, lipids)
INFORMED CONSENT
1 Clinical trial participants undergo the 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*. 2008 and Article 29 Data Protection Working Party (an advisory committee to the European Commission on the European Data Protection Directive) have addressed these considerations in detail in relation to pharmacogenomic research data and provided a list of documents addressing the general issue of return of research results.[34-35]

10. Benefits and Risks Associated with Biomarker Research

Benefits

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

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

Risks

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

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

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

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

11. Privacy, Confidentiality, and Patient Rights

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

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

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

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

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

12.Where to Get More Information?

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

13. What is I-PWG?

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

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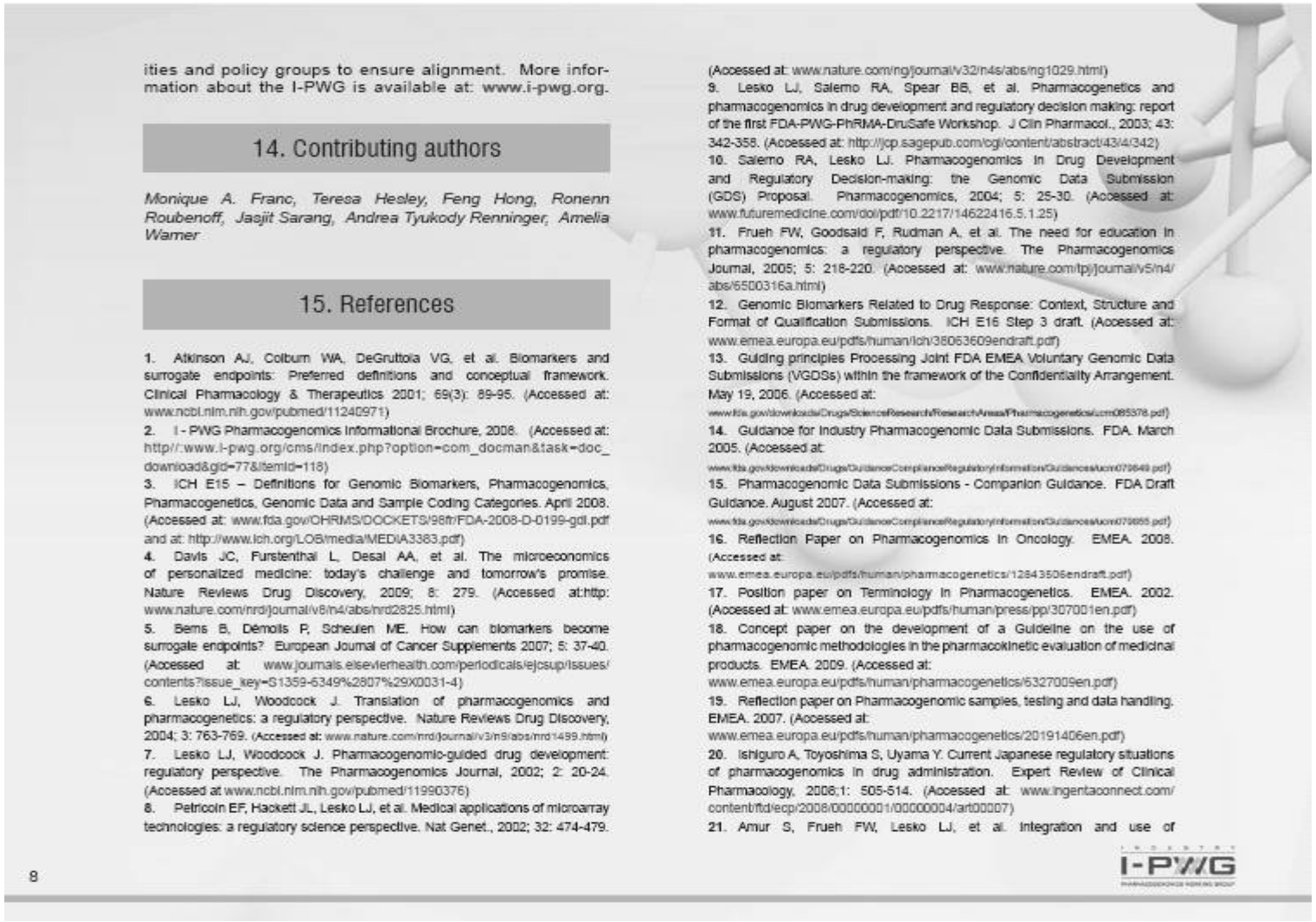

ities and policy groups to ensure alignment. More information about the I-PWG is available at: www.i-pwg.org.

14. Contributing authors

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15. References

1. Atkinson AJ, Colburn WA, DeGruttola VG, et al. Biomarkers and surrogate endpoints: Preferred definitions and conceptual framework. Clinical Pharmacology & Therapeutics 2001; 69(3): 89-95. (Accessed at: www.ncbi.nlm.nih.gov/pubmed/11240971)
2. I - PWG Pharmacogenomics Informational Brochure, 2008. (Accessed at: http//:www.i-pwg.org/cms/index.php?option=com_docman&task=doc_download&gid=77&Itemid=118)
3. ICH E15 – Definitions for Genomic Biomarkers, Pharmacogenomics, Pharmacogenetics, Genomic Data and Sample Coding Categories. April 2008. (Accessed at: www.fda.gov/OHRMS/DOCKETS/98fr/FDA-2008-D-0199-gdl.pdf and at: http://www.ich.org/LOB/media/MEDIA3383.pdf)
4. Davis JC, Furstenthal L, Desai AA, et al. The microeconomics of personalized medicine: today's challenge and tomorrow's promise. Nature Reviews Drug Discovery, 2009; 8: 279. (Accessed at:http: www.nature.com/nrd/journal/v8/n4/abs/nrd2825.html)
5. Bems B, Démolis P, Scheulen ME. How can biomarkers become surrogate endpoints? European Journal of Cancer Supplements 2007; 5: 37-40. (Accessed at: www.journals.elsevierhealth.com/periodicals/ejcsup/issues/contents?issue_key=S1359-6349%2807%29X0031-4)
6. Lesko LJ, Woodcock J. Translation of pharmacogenomics and pharmacogenetics: a regulatory perspective. Nature Reviews Drug Discovery, 2004; 3: 763-769. (Accessed at: www.nature.com/nrd/journal/v3/n9/abs/nrd1499.html)
7. Lesko LJ, Woodcock J. Pharmacogenomic-guided drug development: regulatory perspective. The Pharmacogenomics Journal, 2002; 2: 20-24. (Accessed at www.ncbi.nlm.nih.gov/pubmed/11990376)
8. Petricoin EF, Hackett JL, Lesko LJ, et al. Medical applications of microarray technologies: a regulatory science perspective. Nat Genet., 2002; 32: 474-479. (Accessed at: www.nature.com/ng/journal/v32/n4s/abs/ng1029.html)
9. Lesko LJ, Salerno RA, Spear BB, et al. Pharmacogenetics and pharmacogenomics in drug development and regulatory decision making: report of the first FDA-PWG-PhRMA-DruSafe Workshop. J Clin Pharmacol., 2003; 43: 342-358. (Accessed at: http://jcp.sagepub.com/cgi/content/abstract/43/4/342)
10. Salerno RA, Lesko LJ. Pharmacogenomics in Drug Development and Regulatory Decision-making: the Genomic Data Submission (GDS) Proposal. Pharmacogenomics, 2004; 5: 25-30. (Accessed at: www.futuremedicine.com/doi/pdf/10.2217/14622416.5.1.25)
11. Frueh FW, Goodsaid F, Rudman A, et al. The need for education in pharmacogenomics: a regulatory perspective. The Pharmacogenomics Journal, 2005; 5: 218-220. (Accessed at: www.nature.com/tpj/journal/v5/n4/abs/6500316a.html)
12. Genomic Biomarkers Related to Drug Response: Context, Structure and Format of Qualification Submissions. ICH E16 Step 3 draft. (Accessed at: www.emea.europa.eu/pdfs/human/ich/38063609endraft.pdf)
13. Guiding principles Processing Joint FDA EMEA Voluntary Genomic Data Submissions (VGDSs) within the framework of the Confidentiality Arrangement. May 19, 2006. (Accessed at: www.fda.gov/downloads/Drugs/ScienceResearch/ResearchAreas/Pharmacogenetics/ucm085378.pdf)
14. Guidance for Industry Pharmacogenomic Data Submissions. FDA. March 2005. (Accessed at: www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm079849.pdf)
15. Pharmacogenomic Data Submissions - Companion Guidance. FDA Draft Guidance. August 2007. (Accessed at: www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm079865.pdf)
16. Reflection Paper on Pharmacogenomics in Oncology. EMEA. 2008. (Accessed at: www.emea.europa.eu/pdfs/human/pharmacogenetics/12843506endraft.pdf)
17. Position paper on Terminology in Pharmacogenetics. EMEA. 2002. (Accessed at: www.emea.europa.eu/pdfs/human/press/pp/30700en.pdf)
18. Concept paper on the development of a Guideline on the use of pharmacogenomic methodologies in the pharmacokinetic evaluation of medicinal products. EMEA. 2009. (Accessed at: www.emea.europa.eu/pdfs/human/pharmacogenetics/6327009en.pdf)
19. Reflection paper on Pharmacogenomic samples, testing and data handling. EMEA. 2007. (Accessed at: www.emea.europa.eu/pdfs/human/pharmacogenetics/20191406en.pdf)
20. Ishiguro A, Toyoshima S, Uyama Y. Current Japanese regulatory situations of pharmacogenomics in drug administration. Expert Review of Clinical Pharmacology, 2008;1: 505-514. (Accessed at: www.ingentaconnect.com/content/fd/ecp/2008/00000001/00000004/art00007)
21. Amur S, Frueh FW, Lesko LJ, et al. Integration and use of

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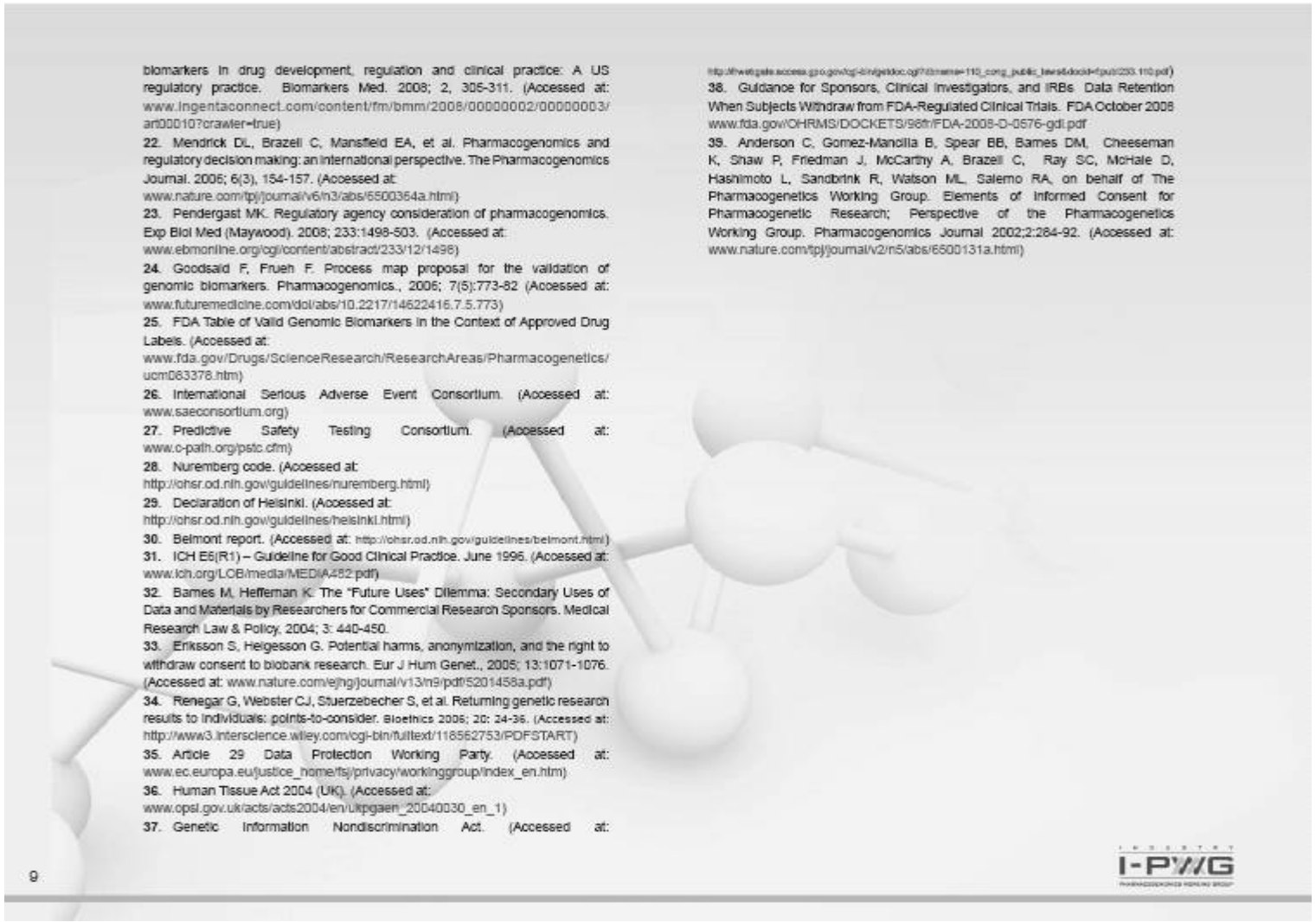

biomarkers in drug development, regulation and clinical practice: A US regulatory practice. Biomarkers Med. 2008; 2, 305-311. (Accessed at: www.ingentaconnect.com/content/fm/bmm/2008/00000002/00000003/art00010?crawler=true)

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

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

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

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

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

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

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

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

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

31. ICH E6(R1) – Guideline for Good Clinical Practice. June 1996. (Accessed at: www.ich.org/LOB/media/MED/A482.pdf)

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

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

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

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

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

37. Genetic Information Nondiscrimination Act. (Accessed at: http://frwebgate.access.gpo.gov/cgi-bin/getdoc.cgi?dbname=110_cong_public_laws&docid=f:pu0233.110.pdf)

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

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


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12.4 ECOG Performance Status

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

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

12.6 Criteria for Evaluating Response in Solid Tumors in Solid Tumors, RECIST 1.1

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

* As published in the European Journal of Cancer:

E.A. Eisenhauer, P. Therasse, J. Bogaerts, L.H. Schwartz, D. Sargent, R. Ford, J., et al. New response evaluation criteria in solid tumors: Revised RECIST guideline (version 1.1). Eur J Cancer. 2009 Jan;45(2):228-47.

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	