Official Protocol Title:	A Phase 1/1b Trial of MK-1966 in Combination with SD-101 in Subjects with Advanced Malignancies
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TITLE:

A Phase 1/1b Trial of MK-1966 in Combination with SD-101 in Subjects with Advanced Malignancies

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SUMMARY OF CHANGES

PRIMARY REASON(S) FOR THIS AMENDMENT:

Section Number (s)	Section Title(s)	Description of Change (s)	Rationale
3.3 4.2.3.6.3	Exploratory Testing Cytokine of Systemic Immune Activation	Cytokine testing updated to include: IL-10, IFN-γ, IL-12p70, IL-13, IL-1β, IL-2, IL-4, IL-6, IL-8, TNF-α and IFN-α2a.	Sections updated to agree with the cytokine testing in the Biomarker Plan.
4.2.3.2 4.2.3.6 7.1.2.6.1	Efficacy Endpoints immune-related RECIST (irRECIST) Solid Tumors	Updated/clarified that when feasible, study subjects can continue on treatment until progression is confirmed by the local site investigator/radiology assessment.	Updated/clarified discontinuing subjects with PD from study based on investigator feedback.
4.2.3.6.1	Target Engagement	Changed “validated” to “qualified ”in the third sentence	A qualified total IL-10 assay is being used for supporting the Phase I clinical studies
5.1.2 (b and e)	Subject Inclusion	Removed “local surgical resection is permitted” was eliminated.	Deleted based on investigator feedback.
5.1.2 (Table 4)	Adequate Organ Function Laboratory Values	AST criterion and footnote c were added.	AST criterion added for subjects with liver metastases and also added language to include adequate PT or partial thromboplastin time (PTT) range for subjects receiving anticoagulant therapy.
5.2 (Table 5)	Trial Treatment	MK-1966 will be administered at least 30 minutes after the SD-101 injection added to footnote 2.	Added to ensure agreement with information in the Pharmacy and Procedures Manual(s).

5.6	Treatment Precaution	Added drugs that should be used with caution through 7 days after each subsequent dose of SD-101.	Updated protocol based on documents received from Dynavax.
5.9	Subject Withdrawal/Discontinuation	Removed/clarified language related to discontinuing subjects with confirmed disease progression.	Revised based on site feedback.
6	Trial Flow Chart Updated	Simplified/clarified multiple footnotes. Added the following: - Required 90 minute observation after SD-101 injection - MK-1966 will be administered at least 30 minutes after the SD-101 injection. - Free T_4, Total T_3 added to clarify TSH testing. - Lab and Procedure collection inconsistencies corrected.	Revised/updated based on discrepancies/feedback from the sites.
7.1.2.6.3.1	Imaging	Added Table 9 (Imaging by Anatomical Coverage) that includes updated imaging requirements.	Updated protocol to include Imaging by Anatomical Coverage Table from Imaging Manual.

ADDITIONAL CHANGE(S) FOR THIS AMENDMENT:

Section Number (s)	Section Title (s)	Description of Change (s)	Rationale
4.1.1.2	SD-101 Background	Reference 0477BF changed to 03QCKP.	Corrected reference error.
5.2.3 5.7	Guidelines for Dose Modification Supportive Care Guidelines	Updated protocol with additional toxicities and Supportive Care Guidelines.	Updated sections to agree with required Merck Oncology Protocol Language.

1.0 TRIAL SUMMARY

Abbreviated Title	Phase 1/1b Trial of MK-1966 in Combination with SD-101 in Subjects with Advanced Malignancies
Sponsor Product Identifiers	MK-1966, SD-101 N/A
Trial Phase	Phase I/Ib
Clinical Indication	Part A- Treatment of subjects with B-cell lymphoma, melanoma, squamous cell cancer of head and neck, breast cancer with dermal metastasis Part B- Treatment of subjects with melanoma Part C- Treatment of subjects with squamous cell cancer of head and neck
Trial Type	Interventional
Type of control	None
Route of administration	MK-1966 given intravenously and SD-101 given intratumorally
Trial Blinding	Unblinded Open-label
Treatment Groups	Part A: Dose escalation of MK-1966 in combination with a fixed dose of SD-101 in subjects with B-cell lymphoma, melanoma, squamous cell cancer of head and neck, breast cancer with dermal metastasis. Part B: Confirmation/Expansion Cohort of maximum tolerated dose/maximum administered dose MTD (maximum tolerated dose) /MAD (maximum administered dose) of MK-1966 with fixed dose SD-101 in melanoma. Part C: Confirmation/Expansion Cohort of MTD/MAD of MK-1966 with fixed dose SD-101 in squamous cell cancer of head and neck.
Number of trial subjects	Approximately 64 subjects will be enrolled.
Estimated duration of trial	The Sponsor estimates that the trial will require approximately 1.8 years from the time the first subject signs the informed consent until the last subject's last study-related phone call or visit.
Duration of Participation	Each subject will participate in the trial 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 enrolled in Part A treatment with MK-1966 and SD-101 and will continue for up to 8 cycles (approximately 24 weeks) of treatment. Treatment in Parts B and C will be with the MTD or MAD of MK-1966 determined in Part A. Subjects in Parts A, B and C may receive up to 8 cycles (approximately 24 weeks) of treatment or continue treatment 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, or administrative reasons requiring cessation of treatment. After the end of treatment (EOT), each subject will be followed for 30 days. Serious adverse events (SAEs) will be collected for 30 days after EOT.

Randomization Ratio	N/A

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

2.0 TRIAL DESIGN

2.1 Trial Design

This is a non-randomized, multi-site, open-label trial of MK-1966 in combination with SD-101 in subjects with B-cell lymphoma, melanoma, squamous cell cancer of head and neck (SCCHN), breast cancer with dermal metastasis (see Section 5.1.2 for enrollment criteria). This trial will use an adaptive design based on the pre-specified criteria of dose limiting toxicity (DLT). For Dose Escalation (Part A) a 3+3 dose escalation design will be utilized (See Section 5.2.1.4). For Dose Confirmation (Parts B and C) the toxicity probability interval (TPI) design [1] will be utilized to refine the estimate of MTD.

In Part A, MK-1966 will be given in combination with SD-101 and will enroll subjects with one of the four potential malignancies described above. Enrollment to each dose level in Part A will occur sequentially, with each successively higher dose level initiating if the preceding dose is deemed tolerable per the DLT criteria (see Section 5.2.2). Subjects will continue at their enrolled dose for the duration of their participation. The study will begin with a 3+3 design to identify a preliminary MTD or MAD of the combination. During 3+3 dose escalation, an initial cohort of 3 subjects will be enrolled to a 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 $\geq 2/3$ or $\geq 2/6$ subjects at a dose level develop DLTs, dose escalation will be terminated, and the study will proceed to the dose confirmation stage at the previous dose level. At least 2 days of observation will occur between each of the first 3 subjects in the first 2 dose levels.

In Parts B and C, dose confirmation will refine the estimate of the tolerability of the MTD/MAD, using a toxicity probability interval. Enrollment to Parts B and C will occur in parallel with treatment allocation accomplished by non-random assignment to either part. Part B will enroll subjects with melanoma and Part C will enroll subjects with SCCHN (see Section 5.1.2 for enrollment criteria).

Subjects will receive assessments at week 12 (or Day 84), week 24 and every 12 weeks that a subject remains in study. Subjects in Parts A, B and C may receive up to 8 cycles (approximately 24 weeks) of treatment or continue treatment 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, or administrative reasons requiring cessation of treatment.

The final number of subjects enrolled in the dose escalation and confirmation parts of the study will depend on the DLT observations, in particular, at what dose the 3+3 design is triggered and what dose is identified as the ready for recommended phase 2 dose (RPTD). For example, in a scenario where dose escalation in Parts A continues to the highest dose with flat dose response so that all 4 doses (including the top one) are given to 6 subjects each in Part A (Refer to section 5.2.1.2) the sample size is 24 subjects. In Parts B and C the sample size for the dose confirmation/expansion phase will be a maximum of 20 subjects. In this scenario, the total sample size across Parts A, B and C is 64 subjects. The final number will depend on empirical safety data and observed DLTs.

The trial will be conducted in conformance with Good Clinical Practices (GCP). Adverse Experiences (AEs) will be evaluated according to criteria outlined in the NCI Common Terminology Criteria for Adverse Experiences (CTCAE), version 4. Approximately 64 subjects evaluable for safety, tolerability, and efficacy will be enrolled in the overall study.

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.

All the information collected from dose escalation phase of the study, Part A, will be reviewed to define the dose to be tested in Part B and C of the trial. Details are described in Section 5.1- Inclusion and Exclusion Criteria and Section 8.0 - Statistical Analysis Plan.

2.2 Trial Diagram

The trial design is depicted in Figure 1.

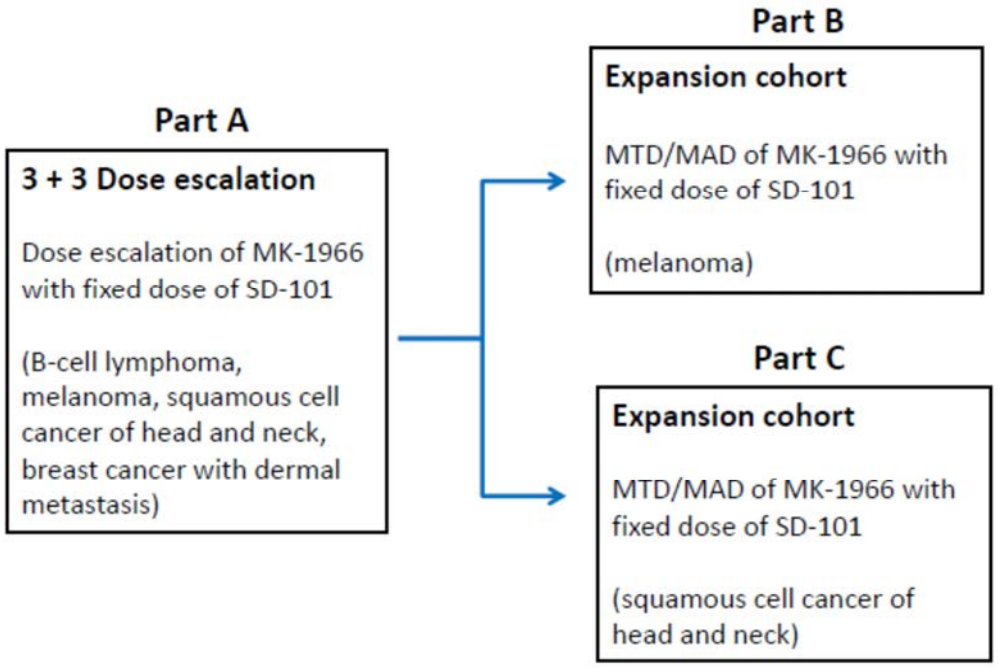


Figure 1 Trial Design

In Part A, combination study with dose escalation of MK-1966 and the recommended phase 2 dose (RPTD) of SD-101 with a 3+3 design to identify a preliminary MTD or MAD. In Part B and C dose confirmation/expansion will refine the estimate of the tolerability of the MTD (or MAD), using a toxicity probability interval [1]

3.0 OBJECTIVE(S) & HYPOTHESIS(ES)

3.1 Primary Objective(s) & Hypothesis(es)

1) **Objective:** To determine the safety and tolerability of MK-1966 in combination with SD-101 and to establish a MTD or MAD in male/female subjects with advanced

malignancies (B-cell lymphoma, melanoma, squamous cell cancer of head and neck, breast cancer with dermal metastasis) of at least 18 years of age.

3.2 Secondary Objective(s) & Hypothesis(es)

1) **Objective**: To characterize the PK profile of MK-1966 when given in combination with SD-101.
2) **Objective**: To evaluate target engagement for MK-1966 as measured by modulation of circulating IL-10 concentrations.

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), progression-free survival (PFS) and overall survival (OS) of subjects with advanced tumors treated with the combination of MK-1966 with SD-101 by Cheson criteria (for B Cell lymphoma) or irRECIST (for melanoma, squamous cell cancer of head and neck, breast cancer with dermal metastasis) as assessed by investigator review.
2) **Objective:** To investigate the relationship between candidate efficacy biomarkers and anti-tumor activity of MK-1966 in combination with SD-101.
    a. Tumor microenvironment features including infiltrating lymphocytes (CD3+ total T cells and CD8+ T cells) and plasmacytoid dendritic cells.
    b. IFNα and its associated gene expression profiles in pre and post treatment peripheral blood and tumor biopsies
    c. To correlate the clinical response to pre-treatment gene sequence expression profiles.
3) **Objective:** To investigate the relationship between anti-tumor activity of MK-1966 in combination with SD-101 with potential patient selection biomarkers PD-L1 and TLR9 in pre-treatment tumor biopsies.
4) **Objective:** To evaluate the effect of MK-1966 in combination with SD-101 on immune activation biomarkers including IL-10, IFN-γ, IL-12p70, IL-13, IL-1β, IL-2, IL-4, IL-6, IL-8 TNF-α and IFN-α2a.
5) **Objective:** To evaluate development of circulating anti-MK-1966.
6) **Objective**: To explore the relationship between genomic variation and response to the treatment(s) administered. Variation across the human genome (germline and tumor) will be analyzed for association with clinical data collected in this study.
7) **Objective**: To evaluate the longitudinal change of tumor size.

4.0 BACKGROUND & RATIONALE

4.1 Background

Detailed background information on MK-1966 and SD-101 is available in the MK-1966 Investigator's Brochure (IB) and the SD-101 IB.

4.1.1 Pharmaceutical and Therapeutic Background

4.1.1.1 MK-1966 Background

MK-1966 is a humanized IgG1/kappa neutralizing monoclonal antibody (mAb) that targets human interleukin (IL)-10. Interleukin-10 is an anti-inflammatory cytokine that is expressed by cells of the innate and adaptive immune system, including dendritic cells (DCs), macrophages, mast cells, natural killer (NK) cells, eosinophils, neutrophils, CD4+ and CD8+ T cells, and B cells (reviewed in [2] and [3]). Binding of dimeric IL-10 to heterodimeric IL-10 receptor activates the Jak/STAT signaling pathway ([4], [5], [6], and [7]). Immunosuppression mediated by IL-10 includes the inhibition of secretion of cytokines from activated macrophages, inhibition of production of CC and CXC chemokines, down-regulation of MHC and costimulatory molecules on DCs, inhibition of a T_H1 response, and induction of regulatory T cells (reviewed in [2]). This known biology of IL-10 supports targeting disruption of the IL-10 pathway in combination with TLR9 agonism.

4.1.1.2 SD-101 Background

The toll-like receptor (TLR) family is a central mediator of innate immunity. Recognition of both pathogen-associated molecular patterns (PAMPs) and damage-associated molecular patterns (DAMPs) by these receptors triggers induction of cytokines and chemokines and activation of immature DCs that in turn induce activation of antigen-specific B and T cells (reviewed in Takeuchi, 2010 [8]). Both pathogen-derived and synthetic TLR agonists have been investigated for treatment of cancer. There are two FDA approved TLR agonists for the treatment of cancer: Bacillus Calmette-Guérin (BCG) and imiquimod. BCG has been demonstrated to agonize TLR2 and TLR4 and is used for intravesical treatment of bladder carcinoma in situ and superficial bladder cancers. Imiquimod is a TLR7 agonist and is used as a topical agent for viral warts and skin cancers (reviewed in [9]).

In humans, TLR9 is expressed in pDCs and B cells [10] and [11]. Various synthetic CpG (cytidine-phosphodiester-guanine)-rich oligodeoxynucleotides (ODNs) that are potent TLR9 agonists have been investigated in the clinic, including Pfizer's CpG-7909 (PF-3512676), Idera's IMO-2055 and IMO-2125, and Dynavax's 1018 ISS and SD-101 (reviewed in [12]). It was demonstrated in Phase 1/2 clinical studies that intralesional administration of CpG-7909 in combination with low-dose radiotherapy in patients with either low-grade B-cell lymphoma or mycosis fungoides resulted in regressions of the injected and non-injected lesions ([13] and [14]).

There are three main classes of CpG ODNs: A, B, and C (reviewed in [12]). CpG-7909, IMO-2055, and 1018-ISS are B-class, and IMO-2125 and SD-101 are C-class. The A-class is a strong inducer of IFN-α from pDCs, and the B-class is a strong inducer of B-cell activation and pDC maturation. The C-class embodies properties of both A- and B-classes.

However, different from the A- and B-classes, the C-class induces high levels of IL-12 from pDCs that have been costimulated through CD40 [15]. The immune activation profile for the CpG C-class potentially sets itself apart as a potent in situ vaccine. In addition, the C-class, via induction of IFN-α, is a potent inducer of cytotoxic activity and interferon gamma (IFN-γ) secretion by NK cells [16].

In addition to their immune stimulatory effects, TLR9 agonists induce an inhibitory feedback loop of suppressive factors, including IL-10. The rationale to combine anti-IL-10 mAb with in situ vaccination of a TLR9 agonist is that an IL-10 blockade will abrogate IL-10-mediated feedback inhibition of TLR9-mediated immune agonism and enable a robust systemic anti-tumor immune response (illustrated in Figure 2 from [12]).

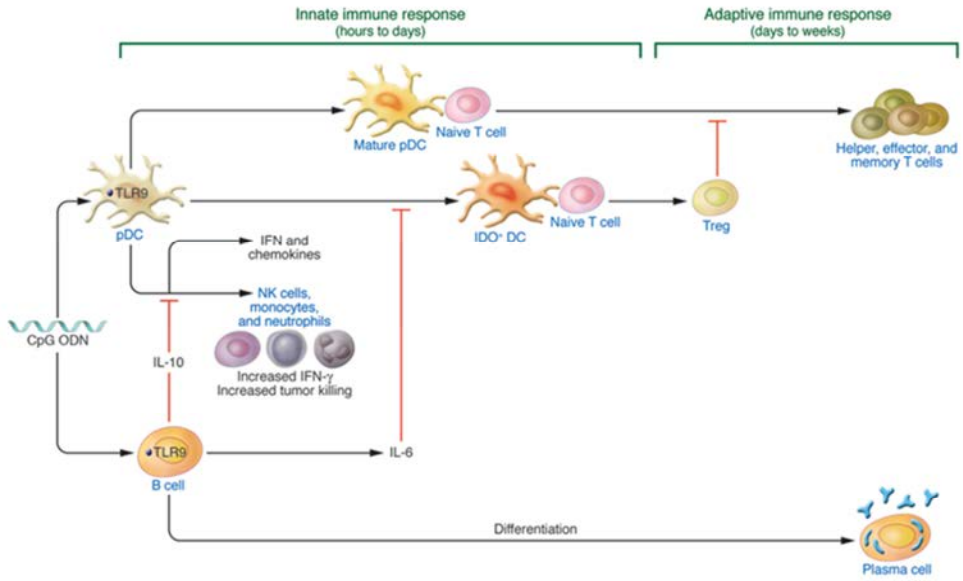


Figure 2 Schematic Diagram Showing Mechanism of Action of TLR9 Agonism and Its Induction of Counter-regulatory Factors Including IL-10

4.1.2 Pre-clinical and Clinical Trials

4.1.2.1 MK-1966 Preclinical and Clinical Trials

MK-1966 does not cross-react with mouse IL-10; thus, a surrogate mouse anti-mouse IL-10 mAb SCH 708974 was used in mouse studies.

Anti-tumor efficacy of SCH 708974 in combination with SD-101 or mouse-specific CpG B-class ODN, CpG 1826 was assessed in the HPV E6/E7+ TC-1 syngeneic mouse bilateral tumor model; this tumor model is non-responsive to anti-PD-1 treatment. SCH 708974 was administered intraperitoneally, and SD-101 and CpG 1826 were administered intratumorally. All test articles were administered every 4 days for a total of 4 doses (Figure 3).

Compared to SD-101 alone (Group 2), administration of SD-101 in combination with SCH 708974 (Group 5) resulted in significantly reduced volumes of injected tumors on Day 12 (multiplicity-adjusted p = 0.00255). In 3 of 8 animals in Group 5, complete regression (CR) was observed. In addition, 3 of 8 animals administered SD-101 in

combination with SCH 708974, CR of non-injected tumors was observed on Day 12. Complete regressions of non-injected tumors were not observed in any other group.

Administration of SCH 708974 in combination with CpG 1826 or SD-101 resulted in comparable number of CRs of injected tumors: 4 of 10 animals in Group 3 and 3 of 8 animals in Group 5. However, administration of SCH 708974 in combination of CpG 1826 did not result in any CRs of non-injected tumors, suggesting greater abscopal effect with a CpG C-class ODN than CpG B-class ODN.

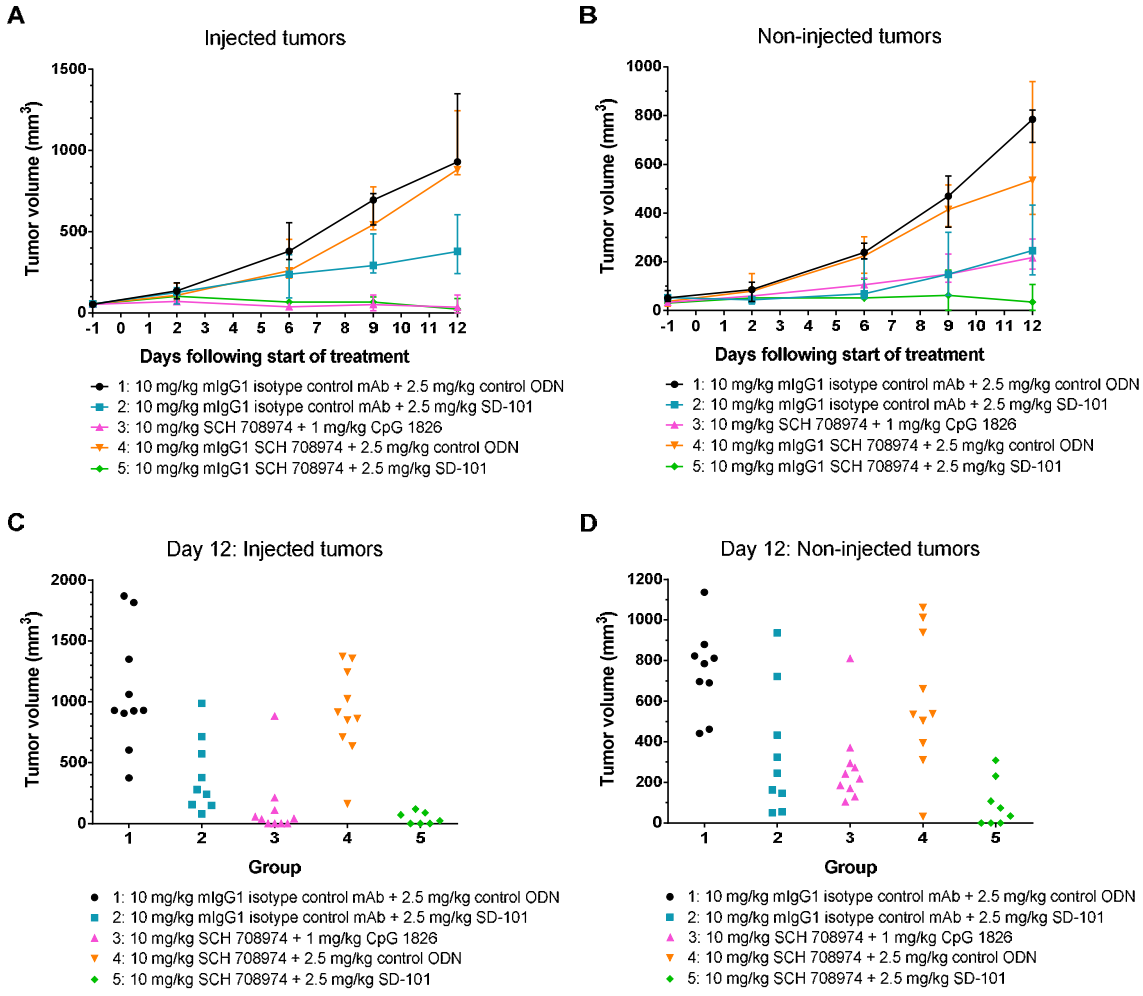


Figure 3 Efficacy of SCH 708974 and SD-101 in HPV E6/E7+ TC-1 Syngeneic Mouse Bilateral Tumor Model

Animals were assigned to groups based on tumor volume (TV) in the right flank (injected tumor) with mean TV of 58 mm^3 on the day prior to treatment. The TV in the right flank ranged from 39 to 87 mm^3 and in the left flank (non-injected tumor) ranged from 0 to 113 mm^3. SCH 708974 and SD-101 were administered intraperitoneally and intratumorally, respectively, every 4 days for a total of 4 doses. In **panel A**, tumor growth curves for injected tumors are presented. In **panel B**, tumor growth curves for non-injected tumors are presented. Tumor volumes are presented as median with 68% confidence intervals.

Individual animal TV on Day 12 for injected and non-injected tumors are presented in **panels C** and **D**, respectively. There were 10 animals per group.

Concentrations of IL-10 in plasma from animals in the HPV E6/E7+ TC-1 mouse tumor model study were determined on Day 13 (Figure 4). Median level of IL-10 in plasma in animals in control group (Group 1) was 124 pg/mL, and in animals administered SD-101 (Group 2) was 1776 pg/mL. Treatments that included SCH 708974 (Groups 3, 4, and 5) resulted in lower median levels of plasma IL-10 than that of control group (Group 1).

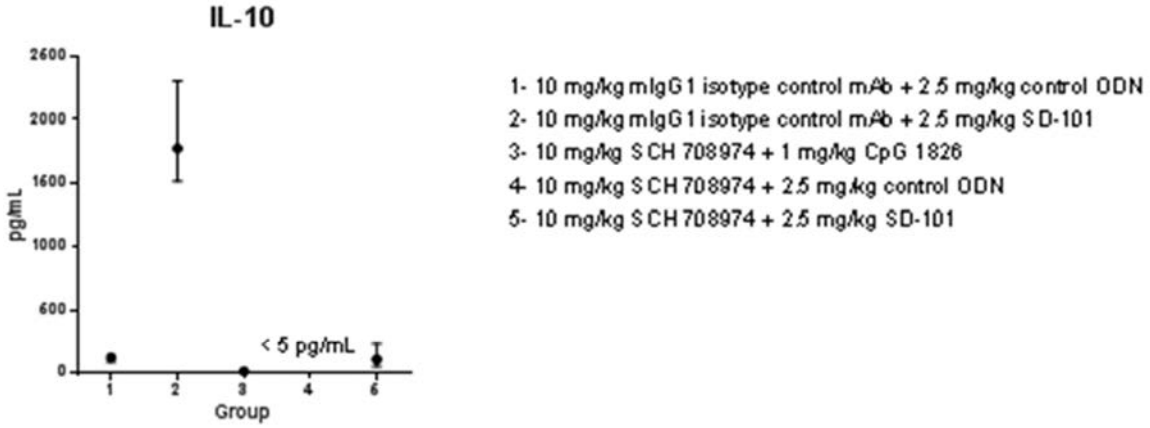


Figure 4 SD-101 Induces IL-10 in HPV E6/E7+ TC-1 Syngeneic Mouse Bilateral Tumor Model

Plasma was collected from animals in study described in Figure 2. Concentrations of IL-10 in the plasma were determined on Day 13. Values are presented as median with 68% confidence intervals. The minimum reportable concentration of IL-10 was 5 pg/mL.

In mice, TLR9 is expressed in monocytes, macrophages, myeloid DCs, activated T cells, B cells, and pDCs ([17], [18], and [19]). Since the expression of TLR9 is broader in mice than in humans, immune modulation by SD-101 in human PBMCs and tumor samples were also assessed in preclinical studies.

SD-101 induced IFN-α2a and IL-10 in human PBMCs (Figure 5). The induction of IFN-α2a showed a "bell-shaped curve" dose-response, which was previously observed [20], likely because very high concentrations of a TLR9 stimulus triggers negative feedback. The data confirms that although TLR9 expression is limited to B cells and pDCs in humans, SD-101 is a potent inducer of IFN-α and IL-10 secretion in human PBMCs.

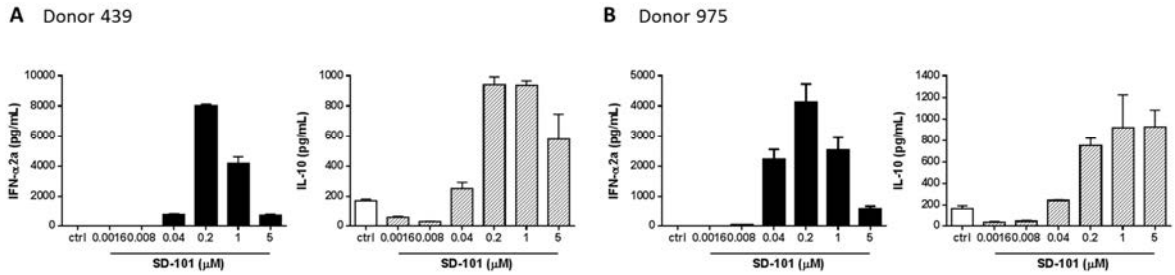


Figure 5 SD-101 Induces IFN-α2a and IL-10 in Human PMBCs

Peripheral blood mononuclear cells were isolated from 2 healthy volunteers (**panel A**, Donor 439 and **panel B**, Donor 975) and stimulated with SD-101 (0.0016, 0.008, 0.04, 0.2, 1, and 5 μM) or control ODN (7 μM) for 48 hours. Values are presented as mean ± standard deviation.

Induction of IFN-α-inducible genes, cytokines, and immune activation markers by SD-101 was also evaluated in the human tumor histoculture. This method allows assessment of the effect of the drug on cancer cells and pre-existing immune cells in the fresh tumor samples for up to 48 hours. In these experiments, 5 samples of renal cell carcinoma (RCC), 3 samples of non-small cell lung cancer, and 1 sample each of bladder and colorectal cancer were evaluated. Induction of immune genes by SD-101 was observed to varying extents among donors, but overall, treatment with SD-101 induced IFN-α-inducible genes (IFN-α2, MCP1, MCP2, OAS2, IP-10, GBP1, ISG-54, MxB, and TRAIL), cytokines (IFN-β1, IL-10, IL-12p35, IL-6, and TNF-α), and immune activation markers (CD80, CD86, CD40, and CD70, and OX40L). Data from a RCC sample are presented in Figure 6. The "bell shaped curve" dose response was also observed.

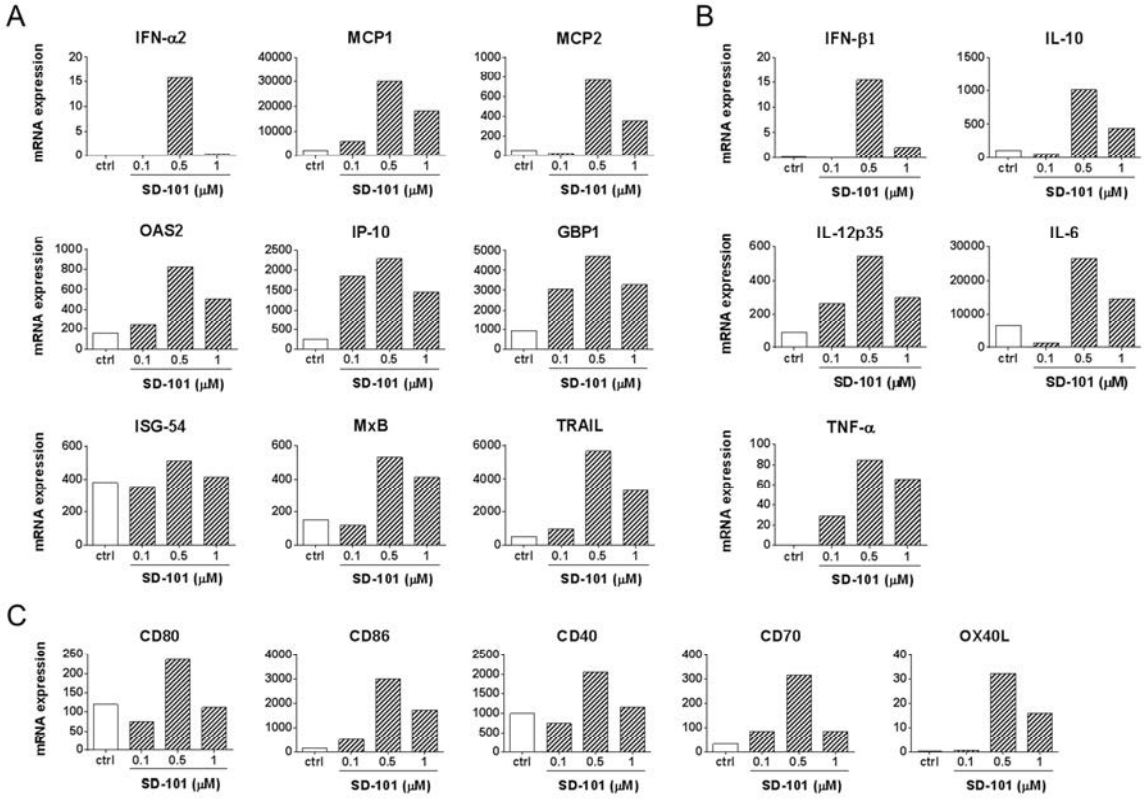


Figure 6 SD-101 Induces mRNA Expression of IFN-α-inducible Genes, Cytokines, and Immune Activation Markers in Human Renal Cell Carcinoma Histoculture

A sample of renal cell carcinoma was treated with SD-101 (0.1, 0.5, and 1 μM) or control ODN (1 μM) for 24 hours. The sample was snap-frozen, and following RNA isolation, gene expression was analyzed using the Fluidigm RTqPCR platform. The activity of SD-101 was assessed by the induction of an IFN-α-inducible gene set (**panel A**), cytokines (**panel B**), and immune cell activation markers (**panel C**).

4.1.3 Ongoing Clinical Trials

4.1.3.1 Ongoing Clinical Trials with Anti-IL-10 Monoclonal Antibody

This is the first clinical trial of MK-1966.

Previously, an anti-IL-10 antibody (MK-7089) was developed by Schering-Plough (merged with Merck 2009) which has the identical amino acid sequence and similar animal PK properties to MK-1966. As they were made in different Chinese Hamster Ovary cell lines they have some differences in glycosylation. MK-7089 was evaluated in a single-dose arm of a Phase 1 study evaluating the safety and tolerability of MK-7089 when administered intravenously in subjects with systemic lupus erythematosus (SLE). MK-7089 was safe when administered as a single dose up to the highest dose tested (10 mg/kg). Mild to moderate adverse events of oral ulcerations reported as aphthous stomatitis, stomatitis and oral ulceration were considered by the investigator to be related to the administration of MK-7089. Adverse events of oral ulcers were treated with local care or topical agents as deemed appropriate by the investigators. Exposure to MK-7089 increased in a dose-related manner through the range of doses (0.3 to 10 mg/kg) evaluated. MK-7089 was slowly eliminated from plasma following doses ranging from 0.3 to 10 mg/kg. Development in SLE was terminated because of low probability of being an effective agent for SLE patients, not because of safety issues. It is expected that doses up to 10 mg/kg of MK-1966 will be tolerated.

4.1.3.2 SD-101 Clinical Trials

In the phase 1, single-blind, dose-escalation study of SD-101 in 26 healthy normal male volunteers, aged 18 years and over (DV3-HNV-01), adverse events (AEs) included flu-like symptoms such as headache, chills, fatigue and pyrexia, as well as injection site reactions such as erythema, induration and pain. DLT's of severe headache, injection site induration and neck pain were observed in 1 subject given 5.0 mg of SD-101, resulting in a halt in dose escalation and accrual. Transient lymphopenia was the most common laboratory abnormality observed. There was no evidence of complement activation, coagulation abnormalities or auto-antibody development.

In the phase 1, single-blind, dose escalation study of SD-101 in 28 men and women, aged 18 to 55 years, with chronic hepatitis C virus (HCV) infection (DV3-HCV-01), SD-101 was administered alone or in combination with ribavirin. Including doses up to 5 mg of SD-101, the majority of AEs were injection site reactions (erythema, swelling, pain and pruritis), influenza-like illness, pyrexia and myalgia. Most AEs were mild or moderate in reported severity. One subject in the SD-101 0.1 mg/ribavirin group experienced a serious adverse event (SAE) of hyperthyroidism that was considered probably related to SD-101 and unrelated to ribavirin. No deaths occurred during the study.

A phase 1/2 trial of SD-101 in combination with low-dose radiation therapy for untreated low-grade B-cell lymphoma is currently ongoing (DV3-LYM-01). Three patients have received 5 doses of 1.0 mg intratumoral SD-101 and 3 patients have received 5 doses of 2.0 mg intratumoral SD-101 without DLTs. The most frequent AEs were transient flu-like illness in the 2.0 mg cohort.

A phase 1, clinical trial of SD-101 in lymphoma patients who have relapsed after allogeneic marrow cell transplantation (NCT01745354) is ongoing. In this trial, patients are receiving low-dose radiation to one site of disease followed by intratumoral injection of SD-101 at doses of 0.3 mg, 1.0 mg, and 3.0 mg in successive cohorts. The first 2 dose cohorts have been completed and the 3.0 mg cohort is being enrolled. SD-101 has been well tolerated and no AEs related to SD-101 have been reported. Several patients have shown objective abscopal tumor responses.

A summary of the clinical studies conducted to date with SD-101 is provided in the Investigator's Brochure.**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-1966 is being developed to enhance the immune response in advanced tumors that have not fully responded or are expected to have inadequate response to other immune activation agents. The subjects selected for this study have tumors that are accessible to intratumoral injection and disease that has progressed after standard of care therapy/treatments and there is no available therapy likely to convey clinical benefit. The selected tumors are deemed good candidates to respond to immune activation therapy from recent clinical information. This trial is the First-In-Human (FIH) trial designed to assess the safety, tolerability, pharmacokinetics and pharmacodynamics of escalating doses of MK-1966 in combination with SD-101 in subjects with advanced tumors that have failed or have low likelihood of responding to monotherapy immune activators. The effect of the combination of MK-1966 and SD-101 on tumor size will be explored.

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 Investigator Brochures (IBs) and Informed Consent documents.

4.2.2 Rationale for Dose Selection/Regimen

Ongoing clinical studies with SD-101, as outlined in section 4.1.3.2 along with relevant nonclinical safety studies, will allow selection of the appropriate SD-101 dose for combination with MK-1966. The FIH dose selection for MK-1966 in this combination therapy will be guided by data from MK-7089 (anti-IL-10 antibody single agent studies in SLE patients— {#P03722}), preclinical efficacy studies in tumor bearing mice, and PK/PD and safety studies in cynomolgus monkeys. Consequently doses above 700 mg of MK-1966 will not be investigated.

4.2.2.1 Rationale for the Use of Comparator/Placebo

This study does not include comparator or placebo.

4.2.2.2 Starting Dose for This Trial

4.2.2.2.1 Rationale for MK-1966 Dose

Cynomolgus monkeys were used for predicting clinical PK of MK-1966 and demonstrating IL-10 target engagement. Human PK was predicted by scaling clearance (CL) and volume of distribution (Vss) parameters in cynomolgus monkeys. Scaling factors were calculated from monkey and human clinical studies conducted for MK-7089 (Table 1).

MK-1966 also showed dose-dependent increases of total IL-10 (a target-engagement biomarker) following multiple-dose administration of MK-1966 (study #14-M100-6618). A bimolecular interaction PK/PD model was used to characterize the relationship between MK-1966 serum concentrations and total IL-10 concentrations, the latter being a surrogate measure of target engagement.

Table 1 Historical Monkey and Human PK Parameters for MK-7089. Estimated Scaling Factor was Used for MK-1966 Exposure Predictions in Human

	CL (mL/day/kg)	*V_{ss}, (mL/Kg)*
MK-7089		
Observed Monkey (SN03248)	5.1	72.8
Observed Human (P03722)	2.1	93.9
Ratio Monkey : Human	2.4	~1
MK-1966		
Observed Monkey (14-M100-6618)	5.6	78
Predicted Human	2.4	78

To select doses of MK-1966 in man for the initial clinical study, percent of IL-10 suppression was predicted using: a) estimated clinical exposure of MK-1966 in man from early data and b) translation of antibody-antigen-binding interaction across species. A bimolecular interaction PK/PD model was used to account for species-specific differences related to binding affinity of MK-1966 to native IL-10, turnover rate, and baseline concentration of IL-10. Table 2 shows predicted IL-10 suppression, a measure of target engagement, at steady-state following administration of MK-1966 (Q3W; dose range 0.1 to 30 mg/kg).

Table 2 Estimated Steady-State Exposure and Target Engagement Following Administration of MK-1966 (IV Q3W)

Dose, mg	AUC/τ, µg/mL	Average % IL-10 suppression	C_{max}, ug/mL	% IL-10 suppression at C_{max}
700	210	92	400	96
210	63	78	120	87
70	21	55	40	70

Combination efficacy in mice with SD-101 and surrogate mouse anti-IL-10 mAb SCH 708974

Efficacy of SD-101 alone (at 0.3 to 3 mg/kg) and in combination with SCH 708974 (1 and 10 mg/kg) was evaluated in a preclinical study in tumor-bearing mice. Results from this study demonstrated up to a 25-fold increase in the apparent potency of SD-101 (Figure 7). Current results suggested no apparent potentiation of SD-101 PD effect (all doses) at 1 mg/kg dose of SCH 708974 under the experimental conditions employed (Figure 7).

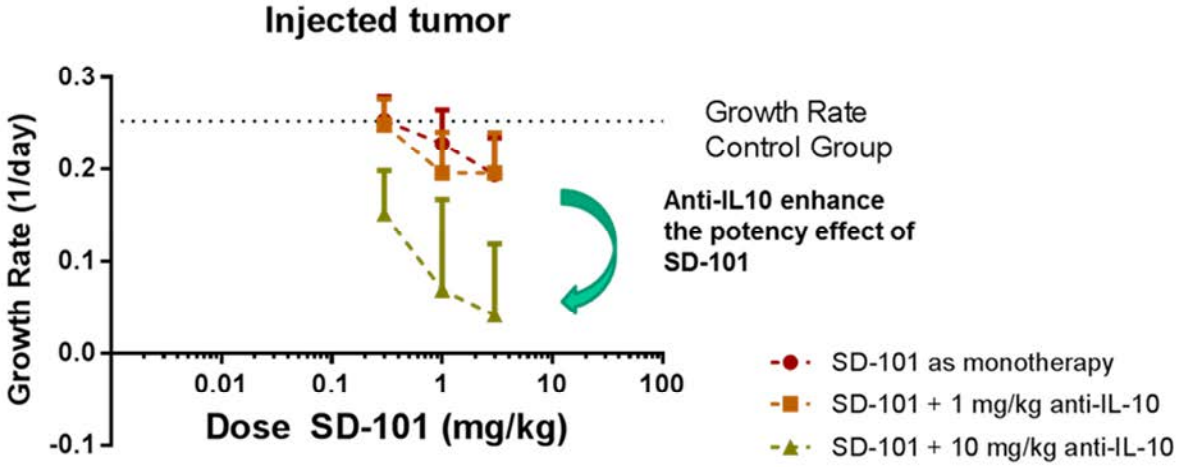


Figure 7 Efficacy of SD-101 Alone (at 0.3 to 3 mg/kg) and in Combination With Surrogate Mouse Anti-IL-10 mAb SCH 708974 (1 and 10 mg/kg).

Combination of SD-101 with SCH 708974 Resulted in up to 25-fold Increases in the Apparent Potency of SD-101. There was Approximately 90 - 100% Inhibition of IL-10 with 1 mg/kg SCH 708974 and 99 - 100% Inhibition of IL-10 with 10 mg/kg SCH 708974.

Nonclinical safety studies with MK-1966

Current studies included a 4-week intravenous toxicity study with an 8-week treatment-free period in cynomolgus monkeys using doses of 25, 75, and 150 mg/kg/week, an intravenous cardiovascular and respiratory telemetry study in cynomolgus monkeys at 75 mg/kg/dose, and an in vitro tissue cross-reactivity study in normal human tissues. In the repeat-dose toxicity study, inflammation of the large intestine in both sexes in the 75 and 150 mg/kg groups was observed, with one early death in the 150 mg/kg males. Large intestinal inflammation fully resolved by the end of the treatment-free period and there were no clinical or postmortem effects in the 25 mg/kg animals, which was determined as the no-observable effect level (NOEL)/no-observable adverse effect level (NOAEL). The systemic exposure at the NOAEL corresponds to 2-fold predicted human exposure based on 10 mg/kg human dose every 2 weeks. Toxicokinetic measurements showed no sex-related differences in exposure, and systemic exposure increased with increasing dose and with repeated dosing. The mean half-life of MK-1966 in the cynomolgus was 12.7 days. Total IL-10, a marker of target engagement, showed increased serum concentration with systemic MK-1966 exposure. Anti-MK-1966 antibodies were detected in the 75 and 150 mg/kg dose groups and were associated with increased elimination of serum MK-1966 and decreased total IL-10 concentration in some animals by the end of the study. In the single dose cardiovascular telemetry study, there was a lack of nocturnal decrease in blood pressure starting at 12 hours post-dose, a lack of

nocturnal decrease of heart rate starting at 30 hours post-dose, and increased body temperature from 30 hours post-dose through the end of the monitoring period at 72 hours post-dose. There were no ECG changes in the toxicity study, and no clinical signs of large intestinal inflammation in the telemetry study. In the tissue cross-reactivity study of MK-1966, specific positive staining was limited to the placenta. An in vitro cytokine release assay in human blood showed no cytokine responses to MK-1966.

MK-1966 Safety

Nonclinical safety studies in relevant pharmacological species reflected no significant toxicity following administration of weekly doses of MK-1966 at 25 mg/kg (NOAEL, section 4.2.2.1). Historical data also indicated absence of drug-related SAEs for MK-7089 (the parental clone of MK-1966) in SLE patients following single bolus administration of doses up to 10 mg/kg (Study #P03722). Additionally, it is expected that following administration of MK-1966 at a 1mg/kg dose (every 3 weeks) serum antibody exposure (AUC) to fall approximately 20-fold lower than the observed NOAEL (25 mg/kg) in the nonclinical safety studies for MK-1966. Results from combination preclinical studies also reflected no apparent potentiation in SD-101 pharmacodynamic effects at the 1-mg/kg dose of Anti-IL-10 surrogate.

SD-101 Safety

Following single agent intratumoral administration of SD-101 at fixed doses of 1, 2, 4, 8 mg in the ongoing clinical studies in cancer patients, no DLT up to 8 mg was observed thus far however, at the 8 mg intra-tumoral dose of SD-101 the subjects developed a flu-like illness and fevers. It is expected, following intra-tumoral administration of SD-101 in the proposed clinical study, serum concentrations to fall below the limit of quantification of the assay (LLOQ=5 ng/ml). The LLOQ of the assay for detection of SD-101 concentrations reflects approximately a 30- and 1000-fold safety window relative to the observed NOEL and NOAEL for SD-101 in previous nonclinical safety studies in cynomolgus monkeys, respectively (Dynavax report study #06-545).

FIH Dose proposal

A starting dose of 70 mg dose of MK-1966 is predicted to have partial target engagement with approximately 30-45% free IL-10 (Table 2) available for binding to IL-10R. From prior experience with MK-7089, treatment-related treatment emergent adverse event data at a 1 mg/kg (70 mg for 70 kg individual) dose was considered relatively safe. Based on the integrated summary outlined above, a FIH dose of 70 mg for combination therapy with fixed dose of 1 mg SD-101 has been chosen for MK-1966.

A fixed dosing regime is planned 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. ([21] and [22]) In the absence of this information for MK-1966, a fixed dose approach has been chosen. An initial fixed dose is proposed as 70 mg, determined based on a 70 kg patient receiving a dose of 1 mg/kg. The effect of body weight on the pharmacokinetics (PK) of MK-1966 and IL-10 target engagement will be evaluated to inform whether future studies will continue with a fixed dose regimen or switch to body weight based dosing.

MK-1966 will be administered over approximately 30 to 60 minutes as an IV infusion depending on the concentration of drug product. Additional information regarding drug preparation and administration can be found in the Procedures Manual.

4.2.2.2.2 Rationale for SD-101 Dose

SD-101 being a TLR9 agonist is expected to induce high levels of IFN-α that may be responsible for anti-tumor effects. IFNs can directly inhibit the proliferation of tumor cells and increase major histocompatibility complex (MHC) class I expression, enhancing antigen recognition. Additionally IFNs have potent effects on tumor infiltrating leukocytes, including enhancing antigen presenting function of dendritic cells, increasing the effector function of T-cells, and activating cytotoxic activity of natural killer cells [23].

The 1 mg and subsequently the 4 mg fixed intratumoral dose of SD-101 is based on previous clinical studies conducted with subcutaneously dosing of SD-101 (DV3-HNV-01, DV3-HCV-01), ongoing clinical study with intratumoral dosing (DV3-LYM-01), mechanism of action, and nonclinical studies with SD-101. The 1 mg dose of SD-101 was chosen as the starting dose as it demonstrated good safety and tolerability in the subjects with lymphoma and will allow a safety margin if co-administration with MK-1966 enhances its potential effects. If treatment with the 1 mg dose of SD-101 and the lowest dose of MK-1966 is tolerated the next cohort will receive a 4 mg dose of SD-101 with the lowest dose of MK-1966. If treatment with 4 mg of SD-101 and the lowest dose of MK-1966 is not tolerated in cohort 2, further dosing with SD-101 will continue at the de-escalated dose of 1 mg.

Based on data from a study in healthy male volunteers (DV3-HNV-01), elevation of biomarkers was seen after a single 0.1 mg subcutaneous dose and increased with doses up to 5 mg. From limited PK data after subcutaneous administration, maximum mean plasma levels were comparable at 3.0 mg (C_{max} = 7 ng/mL; n = 6) and 5.0 mg (C_{max} = 6 ng/mL; n= 2) doses (DV3-HNV-01 CSR). SD-101 demonstrated a dose-dependent IFN-α-inducible gene and serum protein biomarker response. AEs were limited to flu-like symptoms and administration-site pain and induration. Data from DV3-HCV-01 suggest that SD-101 appears to be generally safe and well tolerated with weekly subcutaneous doses of 0.1 mg, 1.0 mg, 3.0 mg, and 5.0 mg (DV3-HCV-01 CSR).

A summary of the clinical studies conducted to date with SD-101 is provided in the IB. For further information, see the IB.

4.2.2.3 Maximum Dose/Exposure for This Trial

Based on the current trial design and available safety data from the ongoing lymphoma trial (DV3-LYM-01), the maximum fixed intratumoral dose of SD-101 to be evaluated is 4 mg.

Dose escalations will primarily depend on maximum feasible target engagement subject to safety evaluations. The maximum clinical dose with adequate safety margins is expected to be 700 mg for MK-1966, which is predicted to achieve >90% suppression of IL-10 in one dosing period (96% suppression of IL-10 at C_{max}). Studies in the appropriate safety species (Cynomolgus monkeys) showed no adverse effects at doses where the C_{max} and AUC values were 2.5-fold and 2-fold higher, respectively, relative to the highest human exposure expected at 700 mg.

4.2.2.4 Rationale for Dose Interval and Trial Design

MK-1966 in combination with SD-101

MK-1966 is not expected to have anti-tumor activity as a stand-alone agent. Data from combination efficacy studies in mouse with SD-101 and a surrogate anti-IL-10 antibody suggest potentiation of tumor growth shrinkage compared to SD-101 alone.

MK-1966 and SD-101 are expected to play complementary roles in stimulating and maintaining a robust innate immune response. SD-101 augments dendritic cell function and MK-1966 will maintain the immune activation seen with SD-101 by inhibiting IL-10 anti-inflammatory effect and immune modulating effect.

The dose interval for MK-1966 is based on preclinical PK data in cynomolgus monkeys and from data collected in the FIH study with MK-7089. These studies have demonstrated a long half-life to justify every 3 week dosing. The dosing of SD-101 has been derived from the studies with this agent in normal healthy volunteers (NHV), subjects with hepatitis C and in subjects with low-grade B cell lymphoma.

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 MK-1966 in combination with SD-101 in subjects with advanced 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-1966 in combination with SD-101, including serious adverse events (SAEs).

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.

4.2.3.2 Efficacy Endpoints

An exploratory endpoint for this trial is to evaluate the anti-tumor activity of MK-1966 in combination with SD-101 in subjects with advanced solid malignancies. Tumor response will be accessed using Cheson criteria for B Cell lymphoma (see Section 4.2.3.5) or irRECIST (see Section 4.2.3.6).

Immunotherapeutic agents, such as MK-1966 and SD-101 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-1966 and SD-101. When feasible, study subjects can continue on treatment until progression is confirmed by the local site investigator/radiology assessment.

4.2.3.3 Pharmacokinetic Endpoints

A secondary objective of this trial is to characterize the PK profile of MK-1966 following administration with fixed dose SD-101. The serum concentration of the antibody will serve as the primary readout for the PK, and these data will be used to derive PK parameters for MK-1966 given in combination with SD-101. Furthermore, the results of these analyses will be used in conjunction with the pharmacodynamics, safety and anti-drug antibody endpoints to help assess future dosing strategies for MK-1966. MK-1966 concentrations in serum will be measured using a validated bioanalytical assay. The PK of SD-101 will not be determined in this study.

4.2.3.4 Pharmacodynamic Endpoints

As a required first step in pharmacologic activity, target engagement is fundamental to dosing strategies. To evaluate anti-IL-10 target engagement, total IL-10 concentration in the periphery (serum) will be monitored. IL-10 concentrations will be collected and reviewed as Part A progresses. IL-10 concentration data may be required prior to the initiation of dose escalation during study. The induction of IFN-α and its associated downstream genes will be used to assess the activity of SD-101.

Additional exploratory analyses will be performed to assess the effect of MK-1966 and SD-101 on immune cells in tumor tissues and in the circulation and are discussed in following sections.

4.2.3.5 Cheson Criteria for Lymphomas

Response to treatment will be evaluated by the investigator at 12 weeks and 24 weeks after the first study injection. Response to treatment will continue to be assessed every 12 weeks that a subject remains in the trial.

Response of lesions will be assessed by CT or CT/PET and bone marrow biopsy using the Cheson criteria for lymphomas [24]. Response will be assessed on the basis of clinical, radiologic, and pathologic (ie, bone marrow) criteria:

1. At a minimum, thoracic, abdominal, and pelvic CT scans will be performed even if those areas were not initially involved because of the unpredictable pattern of recurrence in NHL. CT/PET may be used if they are the standard tools for assessing disease status at a participating institution.
2. Unilateral bone marrow biopsy and aspirates will be performed at Screening if not previously performed or if performed more than 90 days previously with negative results. The bone marrow biopsy will be performed to confirm a complete response (CR) if the subject was initially positive or if it is clinically indicated by new abnormalities in the peripheral blood counts or blood smear.

Response of lesions will be recorded on the CRF based on the definitions in Table 3 as appropriate. Suspected relapse or disease progression must be confirmed by physical exam, laboratory assessments, repeat bone marrow biopsy [24] and CT scan. If confirmed,

progressive disease should be reported to the sponsor within 7 days. Subjects with suspected relapse or disease progression should continue to follow study procedures until they need another therapy. If a subject requires another therapy, date of treatment and type of treatment will be recorded and they will then be removed from the trial.

Tumor progression is defined as ≥ 50% increase from nadir in the sum of the products of the greatest diameters (SPD), as defined in the Cheson response criteria for NHL [24]. The response criteria should be recorded in the database. However, if the subject is evaluated by CT/PET scan then tumor response criteria should be evaluated using updated Cheson criteria [25] which includes CT and PET scans.

Table 3 Response Criteria for Non-Hodgkin's Lymphoma

Response Category	Physical Examination	Lymph Nodes	Lymph Node Masses	Bone Marrow
Complete Response	Normal	Normal	Normal	Normal
Complete Response/ Unconfirmed	Normal	Normal	Normal	Indeterminate
	Normal	Normal	≥ 75% decrease	Normal or indeterminate
Partial Response	Normal	Normal	Normal	Positive
	Normal	≥ 50% decrease	≥ 50% decrease	Irrelevant
	Decrease in liver/spleen	≥ 50% decrease	≥ 50% decrease	Irrelevant
Relapse/ Progression	Enlarging liver/ spleen; new sites	New or increased	New or increased	Reappearance
Source [24]				

4.2.3.6 Immune-related RECIST (irRECIST)

RECIST 1.1 will be adapted to account for the unique tumor response characteristics seen with treatment immunotherapeutic agents. Immunotherapeutic agents such as MK-1966 and SD-101 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 1.1 may, thus, not provide an accurate response assessment of immunotherapeutic agents. With other immunotherapeutic agents, up to 7 % of evaluable patients experienced delayed or early tumor pseudoprogression. Of note, patients who had progressive disease by RECIST 1.1 but not by immune related Response Criteria had longer OS than patients with progressive disease by both criteria. These findings support the need to apply a modification

to RECIST 1.1 that takes into account the unique patterns of atypical response in immunotherapy and enable treatment beyond initial radiographic progression.

Immune-related RECIST (irRECIST) is RECIST 1.1 adapted to account for the unique tumor response seen with immuno-therapeutics as described in [26]. The assessment of unidimensional target lesions and response categories per irRECIST are identical to RECIST 1.1. However, Merck has implemented an adaptation related to new lesions, non-target and tumor burden assessment in order to confirm radiographic progression. irRECIST will be used by local site investigators to assess tumor response and progression, and make treatment decisions.

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

In subjects who have initial evidence of radiological PD by RECIST 1.1, it is at the discretion of the PI whether to continue a subject on study treatment until repeat imaging is obtained (irRECIST subject management). This clinical judgment decision by the site should be based on the subject's overall clinical condition, including performance status, clinical symptoms, and laboratory data. Subjects may receive study treatment and tumor assessment should be repeated ≥ 4 weeks later in order to confirm PD by irRECIST per site assessment. Clinical stability is defined as the following:

- 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

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

Scenarios where PD is confirmed at repeat imaging if ANY of the following occur by irRECIST:

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

If repeat imaging confirms PD due to any of the scenarios listed above, subjects will be discontinued from study therapy (exception noted below and in Section 7.1.2.6.3).

Scenarios where PD is not confirmed at repeat imaging if ALL of the following occur by irRECIST:

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

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

When feasible, study subjects can continue on treatment until progression is confirmed by the local site investigator/radiology assessment This allowance to continue treatment despite initial radiologic progressive disease (PD) takes into account the observation that some subjects can have a transient tumor flare in the first few months after the start of immunotherapy, and then experience subsequent disease response. Subjects that are deemed clinically unstable are not required to have repeat tumor imaging for confirmation of PD.

Tumor flare includes any of the following scenarios:

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

Additional details about irRECIST are referenced in Imaging Manual.

4.2.3.6.1 Target Engagement (TE)

IL-10 target engagement will be assessed by measuring the total circulating IL-10, the combined total concentration of both free IL-10 and the IL-10 that is bound to MK-1966. IL-10 concentrations in serum will be measured using a qualified bioanalytical assay. As the concentration of free IL-10 is expected to be quite low (pg/mL) and the clearance rate of IL-10 bound to MK-1966 is expected to be slow, the target engagement assay is expected to measure primarily MK-1966 bound IL-10.

In previous studies with SD-101, the induction of IFN-α associated genes in the peripheral blood was used to determine target engagement and used for dose selection. IFN-α associated genes ISG-54, MX-b, IP-10 and MCP-1 were monitored and demonstrated to be upregulated greater than 3 fold (3 out of the 4 genes up-regulated at any time point). Dose dependency was observed from 0 to 1.0 mg but from 1.0 to 5.0 mg no dose dependency was observed. IFN-α was not consistently upregulated with SD-101 administration.

4.2.3.6.2 Anti-Drug Antibody (ADA) Assay

1) Screening ADA assay

ADA screening assay (including the Confirmatory test for specificity against the drug, and titer determination for confirmed positive samples) will be developed and validated

in human serum to support clinical studies. A standard bridging ECL assay with the required sensitivity and drug tolerance using MSD platform will be used.

The assay will be validated prior to FIH study start.

2) Neutralizing anti-drug antibody (NAb) assay

A non-cell-based NAb assay in human serum will be developed and validated for further characterization of confirmed ADA positive samples. The assay will be used to support the early phases of the FIH study. A cell based Nab assay will be developed and validated as well once an appropriate cell line is established to support the later phases of the FIH study.

4.2.3.6.3 Cytokines of Systemic Immune Activation

Due to immune stimulation by SD-101 and enhanced immune activation by the administration of SD-101, a panel of cytokine proteins will be monitored including IL-10, IFN-γ, IL-12p70, IL-13, IL-1β, IL-2, IL-4, IL-6, IL-8, TNF-α and IFN-α2a.

4.2.3.6.4 Exploratory RNA Profiling and IHC Markers

The relationship between anti-tumor activity of MK-1966 in combination with SD-101 will be investigated through evaluation of gene expression (including IFN-α) in blood and in pre and post biopsy tumor tissue. Responses will also be correlated to pre-treatment gene expression data with a goal to identify potential patient selection biomarkers.

Multiple immunohistochemistry (IHC) assays are planned and are currently in development to support exploratory biomarker research including CD3, CD8, pDC, TLR9 and PD-L1.

4.2.3.6.5 Exploratory Objective on the Longitudinal Change of Tumor Size

The longitudinal measurement on tumor size will be investigated to collect information on the tumor response to the treatment. Several statistical modeling methods will be explored to analyze tumor size longitudinally based on imaging assessment.

4.2.3.7 Planned Exploratory Biomarker Research

Planned Genetic Analysis

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

4.2.3.8 Future Biomedical Research

The Sponsor will conduct Future Biomedical Research on specimens collected for future biomedical research during this clinical trial. This research may include genetic analyses

(DNA), gene expression profiling (RNA), proteomics, metabolomics (serum, plasma) and/or the measurement of other analytes.

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

4.3 Benefit/Risk

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

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

5.0 METHODOLOGY

5.1 Entry Criteria

5.1.1 Diagnosis/Condition for Entry into the Trial

Male/Female subjects with advanced malignancies, of at least 18 years of age will be enrolled in this trial.

5.1.2 Subject Inclusion Criteria

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

1. Have one of the following diagnoses
    a. A histologically- or cytologically-confirmed low grade B-cell lymphoma which has progressed after standard of care therapy/treatments and there is no available therapy likely to convey clinical benefit.
    b. Unresectable melanoma that in the opinion of the Investigator have progressed after anti-PD-1 therapy, and/or anti-PD-1 and CTLA-4 combination treatments. Subjects who have BRAF V600 mutant melanoma are required to have had a prior treatment regimen that included vemurafenib, dabrafenib, or other approved BRAF and/or MEK inhibitor.
    c. SCCHN that have progressed after standard of care therapy/treatments and there is no available therapy likely to convey clinical benefit. Subjects are

required to have been refractory to platinum (either cisplatin or carboplatin) and cetuximab. Resistance is defined as tumor progression or recurrence within 6 months of platinum or cetuximab therapy in the adjuvant (e.g. with radiation after surgery), primary (e.g. with radiation), recurrent, or metastatic setting. Subject must be resistant to both platinum and cetuximab.

d. Breast cancer with dermal metastasis, which has progressed after standard-of-care therapy/treatments and there is no available therapy likely to convey clinical benefit.

e. Part B will enroll subjects with unresectable melanoma that in the opinion of the Investigator have progressed after anti-PD-1 therapy, and/or anti-PD-1 and CTLA-4 combination treatments. Subjects who have BRAF V600 mutant melanoma are required to have had a prior treatment regimen that included vemurafenib, dabrafenib, or other approved BRAF and/or MEK inhibitor.

f. Part C will enroll SCCHN that have progressed after standard of care therapy/treatments and there is no available therapy likely to convey clinical benefit. Subjects are required to have been refractory to platinum (either cisplatin or carboplatin) and cetuximab. Resistance is defined as tumor progression or recurrence within 6 months of platinum or cetuximab therapy in the adjuvant (e.g. with radiation after surgery), primary (e.g. with radiation), recurrent, or metastatic setting. Subject must be resistant to both platinum and cetuximab.

2. Subjects with melanoma, squamous cell cancer of head and neck or breast cancer with dermal metastasis must have a tumor accessible to intralesional injection and have measurable disease by Cheson or irRECIST criteria.
3. Subjects with B Cell Lymphoma must have:

   a. Biopsy confirmed, low-grade B-cell lymphoma, including follicular (Grade 1, 2, or 3A [27]), or marginal, or CLL/SLL with lymph node involvement that has progressed after standard of care therapy/treatments and there is no available therapy likely to convey clinical benefit.

   b. Measurable disease per Cheson criteria (1 lesion must measure at least 1.5 cm in any diameter or 1.0 cm in the shortest diameter if one of the diameters is not ≥ 1.5 cm), and be palpable and easily accessible in a low-risk site (eg, inguinal, axillary, cervical, subcutaneous) for intratumoral injection.

4. Be ≥18 years of age on day of signing informed consent.
5. Have a performance status of 0 or 1 on the Eastern Cooperative Oncology Group (ECOG) Performance Scale (Appendix 12.4).
6. Have a life expectancy ≥6 months
7. Demonstrate adequate organ function as defined by the following table (Table 4). All screening labs should be performed within 7 days of treatment initiation.

Table 4 Adequate Organ Function Laboratory Values

System	Laboratory Value
Hematological	
Absolute neutrophil count	≥1,500/mcL
Platelets	≥100,00/mcL
Hemoglobin[b]	≥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 **OR** ≤ 5 × ULN for subjects with liver metastases
Coagulation[c]	
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
[b] Hemoglobin should be without transfusion within 4 weeks of Day 1.
[c] If the subject is receiving anticoagulant therapy, the PT or partial thromboplastin time (PTT) should be within the therapeutic range of intended use of anticoagulants.

8. Have voluntarily agreed to participate by giving written informed consent. The subject may also provide consent for Future Biomedical Research. However, the subject may participate in the main trial without participating in Future Biomedical Research
9. Female subjects of childbearing potential must have a negative urine or serum pregnancy test at Screening and again within 72 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.
10. Female subjects of childbearing potential (refer to Section 5.7.2) must be willing to use an adequate method of contraception as outlined in Section 5.7.2– Contraception, for the course of the study through 120 days after the last dose of study medication.

    Note: Abstinence is acceptable if this is the usual lifestyle and preferred contraception for the subject.
11. Male subjects of childbearing potential (refer to Section 5.7.2) must agree to use an adequate method of contraception as outlined in Section 5.7.2– Contraception, starting with the first dose of study therapy through 120 days after the last dose of study therapy.

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

12. Submit archived or fresh tumor sample during screening period as specified in the Procedures Manual.

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-1966 or SD-101.
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 4 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 that has required systemic treatment in past 2 years (i.e. with use of disease modifying agents, corticosteroids or immunosuppressive drugs). Replacement therapy (e.g., thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency, etc.) is not considered a form of systemic treatment.
9. Has an active infection requiring therapy.
10. Has active, 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 disorder(s) that would interfere with cooperation with the requirements of the trial.
15. Is a regular user, as determined by investigator judgment, (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 thoraco- 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 that affect normal activities.
19. Has had major surgery (requiring at least a 3 day hospital stay) in the past 28 days.
20. Has received a live vaccine within 30 days prior to first dose.

5.2 Trial Treatment(s)

The treatment(s) to be used in this trial are outlined below in Table 5.

Table 5 Trial Treatment for MK-1966 and SD-101

Treatment During Part A: Dose Finding					
Drug	**Dose/Potency**	**Dose Frequency**	**Route of Administration**	**Regimen/ Treatment Period††**	**Use**
MK-1966	70 mg 210 mg 700 mg	Day 1, then Q3W	Intravenous over 30 -120 min	Day 1 then Q3W for 7 additional doses	Experimental
SD-101	1 mg 4 mg†	Days 1, 8, 15, 22 then Q3W	Intratumorally	Days 1, 8, 15, 22 then Q3W for 6 additional doses	Experimental
Treatment During Part B and C: Expansion Cohort					
Drug	**Dose/Potency**	**Dose Frequency**	**Route of Administration**	**Regimen/ Treatment Period††**	**Use**
MK-1966	MTD/MAD	Every 3 weeks	Intravenous over 30 -120 min	Day 1 then Q3W for 7 additional doses	Experimental
SD-101	4 mg†	Days 1, 8, 15, 22 then Q3W	Intratumorally	Days 1, 8, 15, 22 then Q3W for 6 additional doses	Experimental

† Note, if the 4 mg SD-101 and 70 mg MK-1966 combination (cohort 2) is not tolerated, then the dose of SD-101 for subsequent cohorts (3 & 4) in part A and expansion cohorts (Parts B and C) will be 1 mg.
††When MK-1966 and SD-101 are scheduled at the same time:
1. SD-101 will be administered first.
2. MK-1966 will be administered at least 30 minutes after the SD-101 injection.

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

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

5.2.1 Dose Selection/Modification

5.2.1.1 Dose Selection (Preparation)

Details on dose calculation, preparation and administration of MK-1966 and SD-101 are provided in the Pharmacy Manual.

5.2.1.2 Dose Escalation

Enrollment to Arm A, (MK-1966 with SD-101) will begin at the 70 mg for MK-1966 and 1 mg for SD-101. The initial dose combination of SD-101 and MK-1966 will test the tolerability of administering both agents in subjects with advanced tumors. The following three dosing cohorts were chosen with administration of the higher fixed dose of SD-101 to increase immune activation combined with escalating doses of MK-1966. All dose levels in Part A will follow 3+3 design. Dose escalation of MK-1966 will continue to identify a preliminary MTD or MAD.

The dosing for each cohort is as follows:

1) 1 mg SD-101 intratumorally and 70 mg MK-1966 intravenously
2) 4 mg SD-101 intratumorally and 70 mg MK-1966 intravenously
3) 4 mg SD-101 intratumorally and 210 mg MK-1966 intravenously
4) 4 mg SD-101 intratumorally and 700 mg MK-1966 intravenously

Note, if the 4 mg SD-101 and 70 mg MK-1966 combination (cohort 2) is not tolerated, then SD-101 will be de-escalated to a 1 mg dose for subsequent cohorts (3 & 4). The study will include up to four dosing cohorts for SD-101 and MK-1966.

5.2.1.2.1 3+3 Dose Escalation

During 3+3 dose escalation, at least 2 days of observation will occur between each of the first 3 subjects at each dose level.

Dose escalation will increase in increments of approximately 3 fold.

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 develops 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 develops a DLT (for a total of 1/6 subjects with a DLT at this dose level), escalation to the next dose level will occur.

- If ≥1 of the 3 new subjects develops a DLT (for a total of ≥2/6 subjects with a DLT at this dose level), the dose escalation stage of the trial will be terminated.

- If ≥2/3 subjects develop a DLT, the dose escalation stage of the trial will be terminated. If the dose directly below the current dose had been studied in at least 3 subjects, the dose directly below the current dose will be considered the preliminary MTD, and the study will proceed to the confirmation/expansion stage. It is conceptually acceptable to de-escalate to an intermediate, not pre-defined and not previously-studied dose, if evaluation of toxicity at such a dose is desired in lieu of proceeding directly to the dose confirmation/expansion stage of the study. If this approach is taken, 3 new subjects should be enrolled at the new intermediate dose, and the aforementioned rules should be used to determine further enrollment at this dose level.
- If the highest candidate dose of MK-1966 is studied during dose escalation, and 0/3 subjects or <2/6 subjects develop a DLT at that dose, then dose escalation will terminate with this finding and this dose level will be taken to the confirmation/expansion stage.

5.2.1.2.2 Dose Confirmation/Expansion

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

Dose confirmation will begin with expansion of the preliminary MTD/MAD identified in the dose escalation stage described in Section 5.2.1.2.1. The dose confirmation part will continue until 20 subjects are studied at the selected dose (combined from dose escalation and dose confirmation) with ≤7 of 20 subjects experiencing a DLT. As subjects become evaluable for DLT assessment, the number of subjects who are evaluable for DLT versus the number of subjects who developed a DLT will be continuously assessed. De-escalation and escalation to eligible doses will occur during dose confirmation as shown in Table 6. Escalation or reduction of dose for either agent will be to the next higher or lower dose on MK-1966 being examined in this study, while keeping SD-101 dose fixed. However dose escalation will not exceed 700 mg of MK-1966 or 4 mg of SD-101. Likewise a cohort dose will not be reduced below 70 mg of MK-1966 or 1 mg of SD-101.

Table 6 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%
Non-informative prior is used: a=1; b=1;
k1=1; k2=1.5; pow=1 per {Ji, 2007 #55124}.

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 6). 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 6). To find out how many more subjects can be enrolled, one can count steps in diagonal direction (down and to the right) from the cell (7 subjects, 3 toxicities) to the first cell marked DU.

If enrollment expands to 20 subjects for a dose level, and ≤7 of the 20 subjects develop a DLT, then the dose confirmation will stop. If enrollment expands to 20 subjects for a dose level and >7/20 subjects develop a DLT, then the next lower dose may be expanded to

further explore the dose-response relationship. Note that while 30% has been the target toxicity rate used to generate the guidelines in Table 6, the observed rate of subjects with DLT at the MTD may be slightly above or below 30%.

5.2.2 Definition of Dose Limiting Toxicity

DLT's will be defined from toxicities observed during the first cycle of treatment (21 days) for each dose level. See Section 5.2.4 for rules on replacement of subjects in the DLT period. The occurrence of any of the following toxicities during Cycle 1, if assessed by the Investigator to be possibly, probably or definitely related to MK-1966 or SD-101 in Arm A, 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 or vomiting 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
    - medical intervention is required, or
    - the abnormality leads to hospitalization, or
    - the abnormality persists for > 1 week
5. Febrile neutropenia Grade 3 or Grade 4
6. Any drug-related AE which caused subject to discontinue treatment during Cycle 1
7. Grade 5 toxicity
8. Delay in initiation of Cycle 2 for >2 weeks due to study drug-related toxicity

5.2.3 Guidelines for Dose Modifications

5.2.3.1 Dose Modification

The Common Terminology Criteria for Adverse Events version 4.0 (CTCAE 4.0) must be used to grade the severity of adverse events. If appropriate, the Investigator may attribute each toxicity event to MK-1966 or SD-101 alone or to the combination arm.

Part A

Subjects will continue at their enrolled dose for the duration of their participation. Holding of one 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. If, in the opinion of the Investigator, the toxicity is related to the combination of two agents, both drugs should be held.

Parts B and C

Dose modifications should be made according to Table 7. 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.

Subjects may have 1 dose modification to MK-1966 or SD-101 throughout the course of the study. If further toxicity occurs or the criteria for resuming treatment are not met, the subject must be discontinued from the agent. If a subject experiences several toxicities and there are conflicting recommendations, follow the most conservative dose adjustment recommended (dose reduction or holding as appropriate to the most severe toxicity).

Reduction or holding of one agent and not the other agents is appropriate if, in the opinion of the Investigator, the toxicity is clearly related to one of the study drugs. If, in the opinion of the Investigator, the toxicity is related to the combination of two agents, both drugs should be held or reduced according to recommended dose modifications.

If in the opinion of the Investigator dose reduction is recommended, either agent can be reduced 1 dose level following consultation with the Sponsor. Only 1 dose reduction (of either agent) is permitted for each subject. If additional dose reduction is warranted, then the subject should be discontinued from the study. Both MK-1966 and SD-101 may only be reduced to the next lowest dose being explored in this study (i.e., MK-1966 210 mg would be reduced to 70 mg). Neither agent may be reduced below the lowest dose being tested in this protocol (MK-1966: 70 mg; SD-101: 1 mg).

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

In all study Parts, both MK-1966 and SD-101 will be held for the adverse events described below in Table 7.

Table 7 MK-1966 and SD-101 Dose Modification Guidelines for Drug-Related Adverse Events

Toxicity	Hold Treatment For	Timing for Restarting Treatment	Treatment Discontinuation
Diarrhea/Colitis	Grade 2-3	Toxicity resolves to Grade 0-1	Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks
	Grade 4	Permanently discontinue	Permanently discontinue
AST, ALT, or Increased Bilirubin	Grade 2	Toxicity resolves to Grade 0-1	Toxicity does not resolve within 12 weeks of last dose
	Grade 3-4	Permanently discontinue (see exception below)[a]	Permanently discontinue
Type 1 diabetes mellitus (if new onset) or Hyperglycemia	T1DM or Grade 3-4	Hold SD-101 and MK-1966 for new onset Type 1 diabetes mellitus or Grade 3-4 hyperglycemia associated with evidence of beta cell failure	Resume SD-101 and MK-1966 when patients are clinically and metabolically stable

Toxicity	Hold Treatment For	Timing for Restarting Treatment	Treatment Discontinuation
Hypophysitis	Grade 2-4	Toxicity resolves to Grade 0-1. Therapy with SD-101 and MK-1966 can be continued while endocrine replacement therapy is instituted	Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks
Hyperthyroidism	Grade 3	Toxicity resolves to Grade 0-1	Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks
	Grade 4	Permanently discontinue	Permanently discontinue
Hypothyroidism		Therapy with SD-101 and MK-1966 can be continued while thyroid replacement therapy is instituted	Therapy with SD-101 and MK-1966 can be continued while thyroid replacement therapy is instituted
Infusion Reaction	Grade 2[b]	Toxicity resolves to Grade 0-1	Permanently discontinue if toxicity develops despite adequate premedication
	Grade 3-4	Permanently discontinue	Permanently discontinue
Injection Reaction	≥ Grade 3	Toxicity resolves to Grade 0-1	Toxicity does not resolve within 12 weeks of last dose
Pneumonitis	2	Toxicity resolves to Grade 0-1	Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks
	3-4 (or recurrent Grade 2)	Permanently discontinue	Permanently discontinue
Renal Failure or Nephritis	2	Toxicity resolves to Grade 0-1	Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks
	3-4	Permanently discontinue	Permanently discontinue
ANC	≤1500 cells/mcL	≥ 1500 cells/mcL	ANC does not increase ≥ 1500 cells/mcL within 12 weeks

Toxicity	Hold Treatment For	Timing for Restarting Treatment	Treatment Discontinuation
All Other Drug-Related Toxicity[c]	3 or Severe	Toxicity resolves to Grade 0-1	Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or less of prednisone or equivalent per day within 12 weeks
	4	Permanently discontinue	Permanently discontinue

AE = adverse event; ALT = alanine transaminase; AR = adverse reaction; AST = aspartate transaminase; T1DM = type 1 diabetes mellitus.

Note: Permanently discontinue for any severe or Grade 3 (Grade 2 for pneumonitis) drug-related AE that recurs or any life-threatening event.

[a] For patients with liver metastasis who begin treatment with Grade 2 AST or ALT, if AST or ALT increases by greater than or equal to 50% relative to baseline and lasts for at least 1 week then patients should be discontinued.

[b] If symptoms resolve within one hour of stopping drug infusion, the infusion may be restarted at 50% of the original infusion rate (e.g., from 100 mL/hr to 50 mL/hr). Otherwise dosing will be held until symptoms resolve and the subject should be premedicated for the next scheduled dose. Refer to Table 8– Infusion Reaction Treatment Guidelines for further management details.

[c] Patients with intolerable or persistent Grade 2 drug-related AE may hold study medication at physician discretion. Permanently discontinue study drug for persistent Grade 2 adverse reactions for which treatment with study drug has been held, that do not recover to Grade 0-1 within 12 weeks of the last dose.

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-1966 or SD-101 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 the Investigator.

5.2.5 Timing of Dose Administration

Minimal dosing interval between SD-101 dosing must be 5 days. 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 1 day 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, patient 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 patient's study record.

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

In Parts A, B and C treatment allocation will manually occur by non-random assignment.

5.4 Stratification

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

5.5 Concomitant Medications/Vaccinations (Allowed & Prohibited)

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

5.5.1 Acceptable Concomitant Medication

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 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, chicken pox, 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. Flu - Mist®) are live attenuated vaccines, and are not allowed.

Glucocorticoids for any purpose other than to modulate symptoms from an adverse event. Glucocorticoids must be below 10 mg daily to restart SD-101 and/or MK-1966 dosing. 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.

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

5.6 Treatment Precaution

IFN-α has been shown to inhibit cytochrome P450 (CYP) enzyme 1A2 (Brennan 2012). Since SD 101 induces IFN-α, SD 101 may inhibit metabolism of drugs by CYP 1A2. CYP 1A2 substrates with narrow therapeutic ranges should be used with caution. The following drugs should be used with caution through 7 days after each subsequent dose of SD-101: caffeine, theophylline, warfarin, tricyclic antidepressants, clozapine, fluvoxamine, ciprofloxacin, propranolol, and verapamil.

5.7 Rescue Medications & Supportive Care

5.7.1 Supportive Care Guidelines

Subjects should receive appropriate supportive care measures as deemed necessary by the treating investigator. Suggested supportive care measures for the management of adverse events with potential immunologic etiology are outlined below. Where appropriate, these guidelines include the use of oral or intravenous 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 MK-1966 or SD-101.

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

- **Diarrhea/Colitis**:

  Subjects should be carefully monitored for signs and symptoms of enterocolitis (such as diarrhea, abdominal pain, blood or mucus in stool, with or without fever) and of bowel perforation (such as peritoneal signs and ileus).

  - All subjects who experience diarrhea/colitis should be advised to drink liberal quantities of clear fluids. If sufficient oral fluid intake is not feasible, fluid and electrolytes should be substituted via IV infusion. For Grade 2 or higher diarrhea, consider GI consultation and endoscopy to confirm or rule out colitis.
  - For **Grade 2 diarrhea/colitis** that persists greater than 3 days, administer oral corticosteroids.
  - For **Grade 3 or 4 diarrhea/colitis** that persists > 1 week, treat with intravenous steroids followed by high dose oral steroids.
  - When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks.

- **Hyperthyroidism or Hypothyroidism**:

  Thyroid disorders can occur at any time during treatment. Monitor patients for changes in thyroid function (at the start of treatment, periodically during treatment, and as indicated based on clinical evaluation) and for clinical signs and symptoms of thyroid disorders.

  - **Grade 2** hyperthyroidism events (and **Grade 3-4** hypothyroidism):
    - In hyperthyroidism, non-selective beta-blockers (e.g. propranolol) are suggested as initial therapy.
    - In hypothyroidism, thyroid hormone replacement therapy, with levothyroxine or liothyroinine, is indicated per standard of care.
  - **Grade 3-4** hyperthyroidism
    - Treat with an initial dose of IV corticosteroid followed by oral corticosteroids. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks. Replacement of appropriate hormones may be required as the steroid dose is tapered.

- **Hepatic**:
  - For **Grade 2** events, monitor liver function tests more frequently until returned to baseline values (consider weekly).
    - Treat with IV or oral corticosteroids
  - For **Grade 3-4** events, treat with intravenous corticosteroids for 24 to 48 hours.
  - When symptoms improve to Grade 1 or less, a steroid taper should be started and continued over no less than 4 weeks.

- **Hypophysitis:**
    - For **Grade 2** events, treat with corticosteroids. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks. Replacement of appropriate hormones may be required as the steroid dose is tapered.
    - For **Grade 3-4** events, treat with an initial dose of IV corticosteroids followed by oral corticosteroids. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks. Replacement of appropriate hormones may be required as the steroid dose is tapered.
- **Management of Infusion Reactions**: Signs and symptoms usually develop during or shortly after drug infusion and generally resolve completely within 24 hours of completion of infusion.

Table 8 below shows treatment guidelines for subjects who experience an infusion reaction associated with administration of MK-1966 or SD-101.

Table 8 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 subject is deemed medically stable in the opinion of the investigator.	None
Grade 2 Requires infusion interruption but responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDS, narcotics, IV fluids); prophylactic medications indicated for < =24 hrs	**Stop Infusion.** Additional appropriate medical therapy may include but is not limited to: IV fluids Antihistamines NSAIDS Acetaminophen Narcotics Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator. If symptoms resolve within one hour of stopping drug infusion, the infusion may be restarted at 50% of the original infusion rate (e.g. from 100 mL/hr to 50 mL/hr). Otherwise dosing will be held until symptoms resolve and the subject should be premedicated for the next scheduled dose. Subjects who develop Grade 2 toxicity despite adequate premedication should be permanently discontinued from further trial treatment administration.	Subject may be premedicated 1.5h (± 30-minutes) prior to infusion of MK-1966 with: Diphenhydramine 50 mg po (or equivalent dose of antihistamine). Acetaminophen 500-1000 mg po (or equivalent dose of analgesic).
Grades 3 or 4 Grade 3: Prolonged (i.e., not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae (e.g., renal impairment, pulmonary infiltrates) Grade 4: Life-threatening; pressor or ventilatory support indicated	**Stop Infusion.** Additional appropriate medical therapy may include but is not limited to: IV fluids Antihistamines NSAIDS Acetaminophen Narcotics Oxygen Pressors Corticosteroids Epinephrine Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator. Hospitalization may be indicated. Subject is permanently discontinued from further trial treatment administration.	No subsequent dosing
Appropriate resuscitation equipment should be available at the bedside and a physician readily available during the period of drug administration. For Further information, please refer to the Common Terminology Criteria for Adverse Events v4.0 (CTCAE) at http://ctep.cancer.gov		

- Management of Injection Site Reaction(s):
    - Subjects should receive full supportive care to treat injection site reactions.. Injection-site reactions are expected to spontaneously subside. Local reactions

are to be treated at the discretion of the treating physician. The site is not to be injected if local pain, tenderness, or swelling persists from a previous injection or other cause; the injection may be postponed until the symptoms have resolved. The injection may be skipped, following agreement with the Medical Monitor.

- **Pneumonitis:** For **Grade 2 events**, treat with systemic corticosteroids. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks.
    - For **Grade 3-4 events**, immediately treat with intravenous steroids. Administer additional anti-inflammatory measures, as needed.
    - Add prophylactic antibiotics for opportunistic infections in the case of prolonged steroid administration.
- **Renal Failure or Nephritis:**
    - For Grade 2 events, treat with corticosteroids
    - For Grade 3-4 events, treat with systemic corticosteroids
    - When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks.
- **Type 1 Diabetes Mellitus** (if new onset, including diabetic ketoacidosis) or ≥ Grade 3 hyperglycemia, if associated with ketosis (ketonuria) or metabolic acidosis (diabetic ketoacidosis)
    - Insulin replacement therapy is recommended for Type 1 diabetes mellitus and for Grade 3-4 hyperglycemia associated with metabolic acidosis or ketonuria.
    - Evaluate patients with serum glucose and a metabolic panel, urine ketones, glycosylated hemoglobin, and C-peptide.

5.8 Diet/Activity/Other Considerations

5.8.1 Diet

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

5.8.2 Contraception

MK-1966 and SD-101 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.

Female subjects will be considered of non-reproductive potential if they are either:

(1) postmenopausal (defined as at least 12 months with no menses without an alternative medical cause; in women < 45 years of age a high follicle stimulating hormone (FSH)

level in the postmenopausal range may be used to confirm a post-menopausal state in women not using hormonal contraception or hormonal replacement therapy. In the absence of 12 months of amenorrhea, a single FSH measurement is insufficient.);

OR

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

OR

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

Female and male subjects of reproductive potential must agree to avoid becoming pregnant or impregnating a partner, respectively, while receiving study drug and for 120 days after the last dose of study drug by complying with one of the following:

(1) practice abstinence† from heterosexual activity;

OR

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

Acceptable methods of contraception are‡:

Single method (one of the following is acceptable):

- intrauterine device (IUD)
- vasectomy of a female subject's male partner
- contraceptive rod implanted into the skin

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

- diaphragm with spermicide (cannot be used in conjunction with cervical cap/spermicide)
- cervical cap with spermicide (nulliparous women only)
- contraceptive sponge (nulliparous women only)
- male condom or female condom (cannot be used together)
- hormonal contraceptive: oral contraceptive pill (estrogen/progestin pill or progestin-only pill), contraceptive skin patch, vaginal contraceptive ring, or subcutaneous contraceptive injection

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

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

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

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

5.8.3 Use in Pregnancy

If a subject inadvertently becomes pregnant while on treatment with MK-1966 or SD-101, 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.

5.8.4 Use in Nursing Women

It is unknown whether MK-1966 or SD-101 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.

5.9 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. Once a subject has discontinued treatment, even though he/she continues to be monitored in the trial, he/she may be allowed to begin treatment again if deemed medically appropriate.

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 4.2.3)
- 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
- Lost to follow-up

5.10 Subject Replacement Strategy

A subject who discontinues from the trial will not be replaced except as described in Section 5.2.3 Replacement of Subjects During DLT Evaluation Period.

5.11 Beginning and End of the Trial

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

5.12 Clinical Criteria for Early Trial Termination

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

6.0 TRIAL FLOW CHART

Dose Escalation and Expansion Cohorts- MK-1966 + SD-101

Trial Period:	Screening Phase	Cycles 1						Cycle 2			Cycle 3			Cycle 4 (Day 1)	Cycle 5-8 (Day 1)	End of Treatment Period	Post-Treatment	Survival FU
																	Safety Follow-up	
Treatment Days:	Screening (Visit 1)	1	2	3	8	9	15	22	29	36	43	50	57	64		At end of Cycle 8[s] or time of treatment discon	30 days post end of Treatment Period	Every 12 weeks
Scheduling Window (Days):	-28 to -1							± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 7
Administrative Procedures																		
Informed Consent	X																	
Inclusion/Exclusion Criteria	X																	
Demographics and Medical History	X																	
Prior and Concomitant Medication Review[o]	X	X			X		X	X	X	X	X	X	X	X	X	X	X	
Clinical Procedures/Assessments[o]																		
Review Adverse Events	X[p]	X			X		X	X	X	X	X	X	X	X	X	X	X[p]	
12-Lead ECG (Local)	X	X						X			X			X	X	X		
Full Physical Examination	X															X		
Directed Physical Examination		X			X		X	X	X	X	X	X	X	X	X			
Vital Signs, Weight, Height[a]	X	X			X		X	X	X	X	X	X	X	X	X	X		
ECOG Performance Status	X	X			X		X	X	X	X	X	X	X	X	X	X		
Trial Treatment Administration[j]																		
MK-1966		X						X			X			X	X			
SD-101[q,r]		X			X		X	X			X			X	X			

Trial Period:	Screening Phase	Cycles 1						Cycle 2			Cycle 3			Cycle 4 (Day 1)	Cycle 5-8 (Day 1)	End of Treatment Period	Post-Treatment	Survival FU
																	Safety Follow-up	
Treatment Days:	Screening (Visit 1)	1	2	3	8	9	15	22	29	36	43	50	57	64		At end of Cycle 8[s] or time of treatment discon	30 days post end of Treatment Period	Every 12 weeks
Scheduling Window (Days):	-28 to -1							± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 3	± 7
Laboratory Procedures/Assessments: Analysis performed by LOCAL laboratory																		
Pregnancy Test – Serum or Urine[b]	X	X						X			X			X	X	X	X	
PT/INR and aPTT	X[f]																	
CBC with Differential[k]	X[f]	X[k]			X		X	X	X	X	X	X	X	X	X	X	X	
Chemistry Panel[k]	X[f]	X[k]			X		X	X	X	X	X	X	X	X	X	X	X	
HIV, Hepatitis B and C[l]	X																	
Thyroid Function (TSH, Free T_4, Total T_3)[k]	X[f]							X			X			X	X	X		
Urinalysis	X[f]	X						X			X			X	X	X		
Laboratory Procedures/Assessments: Analysis performed by Sponsor or Central laboratory																		
MK-1966 Pharmacokinetics[g]		X	X	X	X		X	X	X	X	X	X	X	X	X	X	X	
IL-10[d,h]	X	X	X	X	X		X	X	X	X	X	X	X	X	X	X	X	
Anti-MK-1966 Antibodies		X						X			X			X	X	X	X	
Blood for RNA Analyses[d]		X			X	X[n]	X	X										
Blood for cytokines (plasma)[d]	X	X					X			X								
Blood for Genetics[c,d]		X																

Trial Period:	Screening Phase	Cycles 1						Cycle 2			Cycle 3			Cycle 4 (Day 1)	Cycle 5-8 (Day 1)	End of Treatment Period	Post-Treatment	Survival FU
																	Safety Follow-up	
Treatment Days:	Screening (Visit 1)	1	2	3	8	9	15	22	29	36	43	50	57	64		At end of Cycle 8[s] or time of treatment discon	30 days post end of Treatment Period	Every 12 weeks
Scheduling Window (Days):	**-28 to -1**							**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 3**	**± 7**
Efficacy Measurements																		
irRESIST - melanoma, squamous cell cancer of head and neck, breast cancer with dermal metastasis [e,]	X														X[e]	X		
Cheson Criteria – B Cell Lymphoma[e, i]	X														X[e]	X		
Tumor Tissue Collection																		
Archival and/or Newly Obtained Tissue Collection[d,o]	X							X[t]								X[t]		
Survival Status Telephone Contact																		X[m]

a. Height will be measured at Visit 1 only.
b. For women of reproductive potential, a urine pregnancy test will be performed within 72 hours of receiving the first dose of study medication. If urine pregnancy test cannot be confirmed as negative, a serum pregnancy test is required.
c. Details for collection can be found in Section 7.1.3, Laboratory Procedures/Assessment.
d. If the subject signs the Future Biomedical Research consent, any leftover samples that would be ordinarily discarded at the end of the main study will be retained for Future Biomedical Research.
e. Tumor imaging (ie. CT scan, MRI, CT/PET, etc.) should be performed within 28 days of enrollment. Tumor imaging and response assessment(s) to be performed 12 weeks after first dose, than every 12 weeks until discontinuation or End of Treatment. Imaging assessments should be repeated every 12 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.
f. Laboratory tests at Screening are to be performed within 7 days prior to the first dose of study treatment.
g. MK-1966 Pharmacokinetics (PK) samples will be collected more frequently in Cycles 1-3. On Days 1, 22 and 43 -collect predose, at the end of infusion and 2h after the start of the infusion (+10 minutes). On Day1 of Cycles 4-8 collect PK samples predose. Also collect PK Samples on Days 2, 3, 8, 15, 29, 36, 50, 57, at the treatment discontinuation, and Safety Follow-up visit (30 days post end of treatment).
h. Blood samples for IL-10 Pharmacodynamics (PD) will be drawn at Screening and at times that match PK sampling in footnote “i” above.
i. Unilateral bone marrow biopsy and aspirate will be performed at Screening if not previously performed or if performed more than 90 days previously with negative results. The bone marrow biopsy will be performed to confirm a CR if the subject was initially positive or if it is clinically indicated by new abnormalities in the peripheral blood counts or blood smear (section 4.2.3.5)
j. When SD-101 and MK-1966 are scheduled on the same day, SD-101 will be administered first. MK-1966 will be administered at least 30 minutes after the SD-101 injection.
k. These samples may be performed up to 72 hours prior to dosing. However, in Cycle 1 on Day 1, samples are to be drawn prior to dosing and should be used as the subject’s baseline (not screening) values.
l. 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).
m. Patients who discontinue from treatment or have completed post treatment follow up should be contacted every three months to monitor overall survival (for up to 2 years from last dose of study drug or until the sites are notified by the Sponsor that the survival follow up is no longer required).
n. The Day 9 visit must be 24 hours (+/- 4 hours) after the Day 8 visit.
o. Sample(s) and/or procedures will be collected prior to dosing and when applicable as outlined in the Procedures Manual.
p. Record all AEs occurring from signing of informed consent until 30 days after the last dose of MK-1966 and SD-101. Report all SAEs occurring up to 30 days after the last dose of treatment
q. Dosing with MK-1966 and/or SD-101 will occur within the timeframes outlined in section 5.2.5. and/or the Procedures Manual.
r. After the SD-101 is injected, the injection site should be observed every 15 minutes for at least 90 minutes.
s. End of Cycle 8 is defined as 21 days post Cycle 8, Day 1 or Day 168.
t. The Cycle 2 (or Day 22) and End of Treatment tumor samples are optional.

7.0 TRIAL PROCEDURES

7.1 Trial Procedures

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

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

7.1.1 Administrative Procedures

7.1.1.1 Informed Consent

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

7.1.1.1.1 General Informed Consent

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

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

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

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

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

7.1.1.1.2 Consent and Collection of Specimens for Future Biomedical Research

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

7.1.1.2 Inclusion/Exclusion Criteria

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

7.1.1.3 Subject Identification Card

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

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

7.1.1.4 Medical History

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

7.1.1.5.2 Concomitant Medications

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

If a subject initiates a new anti-cancer therapy within 30 days after the last dose of trial treatment, the 30 day Safety Follow-up visit must occur before the first new dose of the new therapy.

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 anti-cancer treatments including systemic treatments, radiation and surgeries radiations and surgeries regardless of time prior to first dose of trial treatment.

7.1.1.7 Assignment of Screening Number

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

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

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

7.1.1.8 Assignment of Treatment/Randomization Number

All eligible subjects will be allocated, by non-random assignment, and will receive a randomization number. The randomization number identifies the subject for all procedures occurring after treatment allocation. While the subjects are being allocated to their treatment, and not 'randomized', this unique number is termed a randomization number throughout the protocol for operational purposes. Subjects will be manually assigned into Parts A, B and C. The appropriate site staff will forward each subject's registration form as specified in the Procedures Manual.

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

7.1.1.9 Trial Compliance (Study Drug Administration)

Interruptions from the protocol specified treatment(s) for ≥ 12 weeks require consultation between the investigator and the Sponsor and written documentation of the collaborative decision on subject management (see section 5.2.3).

7.1.1.9.1 MK-1966

MK-1966 will be administered using intravenous infusion. The Pharmacy Manual contains specific instructions for the preparation and administration of the MK-1966 infusion solution.

Designated site personnel will be responsible for preparing and administering MK-1966 and will be required to record limited information during each infusion (e.g., infusion date/time,

lot number and expiry date for product administered, total dose/volume administered). See Pharmacy Manual for further details.

SD-101 will be administered before MK-1966 on days when both drugs are scheduled to be used.

7.1.1.9.2 SD-101

SD 101 will be administered by intratumoral injection into Lesion A in part A and up to 4 lesions (Lesion A, Lesion B, Lesion C, Lesion D), the tumor site(s) selected to receive injections of trial treatment in parts B and C. In Parts B and C, if the patient has more than 1 lesion, the investigator shall endeavor to choose the largest and most easily accessible tumor site as Lesion A. In Parts B and C, multiple lesions may be chosen (up to 4 [Lesions A, B, C, D]) and the dose will be equally divided (regardless of size of tumor) among the multiple lesions. In Parts A, B and C, if an injected lesion fully regresses, SD-101 at the dose that was previously administered into the lesion should continue to be injected.

Ultrasound may be used to assess lesion(s). Notation in the source documents should specify location and size (in 2 dimensions) in as much detail as possible.

Designated trial-site personnel will be responsible for preparing and administering the trial SD-101 injection. At minimum, syringes will be labeled with the protocol number, patient initials, and patient number.

Additional details related to SD 101 intratumoral injection(s) will be outlined in the Procedures and/or Pharmacy Manual(s).

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.

This is a dose escalation trial to establish the MTD of MK-1966 in combination with SD-101; 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 MK-1966, new clinically significant abnormal findings should be recorded as AEs.

7.1.2.2.1 Directed Physical Exam

For cycles that do not require a full physical examine per the Trial Flow Chart, the Investigator or qualified designee will perform a directed physical exam as clinically indicated prior to trial treatment administration. New clinically significant abnormal findings should be recorded as AEs.

7.1.2.3 Vital Signs and Weight

The Investigator or qualified designee will take vital signs at screening, prior to the administration of trial treatment at each cycle, and at the 30 day safety follow up visit as specified in the Trial Flow Chart. 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 Trial 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 Trial Flow Chart (Section 6.0).

7.1.2.6 Disease Assessments

7.1.2.6.1 Solid Tumors

Response will be based on irRECIST version 1.1 by investigator assessment.

Immunotherapeutic agents, such as MK-1966 may produce antitumor effects by potentiating endogenous cancer-specific immune response. The response patterns seen with such an approach may extend beyond the typical time course of responses seen with typical cytotoxic agents, and can manifest a clinical response after an initial increase in tumor burden or even the appearance of new lesions. When feasible, study subjects can continue on treatment until

progression is confirmed by the local site investigator/radiology assessment (see Section 4.2.3.6).

7.1.2.6.2 B Cell Lymphoma

Response will be based on the Cheson criteria for lymphoma (see Section 4.2.3.5).

7.1.2.6.2.1 Unilateral Bone Marrow Biopsy and Aspirate

Unilateral bone marrow biopsy and aspirate will be performed at Screening if not previously performed or if performed more than 90 days previously with negative results. The bone marrow biopsy will be performed to confirm a CR if they were initially positive or if it is clinically indicated by new abnormalities in the peripheral blood counts or blood smear.

7.1.2.6.3 Solid Tumors and B Cell Lymphoma

7.1.2.6.3.1 Imaging

The process for image collection and transmission to the central vendor can be found in the Site Imaging Manual. Initial imaging (CT Scans, MRI, CT/PET, etc.) must be performed within 28 days prior to the first dose of treatment, and should be repeated at week 12 (or Day 84), at week 24 and every 12 weeks until confirmed disease progression, the start of new anti-cancer therapy, withdrawal of consent, death or end of the study, whichever comes first.

Table 9 below outlines the imaging that should be performed for each tumor type. The same imaging technique should be performed at each time point.

Table 9 Imaging by Anatomical Coverage

Organ coverage /Indication	**B-Cell lymphoma**	**SCCHN**	**Melanoma**	**Breast Cancer With dermal metastasis**
Chest, Abdomen	Mandatory	Mandatory	Mandatory	Mandatory
Pelvis	Mandatory	If clinically indicated	Mandatory	Mandatory
Soft Tissue Neck	If clinically indicated	Mandatory	If clinically indicated	If clinically indicated
Head	If clinically indicated	If clinically indicated	If clinically indicated	If clinically indicated
Skin Photography	NA	NA	If clinically indicated for cutaneous skin lesions	If clinically indicated for cutaneous skin lesions
Bone	If clinically indicated	If clinically indicated	If clinically indicated	If clinically indicated

The process for image collection and transmission to the central vendor can be found in the Site Imaging Manual. Information for disease assessments may be submitted for central review.

Immunotherapeutic agents, such as MK-1966 and SD-101 may produce antitumor effects by potentiating endogenous cancer-specific immune response. The response patterns seen with such an approach may extend beyond the typical time course of responses seen with typical cytotoxic agents, and can manifest a clinical response after an initial increase in tumor burden or even the appearance of new lesions. Therefore, the subject should not be discontinued from the trial until PD is confirmed.

7.1.2.6.3.2 Tumor Tissue Collection and Correlative Studies Blood Sampling

Subjects may provide tumor sample(s) as specified in Procedures Manual. Sample collection, storage and shipment instructions for correlative study samples, archival tumor samples and newly obtained biopsy specimens will be provided in the Procedures Manual. Archival samples are not required to be submitted within the screening period.

7.1.3 Laboratory Procedures/Assessments

Details regarding specific laboratory procedures/assessments to be performed in this trial are provided below. The total amount of blood/tissue to be drawn/collected over the course of the trial (from pre-trial to post-trial visits), including approximate blood/tissue volumes drawn/collected by visit and by sample type per subject can be found in the Procedure Manual.

7.1.3.1 Laboratory Safety Evaluations (Hematology, Chemistry and Urinalysis)

Laboratory tests for hematology, chemistry and urinalysis are specified in Table 10.

Table 10 Laboratory Tests

Hematology	Chemistry	Urinalysis	Other
Hematocrit	Albumin	Blood	Serum β-human chorionic gonadotropin (β-hCG)[a]
Hemoglobin	Alkaline phosphatase	Glucose	Hepatitis 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
RBC	Bicarbonate or carbon dioxide (CO_2)[b]	Microscopic exam, if abnormal results are noted	blood for correlative studies
Absolute neutrophil count	Calcium	Urine pregnancy test[a]	Blood for genetics
	Chloride		PT (INR)[d]
	Creatinine		aPTT/PTT [d]
	Glucose		TSH (TSH, Free T_4, Total T_3)
	Lactate dehydrogenase (LDH)		
	Phosphorus		
	Potassium		
	Sodium		
	Total Bilirubin		
	Direct Bilirubin, if total bilirubin is elevated above the upper limit of normal		
	Total protein		
	Blood Urea Nitrogen		
	Urea[c]		
	Uric acid		

a. Perform on women of childbearing potential only. Urine pregnancy test is preferred. If the urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required.
b. If these tests are not done as part of standard of care in your region then these tests do not need to be performed.
c. Blood Urea Nitrogen is preferred; if not available urea may be tested.
d. Coagulation factors (PT/INR and aPTT/PTT) should be tested as part of the screening procedures for all subjects. Any subject receiving anticoagulant therapy should have coagulation factors monitored closely throughout the trial.

Laboratory tests for Screening should be performed within 7 days prior to the first dose of MK-1966 and SD-101. 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 study treatment

7.1.3.2 Pharmacokinetic/Pharmacodynamic Evaluations

7.1.3.2.1 Blood Collection (Serum) for MK-1966

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

The time points for PK sampling are described in Section 6.0-Trial Flow Chart.

7.1.3.2.2 Blood Collection for Anti- MK-1966 Antibodies (ADA)

Sample collection, storage and shipment instructions for anti-MK-1966 antibodies (ADA) samples will be provided in the Procedures Manual.

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

7.1.3.3 Planned Genetic Analysis Sample Collection

Sample collection, storage and shipment instructions for Planned Genetic Analysis samples will be provided in the Procedures Manual. Sample(s) should be drawn for planned analysis of the association between genetic variants in DNA and drug response. If there is either a documented law or regulation prohibiting collection, or if the IRB/IEC does not approve the collection of the sample for these purposes, then this sample will not be collected at that site. If the sample is collected, leftover extracted DNA will be stored for future biomedical research if the subject signs the FBR consent. If the planned genetic analysis is not approved, but FBR is approved and consent is given, this sample will be collected for the purpose of FBR.

7.1.3.4 Future Biomedical Research Sample Collection

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

- Leftover DNA for future research.
- Leftover main study tumor stored for future research
- Leftover RNA
- Leftover Serum and Plasma

7.1.4 Other Procedures

7.1.4.1 Withdrawal/Discontinuation

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

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

7.1.4.1.1 Withdrawal From Future Biomedical Research

Subjects may withdraw their consent for Future Biomedical Research and have their specimens and all derivatives destroyed. Subjects may withdraw consent at any time by contacting the principal investigator for the main trial. If medical records for the main trial are still available, the investigator will contact the Sponsor using the designated mailbox (clinical.specimen.management@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 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 MK-1966 and SD-101

7.1.5 Visit Requirements

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

7.1.5.1 Screening

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

Screening procedures may be repeated after consultation with the Sponsor.

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 72 hours prior to first dose of trial treatment. If urine pregnancy results cannot be confirmed as negative, a serum pregnancy test, performed by the local study site laboratory, will be required.
- Tumor imaging must be performed within 28 days prior to the first dose of trial treatment.

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(s) will be assigned a dose levels by the sponsor. MK-1966 and SD- 101 treatment will be administered as outlined in Section 5.2 for 8 cycles (approximately 24 weeks) of study medication in Part A, B, C, or administrative reasons requiring cessation of treatment. After the end of treatment (EOT), each subject will be followed for 30 days. Serious adverse events (SAEs) will be collected for 30 days after EOT.

7.1.5.2.1 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.

7.2 Assessing and Recording Adverse Events

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

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

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

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

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

All adverse events that occur after the consent form is signed but before treatment allocation/randomization must be reported by the investigator if they cause the subject to be excluded from the trial, or are the result of a protocol-specified intervention, including but not limited to washout or discontinuation of usual therapy, diet, placebo treatment or a procedure. From the time of treatment allocation/randomization through 14 days following cessation of treatment, all adverse events must be reported by the investigator. Such events will be recorded at each examination on the Adverse Event case report forms/worksheets. The reporting timeframe for adverse events meeting any serious criteria is described in section 7.2.3.1. The investigator will make every attempt to follow all subjects with non-serious adverse events for outcome.

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

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

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

For purposes of this trial, an overdose will be defined as any dose exceeding (by > 50%) the prescribed dose for SD-101 and/or MK-1966. No specific information is available on the treatment of overdose of MK-1966. In the event of overdose, MK-1966 should be discontinued and the subject should be observed closely for signs of toxicity. Appropriate supportive treatment should be provided if clinically indicated.

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

If a dose of Sponsor's product or vaccine meeting the protocol definition of overdose is taken without any associated clinical symptoms or abnormal laboratory results, the overdose is

reported as a non-serious Event of Clinical Interest (ECI), using the terminology "accidental or intentional overdose without adverse effect."

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

7.2.2 Reporting of Pregnancy and Lactation to the Sponsor

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

Pregnancies and lactations that occur after the consent form is signed but before treatment allocation/randomization must be reported by the investigator if they cause the subject to be excluded from the trial, or are the result of a protocol-specified intervention, including but not limited to washout or discontinuation of usual therapy, diet, placebo treatment or a procedure. Pregnancies and lactations that occur from the time of treatment allocation/randomization through 14 days following cessation of Sponsor's product must be reported by the investigator. All reported pregnancies must be followed to the completion/termination of the pregnancy. Pregnancy outcomes of spontaneous abortion, missed abortion, benign hydatidiform mole, blighted ovum, fetal death, intrauterine death, miscarriage and stillbirth must be reported as serious events (Important Medical Events). If the pregnancy continues to term, the outcome (health of infant) must also be reported.

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

7.2.3 Immediate Reporting of Adverse Events to the Sponsor

7.2.3.1 Serious Adverse Events

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

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

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

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

Refer to Table 11 for additional details regarding each of the above criteria.

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

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

For the time period beginning at treatment allocation/randomization through 14 days following cessation of treatment, any serious adverse event, or follow up to a serious adverse event, including death due to any cause, whether or not related to the Sponsor's product, must be reported within 24 hours to the Sponsor either by electronic media or paper. Electronic reporting procedures can be found in the EDC data entry guidelines. Paper reporting procedures can be found in the Investigator Trial File Binder (or equivalent).

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

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

7.2.3.2 Events of Clinical Interest

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

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

For the time period beginning at treatment allocation/randomization through 14 days following cessation of treatment, any ECI, or follow up to an ECI, whether or not related to the Sponsor's product, must be reported within 24 hours to the Sponsor, either by electronic media or paper. Electronic reporting procedures can be found in the EDC data entry guidelines. Paper reporting procedures can be found in the Investigator Trial File Binder (or equivalent).

Events of clinical interest for this trial include:

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

than 2X the upper limit of normal, as determined by way of protocol-specified laboratory testing or unscheduled laboratory testing.*

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

7.2.4 Evaluating Adverse Events

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

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

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

Table 11 Evaluating Adverse Events

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

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

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

7.2.5 Sponsor Responsibility for Reporting Adverse Events

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

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 Sections 8.2 through 8.12.

Study Design Overview	Phase 1/1b Trial MK-1966 in combination with SD-101 in Subjects With Advanced Malignancies. A 3+3 design in part A to identify preliminary MTD; TPI design for dose confirmation on two malignancies (melanoma and squamous cell cancer of head and neck), followed by approximately 24 weeks follow-up as an expansion cohort on both malignancies.
Analysis Populations	Safety: All Subjects as Treated (ASaT) PK and target engagement (secondary): Per-Protocol (PP) Efficacy (exploratory): Full Analysis Set (FAS)
Primary Endpoint(s)	Safety: DLT
Key Secondary Endpoints	PK parameters of MK-1966 in combination with SD-101 Target engagement for MK-1966
Statistical Methods for Key Efficacy/Immunogenicity/ Pharmacokinetic Analyses	Serum concentrations of MK-1966 will be summarized by planned visit and time for each dose separately; PK parameters will be summarized by dose. Target engagement will be summarized by planned visit and time for each dose separately.
Treatment Assignment	Subjects are allocated to increasing doses of MK-1966 co-administered with SD-101 without randomization; the study is open-label
Statistical Methods for Key Safety Analyses	DLT and adverse experiences will be summarized as counts and frequencies for the dose level with at least three subjects. The estimate of the DLT rate among subjects treated with the RPTD and the 80% Bayesian probability interval for the estimate will be provided.
Interim Analyses	Study has no interim analyses
Multiplicity	No multiplicity adjustment is planned in this Phase I/Ib study.
Sample Size and Power	The sample size of the dose escalation (Part A), and dose confirmation/expansion (Parts B and C) depends on the observed DLT profiles of MK-1966 co-administered with SD-101. The sample size of approximately 64 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 approximately 24 weeks 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 and serious adverse events (SAEs) 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

Secondary PK endpoints and exploratory efficacy endpoints and their definitions are presented below.

PK endpoints- serum concentrations of MK-1966 and derived PK parameters.

Target engagement endpoints – Total IL-10, free IL-10, to be used in descriptive analyses

Exploratory endpoints

Exploratory endpoints are documented in a supplemental SAP (sSAP). Additional supportive analyses of these endpoints based on irRECIST or Cheson criteria and, if needed, central review might be conducted.

8.4.4 Derivations of Safety Endpoints

Description of safety measures is provided in Section 7.

8.5 Analysis Populations

8.5.1 Safety Analysis Populations

The All-Patients-as-Treated (APaT) population will be used for the analysis of safety data in this study. The APaT population consists of all subjects who received at least one dose of study treatment. In case of treatment administration errors, subjects will be analyzed according to the treatment they actually received. For DLT evaluation, APaT 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 one laboratory or vital sign measurement obtained subsequent to at least one dose of study treatment is required for inclusion in the analysis of each specific parameter. To assess change from baseline, a baseline measurement is also required.

8.5.2 Pharmacokinetic Analysis Populations

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

8.5.3 Efficacy Analysis Populations

The full analysis set populations FAS are defined as all subjects with a baseline scan with measurable disease by investigator assessment who were administered MK-1966 and SD-101 (FAS). 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

The statistical methods for efficacy analyses are documented in a supplemental SAP (sSAP).

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 MK-1966 in combination with SD-101 dose level that had at least three subjects treated and listed for other dose levels. The estimate of the DLT rate among subjects treated with the RPTD and the 80% Bayesian probability interval with non-informative prior for the estimate will be provided. Laboratory assessments, vital signs, and other safety endpoints will be summarized as appropriate.

In addition, the broad clinical and laboratory AE categories consisting of the percentage of subjects with any AE, a drug related AE, a serious AE, an AE which is both drug-related and serious, and who discontinued due to an AE will be summarized for dose levels with at least 3 subjects treated and listed for other doses. Percentages of subjects in these categories among subjects treated with RPTD and 80% confidence intervals for the estimated percentages calculated using the Clopper-Pearson method will be provided.

8.6.3 Summaries of Baseline Characteristics, Demographics, and Other Analyses

8.6.3.1 Demographic and Baseline Characteristics

The number and percentage of subjects screened, 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 APaT population, the set of subjects treated with the RPTD dose for combination of MK-1966 with SD-101.

8.6.3.2 Pharmacokinetics and Pharmacodynamics Modeling Analysis

Serum concentrations of MK-1966 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.

Target engagement will be summarized by planned visit and time for each dose separately. Change from baseline in INF-alpha inducible gene expression will be estimated.

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

8.6.3.3 Interim Analyses

No interim analyses are planned for this study.

8.6.3.4 Multiplicity

There will be no multiplicity control in this study.

8.6.3.5 Sample Size and Power Calculations

Dose Escalation and Dose Confirmation/Expansion

The primary purpose of the dose escalation and dose confirmation/expansion parts of the trial is to investigate the safety and tolerability of MK-1966 co-administered with SD-101 in adult subjects with advanced malignancies (Parts A-C) and to establish RPTD for MK-1966 co-administered with SD-101.

The final number of subjects enrolled in the dose escalation and confirmation/expansion parts of the study will depend on the empirical safety (DLT) observations, in particular, at what dose is identified as the RPTD. 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/expansion part. The study duration is derived as the time from the first subject's first dose to the end of 6-month treatment period following the enrollment of the last subject.

The enrollment time was conservatively estimated assuming that during 3+3 parts and the dose confirmation/expansion a subject can be enrolled every week. The sample size for each malignancy is 20 subjects, for the purpose of efficacy assessment in exploratory objectives.

Scenario 1. No DLTs during Parts A-C. For MK-1966 with SD-101, in a scenario where no DLTs are encountered during the dose escalation and confirmation/expansion parts so that Part A continues to the highest dose in Table 5, the sample size to determine the MTD is 32 subjects (12 in Part A, 20 from Parts B and C). The total sample size is 52 subjects (12 subjects across 3 doses in Part A, 20 subjects on RPTD in Part B, and another 20 subjects on RPTD in Part C).

It will take 52 weeks to enroll 52 subjects in Parts A-C. Thus, in this scenario the enrollment time across Parts A-C is 52 weeks and the time required to determine the MTD is 35 weeks for 32 subjects. The study duration then is approximately 52 weeks + 24 weeks or 1.8 years. If dose escalation stops at a dose below the highest dose, the study might require less than 52 subjects and the enrollment duration shorter than 52 weeks.

Scenario 2: Flat DLT dose response. Suppose dose escalation in Parts A continues to the highest dose with flat dose response so that all 4 doses (including the top one) are given to 6 subjects each in Part A. Also suppose that the top dose is confirmed as the RPTD dose without de-escalation in Parts B and C. Thus, the sample size to determine the MTD is 44 subjects (24 in Part A, 20 in Parts B and C). The total sample size is 64 subjects (24 in Part A, 20 in Part B, and 20 in Part C).

It will take 64 weeks to enroll 64 subjects in Parts A-C. Thus, in this scenario the enrollment time across Parts A-C is 64 weeks and the time required to determine the two MTDs is 47 weeks for 44 subjects. The study duration then is approximately 64 weeks + 24 weeks or 1.8 years.

Any dose de-escalations and/or re-escalations in Parts B and/or C will increase the sample size in this example.

8.6.4 Precision of the DLT rate at RPTD

Since the TPI approach will be used during the dose confirmation/expansion parts B and C, the estimated DLT rate, and its 80% Bayesian Probability Interval (PI) will be calculated from the posterior distribution of the DLT rate at RPTD using the model specified in the TPI approach. If 20 subjects are finally dosed at RPTD during the dose confirmation/expansion stage, the estimated DLT rate and its 80% PI should be similar to one of the rows in Table 12.

Table 12 Precision of the Estimated DLT rates at RPTD

Number of Subjects dosed at RPTD	Number of DLT Events	Estimated DLT Rate	Lower Bound of 80% PI	Upper Bound of 80% PI
20	2	0.10	0.036	0.206
20	3	0.15	0.069	0.267
20	4	0.20	0.105	0.325
20	5	0.25	0.144	0.381
20	6	0.30	0.185	0.435
20	7	0.35	0.228	0.487
Assume non-informative prior distribution of DLT.				

8.7 Subgroup Analyses and Effect of Baseline Factors

No subgroup analyses will be performed.

8.8 Compliance (Medication Adherence)

Drug accountability data for trial treatment will be collected during the study. Percent compliance with drug administration will be calculated for each subject for MK-1966 and SD-101 separately.

For MK-1966 and SD-101, percent compliance will be calculated as following:

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

For MK-1966, "Number of Doses that Should have been Taken" will be calculated as the minimum of the two numbers: 4 and (1 plus the number (integer) of 3-week intervals that fit between the date of the first dose and the date of the last dose of MK-1966).

For SD-101, "Number of Doses that Should have been Taken" will be calculated as 1 plus the number (integer) of 3-week intervals that fit between the date of the first dose and the date of the last dose of SD-101.

8.9 Extent of Exposure

A subject's extent of exposure to MK-1966 is defined as the total number of doses of MK-1966 the subject received. A subject's extent of exposure to SD-101 is defined as the total number of doses of SD-101 the subject received.

Extent of Exposure will be summarized for MK-1966 in combination with SD-101 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 13.

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 13 Product Descriptions

Product Name & Potency	Dosage Form
MK-1966 50 mg/mL, 4 mL	Concentrate for solution for infusion
SD-101 16 mg/mL, .75 mL	Injection

Other supplies not indicated in Table 13 may be provided centrally by the Sponsor or locally by the trial site, subsidiary or designee, depending on local country operational or regulatory requirements.

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.

Subjects will be dosed using open label vials. No kitting is required.

9.3 Clinical Supplies Disclosure

This trial is open-label; therefore, the subject, the trial site personnel, the Sponsor and/or designee are not blinded. MK-1966 and SD-101 (name, strength or potency) is included in the label text; random code/disclosure envelopes or lists are not provided.

9.4 Storage and Handling Requirements

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

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

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

9.5 Discard/Destruction/Returns and Reconciliation

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

discard and destruction is appropriate, the investigator is responsible for ensuring that a local discard/destruction procedure is documented.

10.0 ADMINISTRATIVE AND REGULATORY DETAILS

10.1 Confidentiality

10.1.1 Confidentiality of Data

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

10.1.2 Confidentiality of Subject Records

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

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

10.1.3 Confidentiality of Investigator Information

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

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

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

investigators. By signing this protocol, the investigator expressly consents to these uses and disclosures.

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

10.1.4 Confidentiality of IRB/IEC Information

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

10.2 Compliance with Financial Disclosure Requirements

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

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

10.3 Compliance with Law, Audit and Debarment

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

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

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

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

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

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

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

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

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

Persons debarred from conducting or working on clinical trials by any court or regulatory authority will not be allowed to conduct or work on this Sponsor's trials. The investigator will immediately disclose in writing to the Sponsor if any person who is involved in

conducting the trial is debarred or if any proceeding for debarment is pending or, to the best of the investigator's knowledge, threatened.

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

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

10.4 Compliance with Trial Registration and Results Posting Requirements

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

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

10.5 Quality Management System

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

10.6 Data Management

The investigator or qualified designee is responsible for recording and verifying the accuracy of subject data. By signing this protocol, the investigator acknowledges that his/her

electronic signature is the legally binding equivalent of a written signature. By entering his/her electronic signature, the investigator confirms that all recorded data have been verified as accurate.

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

10.7 Publications

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

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

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

Authorship credit should be based on 1) substantial contributions to conception and design, or acquisition of data, or analysis and interpretation of data; 2) drafting the article or revising it critically for important intellectual content; and 3) final approval of the version to be published. Authors must meet conditions 1, 2 and 3. Significant contributions to trial execution may also be taken into account to determine authorship, provided that

contributions have also been made to all three of the preceding authorship criteria. Although publication planning may begin before conducting the trial, final decisions on authorship and the order of authors' names will be made based on participation and actual contributions to the trial and writing, as discussed above. The first author is responsible for defending the integrity of the data, method(s) of data analysis and the scientific content of the manuscript.

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

11.0 LIST OF REFERENCES

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

[2] Moore KW, de Waal Malefyt R, Coffman RL, O'Garra A. Interleukin-10 and the interleukin-10 receptor. Annu Rev Immunol. 2001;19:683-765.

[3] Saraiva M, O'Garra A. The regulation of IL-10 production by immune cells. Nat Rev Immunol. 2010 Mar;10(3):170-81.

[4] Ho AS, Wei SH, Mui AL, Miyajima A, Moore KW. Functional regions of the mouse interleukin-10 receptor cytoplasmic domain. Mol Cell Biol. 1995 Sep;15(9):5043-53.

[5] Finbloom DS, Winestock KD. IL-10 induces the tyrosine phosphorylation of tyk2 and Jak1 and the differential assembly of STAT1 alpha and STAT3 complexes in human T cells and monocytes. J Immunol. 1995 Aug 1;155(3):1079-90.

[6] Meraz MA, White JM, Sheehan KC, Bach EA, Rodig SJ, Dighe AS, et al. Targeted disruption of the Stat1 gene in mice reveals unexpected physiologic specificity in the JAK-STAT signaling pathway. Cell. 1996 Feb 9;84(3):431-42.

[7] Takeda K, Clausen BE, Kaisho T, Tsujimura T, Terada N, Förster I, et al. Enhanced Th1 activity and development of chronic enterocolitis in mice devoid of Stat3 in macrophages and neutrophils. Immunity. 1999 Jan;10(1):39-49.

[8] Takeuchi O, Akira S. Pattern recognition receptors and inflammation. Cell. 2010 Mar 19;140(6):805-20.

[9] Vacchelli E, Galluzzi L, Eggermont A, Fridman WH, Galon J, Sautès-Fridman C, et al. Trial watch: FDA-approved Toll-like receptor agonists for cancer therapy. Oncoimmunology. 2012 Sep 1;1(6):894-907.

[10] Hornung V, Rothenfusser S, Britsch S, Krug A, Jahrsdörfer B, Giese T, et al. Quantitative expression of toll-like receptor 1-10 mRNA in cellular subsets of human peripheral blood mononuclear cells and sensitivity to CpG oligodeoxynucleotides. J Immunol. 2002 May 1;168(9):4531-7.

[11] Ketloy C, Engering A, Srichairatanakul U, Limsalakpetch A, Yongvanitchit K, Pichyangkul S, et al. Expression and function of Toll-like receptors on dendritic cells and other antigen presenting cells from non-human primates. Vet Immunol Immunopathol. 2008 Sep 15;125(1-2):18-30.

[12] Krieg AM. Development of TLR9 agonists for cancer therapy. J Clin Invest 2007;117(5):1184-94.

[13] Kim YH, Gratzinger D, Harrison C, Brody JD, Czerwinski DK, Ai WZ, et al. In situ vaccination against mycosis fungoides by intratumoral injection of a TLR9 agonist combined with radiation: a phase 1/2 study. Blood. 2012 Jan 12;119(2):355-63.

[14] Brody JD, Ai WZ, Czerwinski DK, Torchia JA, Levy M, Advani RH, et al. In situ vaccination with a TLR9 agonist induces systemic lymphoma regression: a phase I/II study. J Clin Oncol. 2010 Oct 1;28(28):4324-32.

[15] Duramad O, Fearon KL, Chan JH, Kanzler H, Marshall JD, Coffman RL, et al. IL-10 regulates plasmacytoid dendritic cell response to CpG-containing immunostimulatory sequences. Blood. 2003 Dec 15;102(13):4487-92.

[16] Marshall JD, Heeke DS, Abbate C, Yee P, Van Nest G. Induction of interferon-gamma from natural killer cells by immunostimulatory CpG DNA is mediated through plasmacytoid-dendritic-cell-produced interferon-alpha and tumour necrosis factor-alpha. Immunology. 2006 Jan;117(1):38-46.

[17] Martin-Orozco E, Kobayashi H, Van Uden J, Nguyen MD, Kornbluth RS, Raz E. Enhancement of antigen-presenting cell surface molecules involved in cognate interactions by immunostimulatory DNA sequences. Int Immunol. 1999 Jul;11(7):1111-8.

[18] Gelman AE, Zhang J, Choi Y, Turka LA. Toll-like receptor ligands directly promote activated CD4+ T cell survival. J Immunol. 2004 May 15;172(10):6065-73.

[19] Iwasaki A, Medzhitov R. Toll-like receptor control of the adaptive immune responses. Nat Immunol. 2004 Oct;5(10):987-95.

[20] Marshall JD, Fearon KL, Higgins D, Hessel EM, Kanzler H, Abbate C, et al. Superior activity of the type C class of ISS in vitro and in vivo across multiple species. DNA Cell Biol. 2005 Feb;24(2):63-72.

[21] 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.

[22] 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.

[23] Hervas-Stubbs S, Perez-Gracia JL, Rouzaut A, Sanmamed MF, Le Bon A, Melero I. Direct effects of type I interferons on cells of the immune system. Clin Cancer Res. 2011 May 1;17(9):2619-27.

[24] Cheson BD, Horning SJ, Coiffier B, Shipp MA, Fisher RI, Connors JM, et al. Report of an international workshop to standardize response criteria for non-Hodgkin's lymphomas. J Clin Oncol 2010;17(4):1244-53.

[25] Cheson BD, Pfistner B, Juweid ME, Gascoyne RD, Specht L, Horning SJ, et al. Revised response criteria for malignant lymphoma. J Clin Oncol 2007;25:579-86.

[26] Nishino M, Giobbie-Hurder A, Gargano M, Suda M, Ramaiya NH, Hodi FS. Developing a common language for tumor response to immunotherapy: immune-related response criteria using unidimensional measurements. Clin Cancer Res. 2013 Jul 15;19(14):3936-43.

[27] Swerdlow SH, Campo E, Harris NL, Jaffe, ES, Pileri SA, Stein H, editors. WHO classification of tumours of haematopoietic and lymphoid tissues. 4th ed. Lyon: International Agency for Research on Cancer (IARC); c2008. Chapter 10, Mature B-cell neoplasms: primary mediastinal (thymic) large B-cell lymphoma; p. 250-1.

12.0 APPENDICES

12.1 Merck Code of Conduct for Clinical Trials

Merck*
Code of Conduct for Clinical Trials

I. Introduction

A. Purpose

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

B. Scope

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

II. Scientific Issues

A. Trial Conduct

1. Trial Design

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

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

2. Site Selection

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

3. Site Monitoring/Scientific Integrity

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

B. Publication and Authorship

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

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

III. Subject Protection

A. IRB/ERC review

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

B. Safety

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

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

C. Confidentiality

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

D. Genomic Research

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

IV. Financial Considerations

A. Payments to Investigators

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

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

B. Clinical Research Funding

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

C. Funding for Travel and Other Requests

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

V. Investigator Commitment

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

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

12.2 Collection and Management of Specimens for Future Biomedical Research

1. Definitions

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

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

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

d. DNA: Deoxyribonucleic acid.

e. RNA: Ribonucleic acid.

2. Scope of Future Biomedical Research

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

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

3. Summary of Procedures for Future Biomedical Research

a. Subjects for Enrollment

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

b. Informed Consent

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

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

c. eCRF Documentation for Future Biomedical Research Specimens

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

d. Future Biomedical Research Specimen Collections

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

4. Confidential Subject Information for Future Biomedical Research

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

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

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

5. Biorepository Specimen Usage

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

6. Withdrawal From Future Biomedical Research

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

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

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

7. Retention of Specimens

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

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

8. Data Security

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

9. Reporting of Future Biomedical Research Data to Subjects

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

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

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

10. Future Biomedical Research Study Population

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

11. Risks Versus Benefits of Future Biomedical Research

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

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

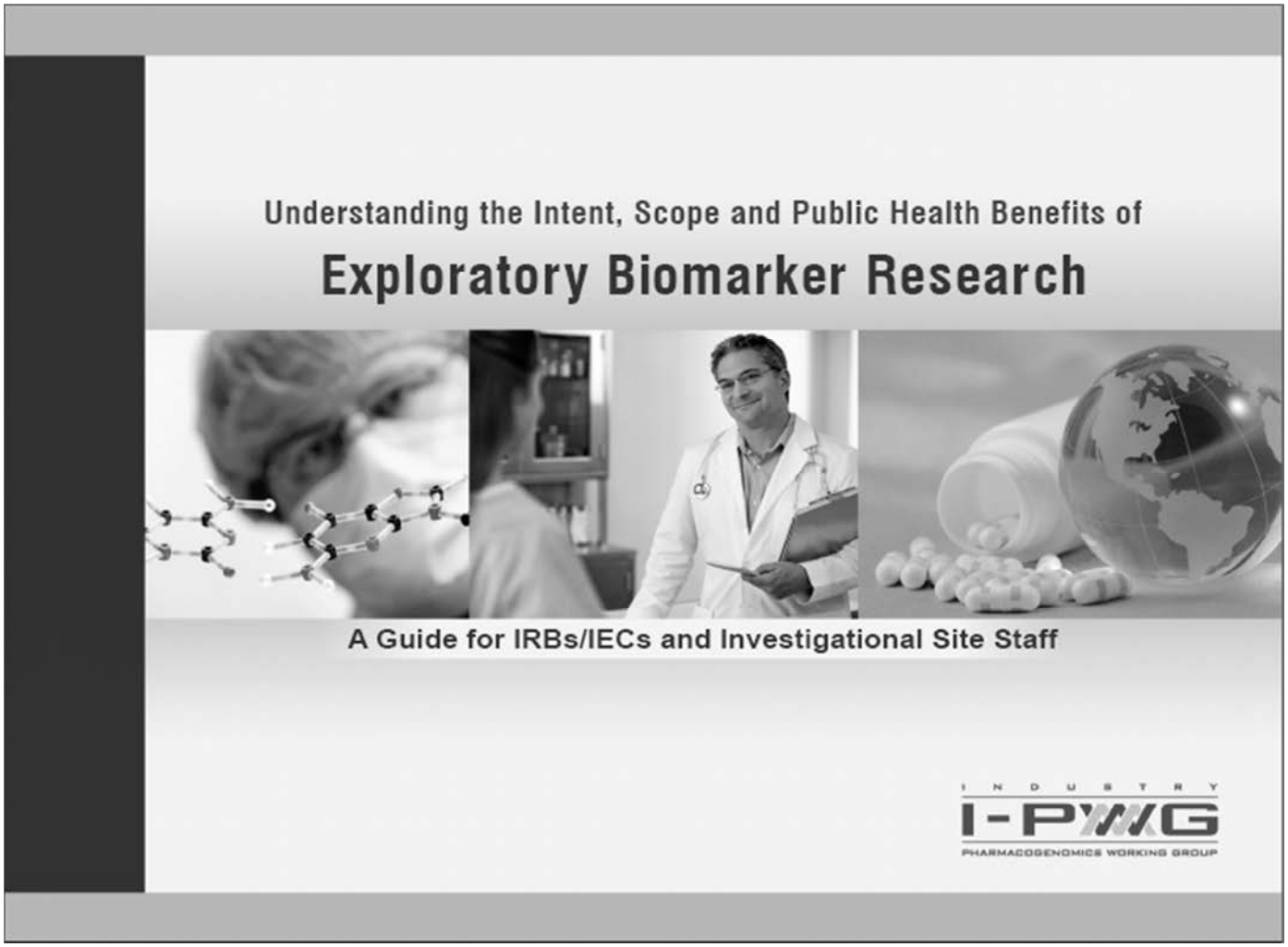
12. Questions

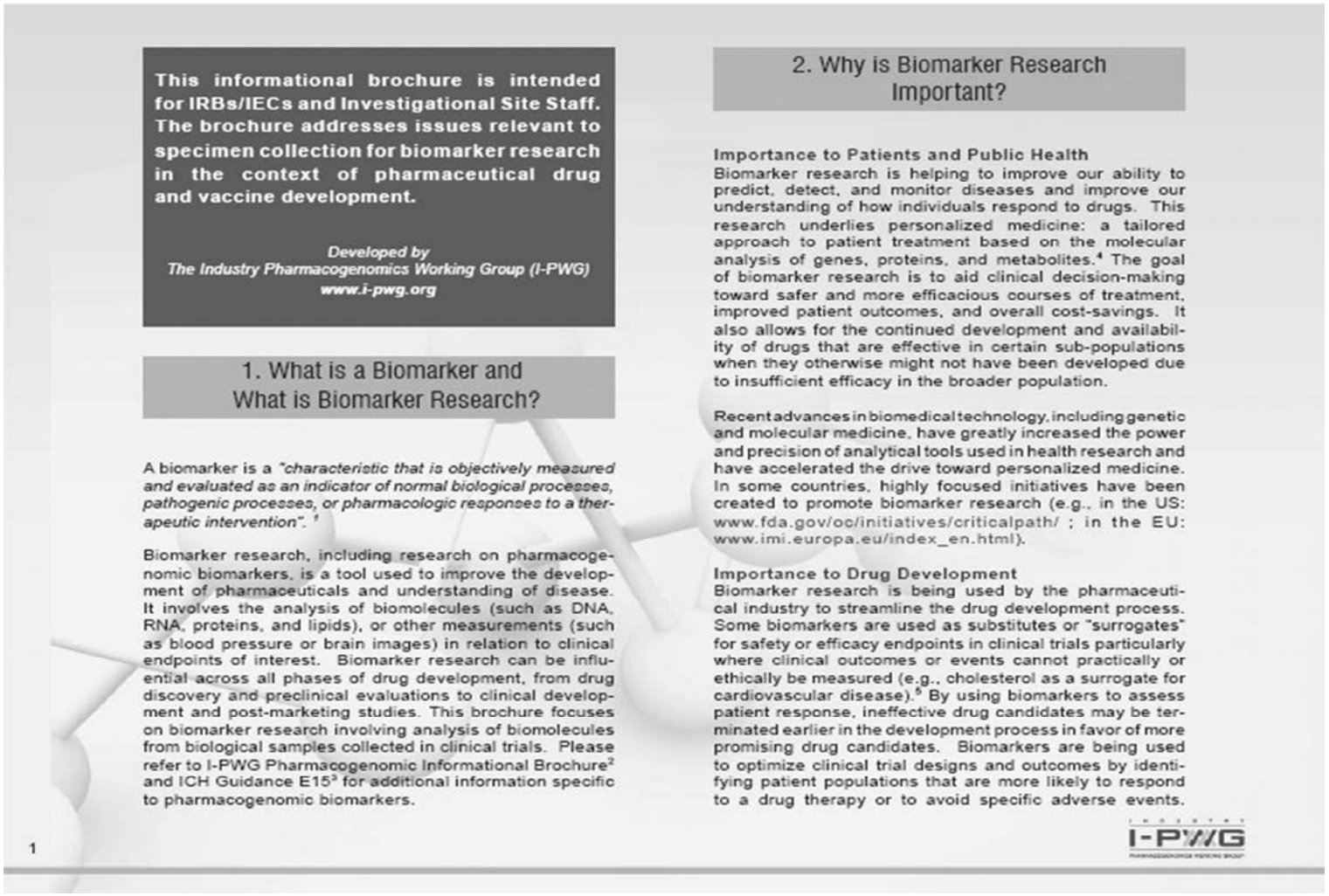
Any questions related to the future biomedical research should be e-mailed directly to clinical.specimen.management@merck.com.

13. References

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

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





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

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

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

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

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

2. Why is Biomarker Research Important?

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

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

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

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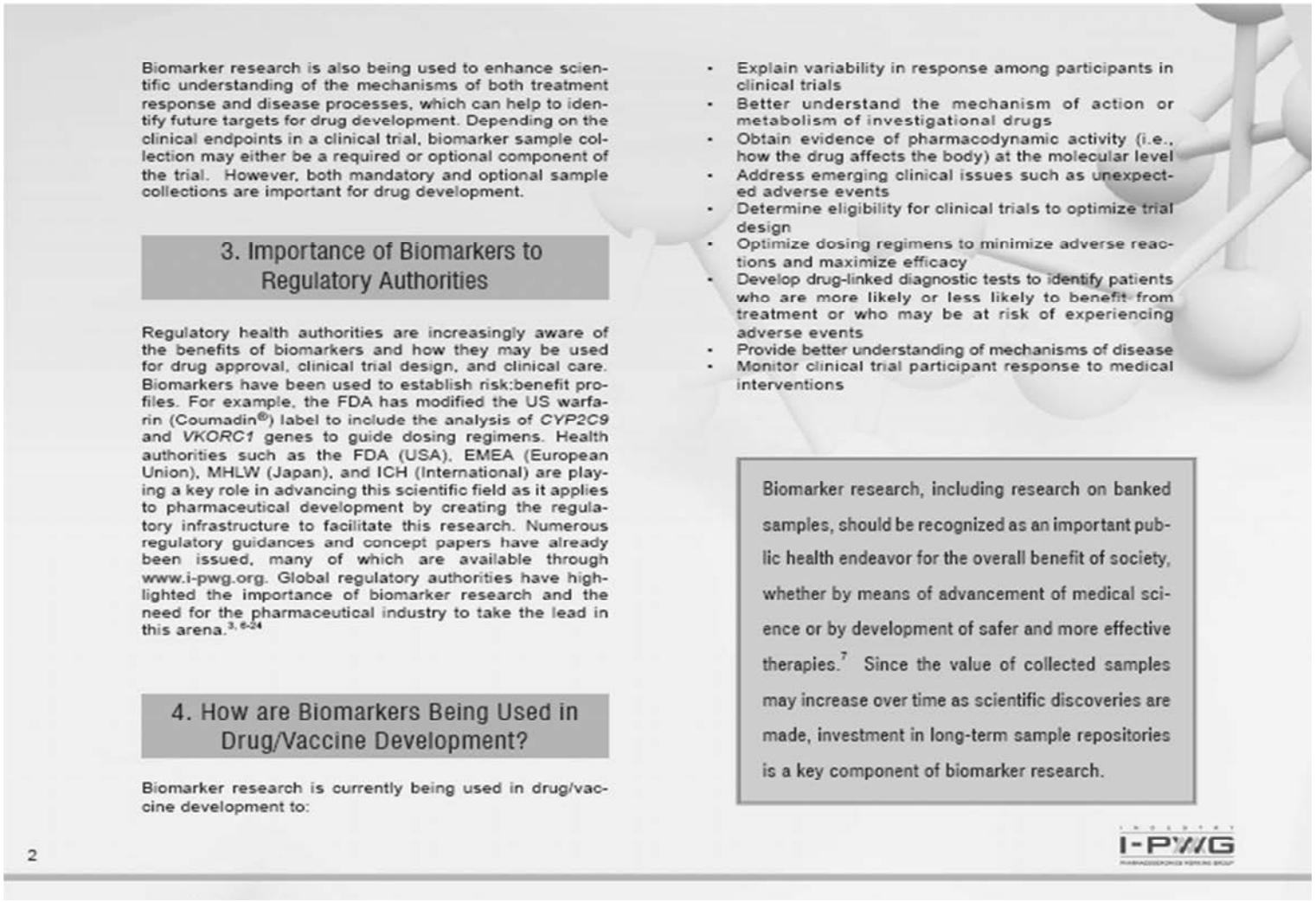
Biomarker research is also being used to enhance scientific understanding of the mechanisms of both treatment response and disease processes, which can help to identify future targets for drug development. Depending on the clinical endpoints in a clinical trial, biomarker sample collection may either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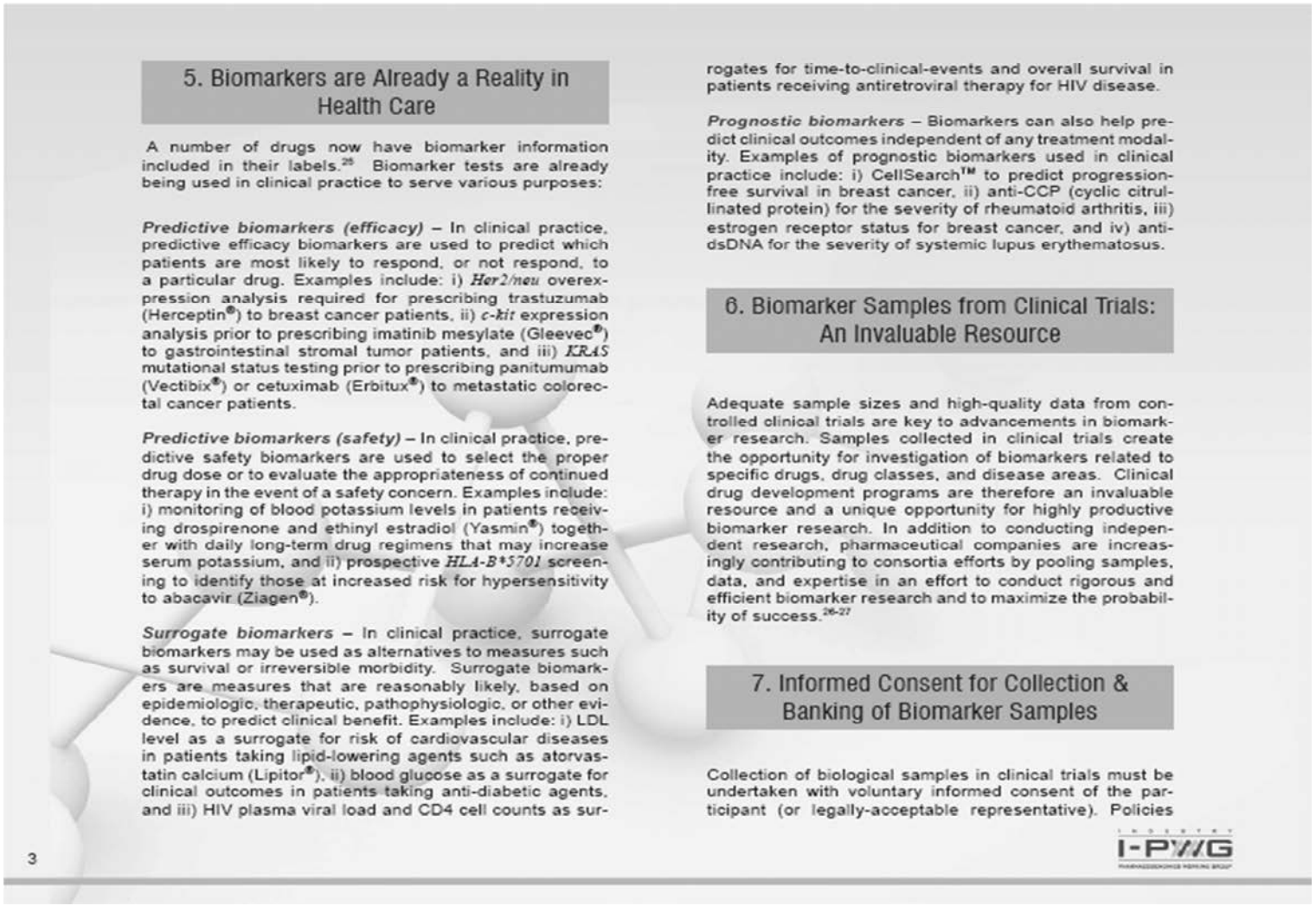

5. Biomarkers are Already a Reality in Health Care

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

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

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

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

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

6. Biomarker Samples from Clinical Trials: An Invaluable Resource

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

7. Informed Consent for Collection & Banking of Biomarker Samples

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

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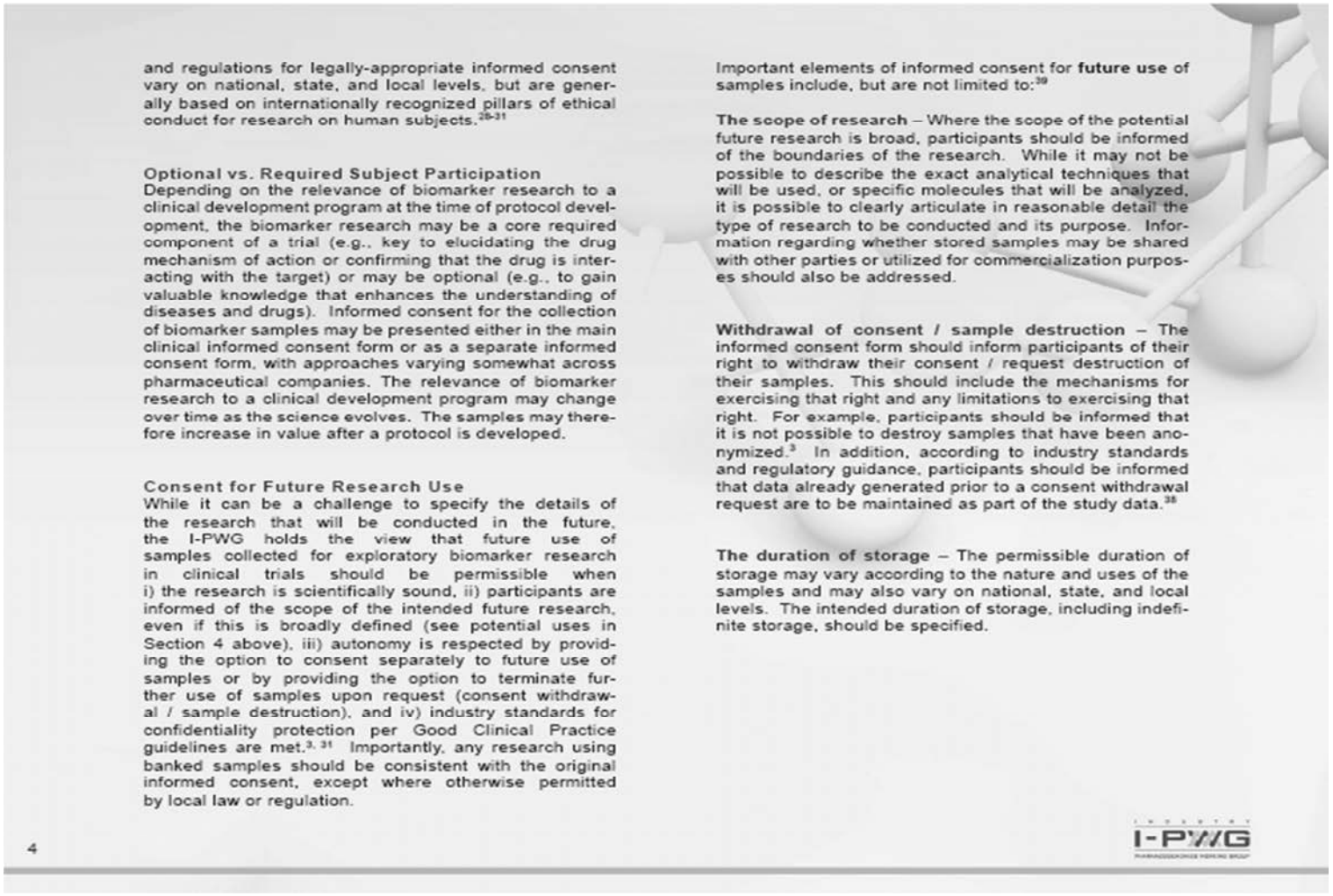

and regulations for legally-appropriate informed consent vary on national, state, and local levels, but are generally based on internationally recognized pillars of ethical conduct for research on human subjects.[26-31]

Optional vs. Required Subject Participation

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

Consent for Future Research Use

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

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

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

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

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

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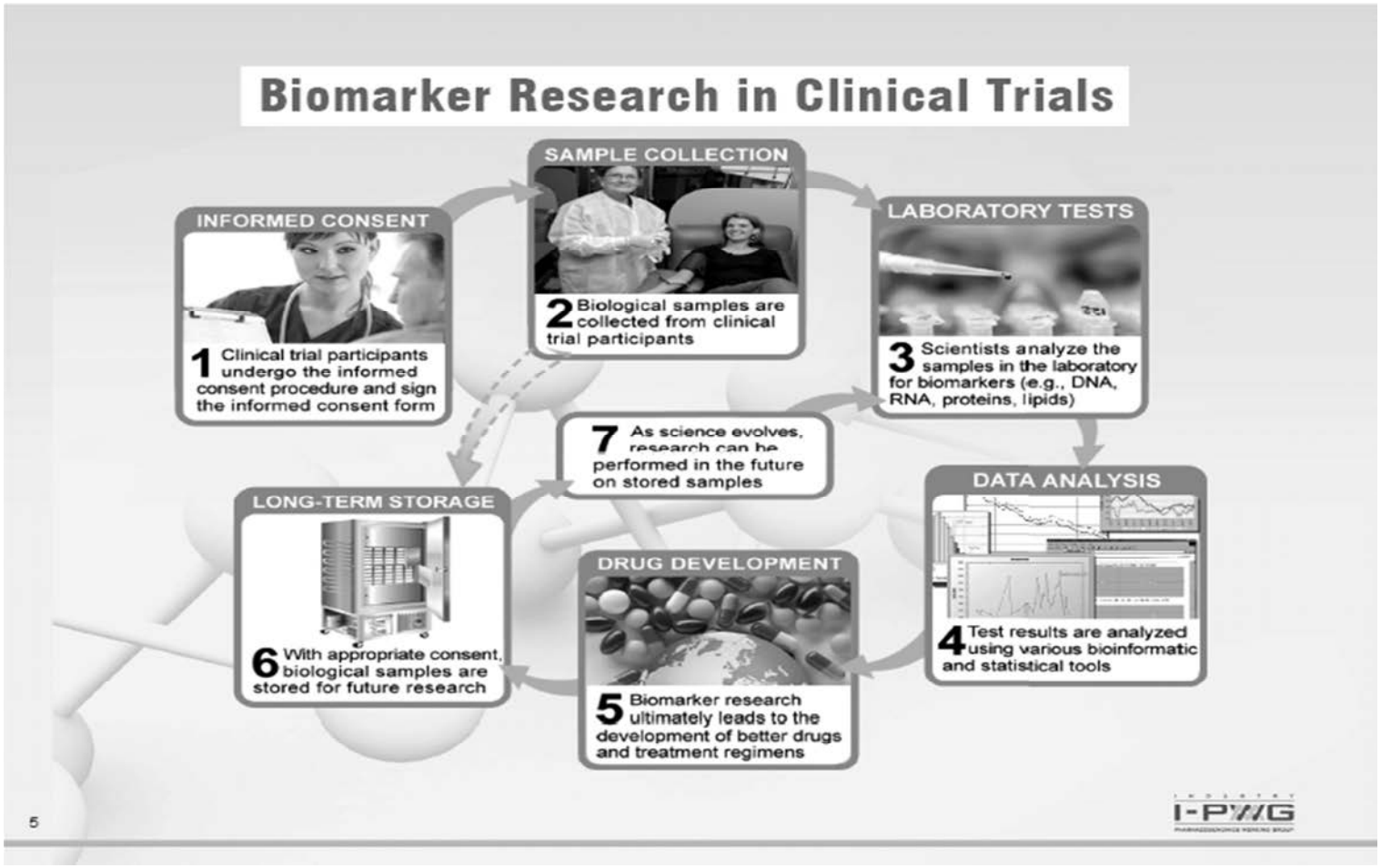
Biomarker Research in Clinical Trials
SAMPLE COLLECTION
2 Biological samples are collected from clinical trial participants
LABORATORY TESTS
3 Scientists analyze the samples in the laboratory for biomarkers (e.g., DNA, RNA, proteins, lipids)
INFORMED CONSENT
1 Clinical trial participants undergo the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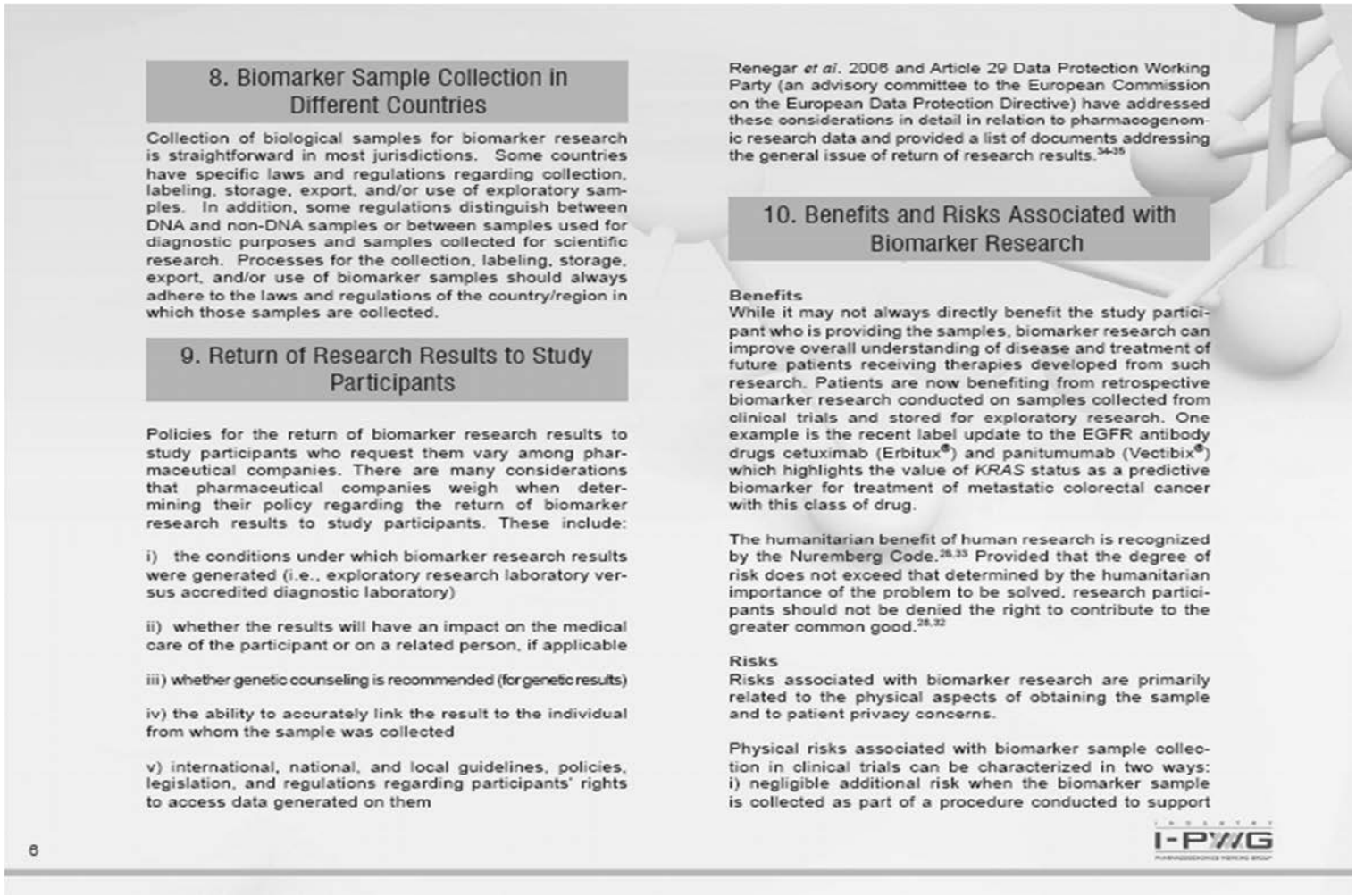

8. Biomarker Sample Collection in Different Countries

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

9. Return of Research Results to Study Participants

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

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

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

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

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

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

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

10. Benefits and Risks Associated with Biomarker Research

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

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

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

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

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

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

11. Privacy, Confidentiality, and Patient Rights

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

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

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

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

Exploratory biomarker research in pharmaceutical development is commonly conducted in research laboratories that are not accredited to perform diagnostic tests used for healthcare decision-making. Therefore, results from exploratory biomarker research usually are not appropriate for use in making decisions about a trial participant's health. In addition, exploratory research data should not be included as part of a participant's medical record accessible for use by insurance companies. Legislation and policies to protect individuals against discrimination based on genetic information continually evolve based on social, ethical, and legal considerations. Examples of such legislation include the Human Tissue Act 2004 (UK) and the Genetic Information Nondiscrimination Act (GINA) 2008 (USA).[35-37]

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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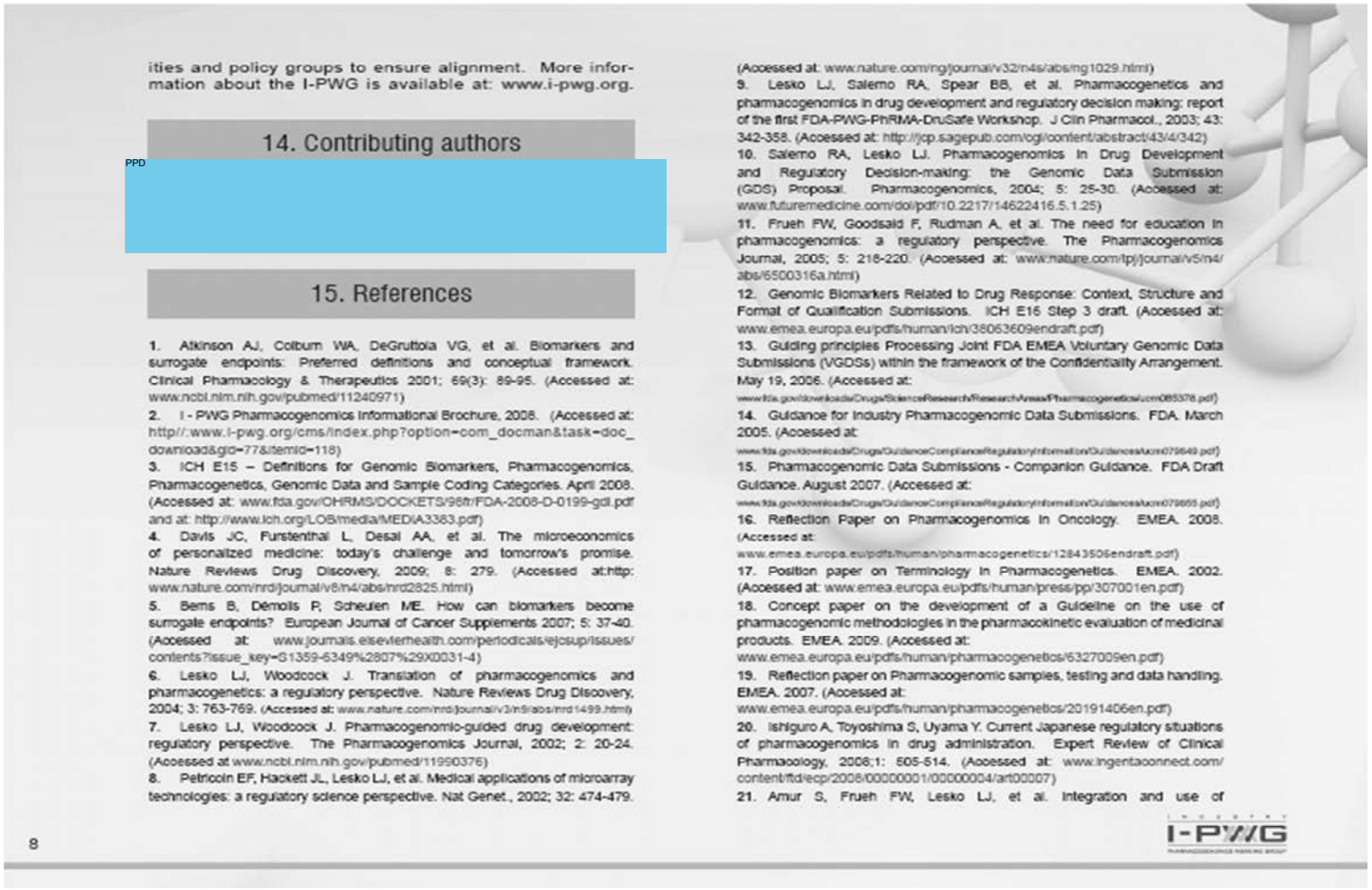

ities and policy groups to ensure alignment. More information about the I-PWG is available at: www.i-pwg.org.

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/ftd/ecp/2008/00000001/00000004/art00007)
21. Amur S, Frueh FW, Lesko LJ, et al. Integration and use of

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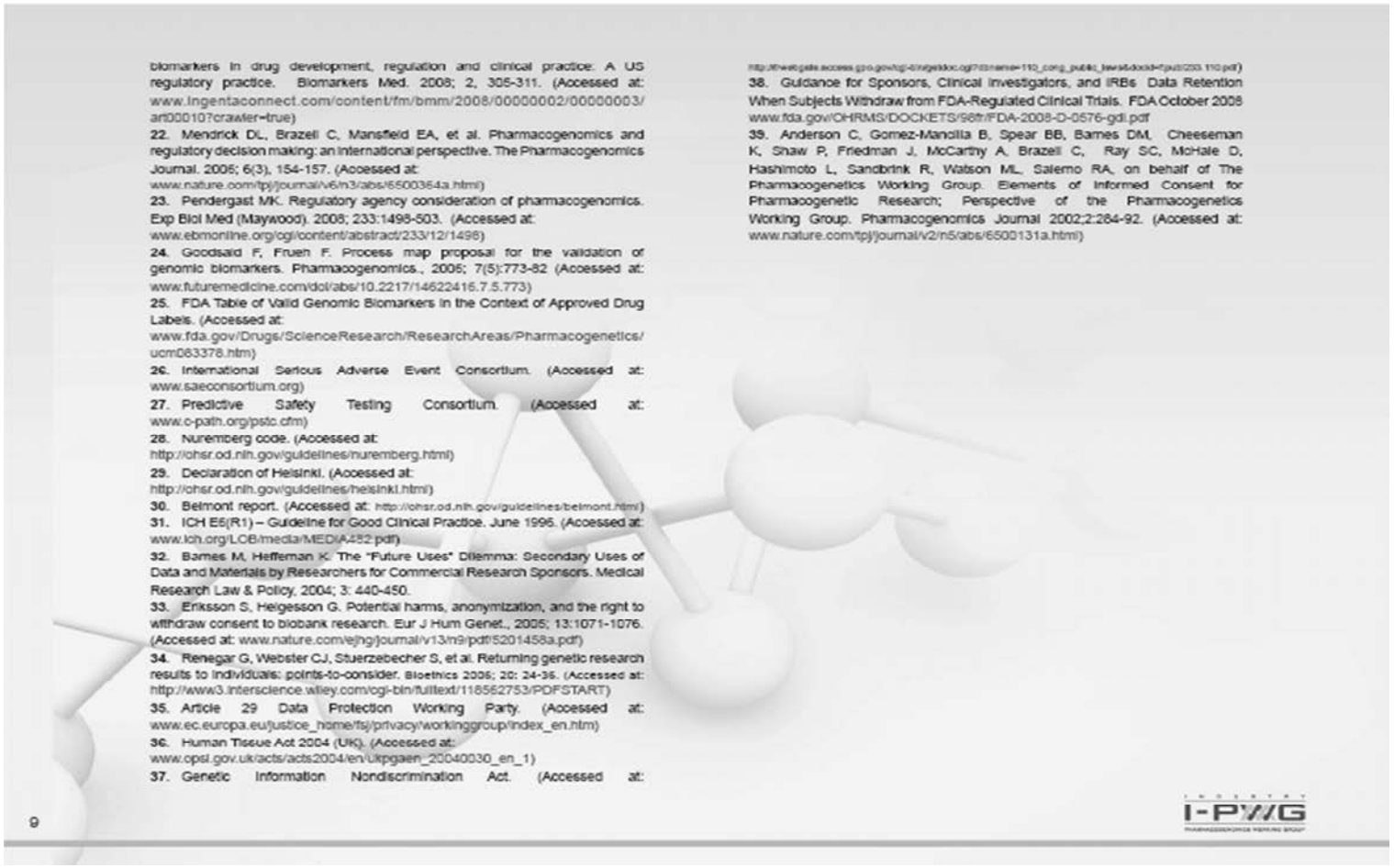

biomarkers in drug development, regulation and clinical practice: A US regulatory practice. Biomarkers Med. 2008; 2, 305-311. (Accessed at: www.ingentaconnect.com/content/fm/bmm/2008/00000002/00000003/art00010?crawler=true)

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/233/12/1498)

24. Goodsaid F, Frueh F. Process map proposal for the validation of genomic biomarkers. Pharmacogenomics., 2005; 7(5):773-82 (Accessed at: www.futuremedicine.com/doi/abs/10.2217/14622416.7.5.773)

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

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

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

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

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

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

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

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

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

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

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

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

37. Genetic Information Nondiscrimination Act. (Accessed at: http://www.gpo.gov/fdsys/pkg/PLAW-110publ233/pdf/PLAW-110publ233.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;2:264-92. (Accessed at: www.nature.com/tpj/journal/v2/n5/abs/6500131a.html)


www.i-pwg.org

12.4 ECOG Performance Status

GRADE	ECOG PERFORMANCE STATUS
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all selfcare but unable to carry out any work activities; up and about more than 50% of waking hours
3	Capable of only limited selfcare; confined to bed or chair more than 50% of waking hours
4	Completely disabled; cannot carry on any selfcare; totally confined to bed or chair
5	Dead

*Oken M, Creech R, Tormey D, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. *Am J Clin Oncol.* 1982;5:649-655

http://ecog-acrin.org/resources/ecog-performance-status

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

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

12.6 List of Abbreviations and Definitions of Terms

Abbreviation or Term	Definition
AE	adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
BCG	Bacillus Calmette-Guérin
BOR	best overall response
CBC	complete blood count
CpG	Cytidine-phospho-guanosine
Cr	creatinine
CrCl	creatinine clearance
CFR	Code of Federal Regulations
CR	complete response, complete remission
CRF	case report form
CRO	Contract Research Organization
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
DAMPs	damage-associated molecular patterns
DCR	disease control rate
DLT	dose-limiting toxicity
DOR	duration of response
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EOT	end of treatment
eCRF	electronic case report form
EDC	electronic data capture
FDA	United States Food and Drug Administration
FIH	first in human
FSH	follicle stimulating hormone
GCP	good clinical practice
GFR	Glomerular Filtration Rate
HCV	hepatitis C virus
Hgb	hemoglobin

Abbreviation or Term	Definition
HIV	human immunodeficiency virus
ICF	informed consent form
ICH	International Conference on Harmonisation
IL	human interleukin
IFN-γ	interferon gamma
IRB/IEC	Institutional Review Board/Independent Ethics Committee
LDH	lactate dehydrogenase
mAB	monoclonal antibody
MAD	maximum administered dose
MTD	maximum tolerated dose
NHV	normal healthy volunteers
NOAEL	no-observable adverse effect level
NOEL	no-observable effect level
ODNs	oligodeoxynucleotides
ORR	objective response rate
OS	overall survival
PAMPs	pathogen-associated molecular patterns
PD	pharmacodynamics
PET	Positron Emission Tomography
PFS	progression-free survival
PK	pharmacokinetics
PR	partial response, partial remission
RPTD	recommended phase 2 dose
RCC	renal cell carcinoma
SAE	serious adverse event
SCCHN	squamous cell cancer of head and neck
SD	standard deviation
SLE	systemic lupus erythematosus
TPI	toxicity probability interval
TLR	toll-like receptor
TV	tumor volume

13.0 SIGNATURES

13.1 Sponsor's Representative

TYPED NAME	
TITLE	
SIGNATURE	
DATE SIGNED	

13.2 Investigator

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

TYPED NAME	
TITLE	
SIGNATURE	
DATE SIGNED	