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TITLE:

A Phase Ib/II Study to Evaluate the Safety and Tolerability of Preladenant as a Single Agent and in Combination with Pembrolizumab in Subjects with Advanced Malignancies

IND NUMBER: [133717]

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SUMMARY OF CHANGES

PRIMARY REASON(S) FOR THIS AMENDMENT:

Section Number (s)	Section Title(s)	Description of Change (s)	Rationale
1.0 2.1 6.0 7.1.5.3.2 7.2	Trial Summary Trial Design Flow chart Safety Follow-up Visit Assessing and Recording Adverse Events	The protocol collection period for AEs was revised to 90 days after treatment discontinuation, 30 days if the subject initiates new anticancer therapy less than 30 days after study treatment discontinuation, or the day new anticancer therapy is initiated if between 30 days and 90 days after study treatment discontinuation.	This change was made at the request of the FDA to allow late toxicities that can be observed with immunomodulatory agents to be collected.
2.1 2.2 4.2.2 5.2 Trial Treatment(s)	Trial Design Trial Diagram Rationale for Dose Selection/Regimen	The starting dose has been changed from 10 mg BID to 25 mg BID. A 10 mg BID (DL-1) dose is added as an alternative dose should 25 mg BID prove to be intolerable	This change was made at the request of the FDA to ensure the dose escalation from DL1 to DL2 does not exceed 2 fold.
5.1.2	Subject Inclusion Criteria	Subjects to be enrolled to the study are defined as refractory to or intolerant of existing therapy(ies) known to provide clinical benefit for their condition.	This change was made at the request of the FDA to ensure patients to be enrolled in this trial are those who have exhausted all current approved therapeutic options.
5.1.3	Subject Exclusion Criteria	Examples of A2a receptor antagonists CPI-444, HTL1071, PBF-509 are added to exclusion criteria # 3.	This change was made at the request of the FDA to clarify A2a receptor antagonists that preclude trial inclusion.

Section Number (s)	Section Title(s)	Description of Change (s)	Rationale
5.2.2.1	Replacement of Subjects in DLT period	The protocol was clarified to better describe the situation when patients are experiencing DLT but allowed to remain in the trial. Language is added to define "the subject is deriving clinical benefit upon resolution of the DLT to a ≤ Grade 1 adverse event and after discussion with the sponsor."	This change was made at the request of the FDA as an extra safety precaution.
5.2.3	Guideline for Dose Modification and Treatment Discontinuation"	The protocol was clarified the section is applicable to both part 1 and part 2.	This change was made at the request of the FDA for clarification.
6.1	Flow Chart	Vital sign measurements were added to cycle 1 day 8 visit for both preladenant monotherapy arm and in combination with pembrolizumab arm.	This change was made at the request of the FDA as an extra safety precaution.
5.1.2	Subject Inclusion Criteria (Table 2)	The protocol was clarified in Coagulation section for INR and PT values when patients are using anticoagulant therapy.	This change was made at the request of FDA for clarification.
5.2.3.2	Table 8	Delete language "Appropriate resuscitation equipment should be available in the room and a physician readily available during the period of drug administration." Since it is no longer applicable in current study.	The language is not applicable in this study.

Section Number (s)	Section Title(s)	Description of Change (s)	Rationale
5.2.2	Definition of Dose-Limiting Toxicities	The duration of any Grade 3 or Grade 4 non-hematologic laboratory value was changed from 1 week to 72 hours.	This change was made at the request of the FDA as an extra safety precaution.
5.2.2	Definition of Dose-Limiting Toxicities	Liver function test was eliminated from the exceptions for any Grade 3 or Grade 4 non-hematologic laboratory value.	This change was made at the request of the FDA as an extra safety precaution.
5.2.2	Definition of Dose-Limiting Toxicities	Liver test abnormalities (Hy's Law) was added to the definition of DLT.	This change was made at the request of the FDA as an extra safety precaution.
5.5.2.2	Prohibited Concomitant Medications for Pembrolizumab	Protocol was clarified for glucocorticoids dose limit and conditions for pembrolizumab prohibited medication.	This change was made at the request of FDA for clarification.

ADDITIONAL CHANGE(S) FOR THIS AMENDMENT:

No additional changes.

1.0 TRIAL SUMMARY

Abbreviated Title	PhIb/II Study of Preladenant +/- Pembrolizumab in Subjects with Solid Tumor
Sponsor Product Identifiers	Preladenant (MK-3814) and pembrolizumab (MK-3475)
Trial Phase	Phase Ib/II
Clinical Indication	Treatment of Advanced Solid Tumors
Trial Type	Interventional
Type of control	No treatment control
Route of administration	Oral (preladenant) and intravenous (pembrolizumab)
Trial Blinding	Unblinded Open-label
Treatment Groups	During Part 1 (dose escalation and confirmation phase) subjects will be allocated to one of two treatment arms: Arm 1: preladenant in monotherapy Arm 2: preladenant in combination with pembrolizumab During Part 2 (expansion phase) subjects will be allocated to Arm 2 (preladenant in combination with pembrolizumab) in 2 select tumor cohorts.
Number of trial subjects	Approximately 100-120 subjects will be enrolled.
Estimated duration of trial	The Sponsor estimates that the trial will require approximately 42 months from the time the first subject signs the informed consent until the last subject's last study-related phone call or visit.
Duration of Participation	Each subject will participate in the trial for up to 28 months from the time the subject signs the informed consent form (ICF) through the final protocol-specified contact. After a screening phase of up to 28 days, each subject will be receiving assigned treatment for up to 24 months. After treatment discontinuation, subjects will be monitored for adverse events (AEs) and serious adverse events (SAEs) for 90 days. Subjects who initiate new anticancer therapy less than 30 days after study treatment discontinuation will be monitored for AEs/SAEs for 30 days. Subjects who initiate new anticancer therapy between 30 days and 90 days after study treatment discontinuation will be monitored for AEs/SAEs until the day new anticancer therapy is initiated. Subjects will be treated until progressive disease, unacceptable toxicity, intercurrent illness that prevents further administration of treatment, investigator's decision to withdraw treatment, subject withdrawal of consent, pregnancy of the subject, noncompliance with trial treatment or procedure requirements, subject completes treatment, or administrative reasons requiring cessation of treatment, at which point they will be discontinued from the study. Upon disease progression, subjects in the monotherapy arm will be able to cross-over to the combination regimen.

Randomization Ratio	N/A

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

Preladenant will be used throughout the protocol to refer to MK-3814 as supplied by the Sponsor.

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

2.0 TRIAL DESIGN

2.1 Trial Design

This is a multicenter, worldwide, open label, non-randomized, Phase Ib/II study of preladenant in monotherapy and in combination with pembrolizumab in subjects with a histologically or cytologically confirmed diagnosis of advanced solid tumor that has not responded to conventional therapy.

This study will evaluate the safety, tolerability and preliminary efficacy of preladenant administered in monotherapy (Arm 1), and in combination with pembrolizumab (Arm 2). There are two parts in this study, dose escalation and confirmation (Part 1) (Section 5.2.1.2) and cohort expansion (Part 2) which will include two select tumor cohorts (Section 5.2.1.3).

Subjects will be allocated to receive preladenant in monotherapy (Arm 1) or preladenant in combination with pembrolizumab (Arm 2) using an interactive voice response system/integrated web response system (IVRS/IWRS). In Arm 1 and Arm 2, preladenant will be administered orally (p.o.) twice a day (BID) every day of each 21-day cycle. In Arm 2, pembrolizumab will be administered intravenously (IV) every 3 weeks, on Day 1 of each cycle. Archived tumor-specimen (or fresh tumor biopsy) are required prior to enrollment on the study. The subject must also agree to undergo an on-treatment tumor biopsy, assuming this is considered acceptable from a safety perspective by the subject's physician.

In Part 1 of the study, a modified Toxicity Probability Interval (mTPI) design [1] will be used to identify and confirm the recommended Phase II dose (RP2D) of preladenant in Arm 1 (preladenant as a single agent), and in Arm 2 (preladenant in combination with pembrolizumab). Four pre-determined dose levels (DL1 to DL4) of preladenant will be evaluated independently in each arm: 25 mg BID, 50 mg BID, 100 mg BID, and 200 mg BID. A 10 mg BID de-escalation dose (DL-1) will be used as an alternative dose level should 25 mg BID prove to be intolerable. Lower and/or higher doses of preladenant may be explored depending on the combined safety, pharmacokinetic (PK), and pharmacodynamics (PD) data available at each dose level. The dose of pembrolizumab in Arm 2 will remain constant at 200 mg every 3 weeks.

Subjects who received at least one and up to five prior lines of therapy will be initially enrolled to receive preladenant at 25 mg twice a day in monotherapy (Arm 1). Treatment allocation will be accomplished by non-random assignment. Enrollment in Arm 1 (preladenant in monotherapy) at DL2 (Dose Level 2) will begin once all subjects complete Cycle 1 at DL1 (Dose Level 1) of Arm 1 and a dose escalation decision has been made. Enrollment in Arm 2 (preladenant in combination with pembrolizumab) at DL1 will also begin once all subjects complete Cycle 1 at DL1 of Arm 1 and a dose escalation decision has been made. Thus, the starting dose of preladenant in the combination arm will generally be one level below the dose level being tested concurrently in the preladenant monotherapy arm.

Barring dose limiting toxicities (DLTs) during Cycle 1, additional subjects will be enrolled and dose-finding will proceed according to an algorithm based on the mTPI method, targeting a preladenant dose with a 30% DLT rate for each arm to determine the respective RP2D (see Section 5.2.1.2).

In Part 2, two expansion cohorts targeting a specific tumor type will enroll approximately 30 subjects each. Subjects with select advanced solid tumors who received at least one and up to five prior lines of therapy will be enrolled to further evaluate safety and efficacy of preladenant in combination with pembrolizumab at the RP2D defined in Part 1 Arm 2 (See Section 5.2.1.3).

Additional lower and/or higher doses of preladenant in combination with pembrolizumab may also be explored in Part 2, if they were previously assessed in Part 1, and were deemed generally safe and tolerable. The final RP2D for future studies will be confirmed using all available safety information (including early and late toxicities from Parts 1 and 2), as well as PK and PD data, and preliminary efficacy assessments.

Preliminary efficacy will be evaluated using overall response rate (ORR) assessed by the investigator based on the Response Evaluation Criteria In Solid Tumors version 1.1 (RECIST 1.1) as a secondary objective. The duration of response (DOR), disease control rate (DCR) and progression-free survival (PFS) based on RECIST 1.1 as assessed by the investigator, as well as overall survival (OS) will be evaluated as exploratory objectives. ORR and PFS will be also assessed by immune-related RECIST (irRECIST) (see Section 4.2.3.2). In Part 2, a futility check will be performed in each of the select solid tumor cohorts (see Section 8.7).

Subjects will be monitored carefully for the development of adverse events (AEs), and for clinical and/or radiographic evidence of disease progression according to RECIST 1.1. However, irRECIST could be used by the investigator for treatment decision. In subjects who have initial evidence of radiological progressive disease by RECIST 1.1, it will be at the discretion of the investigator whether to continue a subject on study treatment until repeat imaging is obtained (see Section 4.2.3.2).

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

There will be no intra-subject dose escalation for subjects enrolled in this study. The definition of DLTs and criteria for dose modification of preladenant are outlined in Sections 5.2.2 and 5.2.3.1. Pembrolizumab will be administered at a fixed dose of 200 mg every 3 weeks, which will not be modified.

Subjects may receive study treatment (preladenant in monotherapy in Arm 1 or in combination with pembrolizumab in Arm 2, or pembrolizumab alone in Arm 2 if only preladenant was discontinued) for up to 35 cycles (24 months) (see Section 5.2.1.4).

Subjects who discontinue preladenant in monotherapy (Arm 1) due to progressive disease may, at the investigator's discretion and after consultation with the Sponsor, cross-over to the combination treatment (Arm 2) (see Sections 4.2.3.1 and 4.2.3.2). It will be at the discretion of the investigator whether to continue a subject on study treatment until repeat imaging is obtained. Once they discontinue from any part of the study, subjects will be treated at the discretion of the physician.

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

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

Subjects who discontinue treatment for reasons other than confirmed progressive disease will have post-treatment follow-up for disease status (including imaging) until progressive disease, initiating a new anti-cancer therapy, discontinuing from the study participation, or becoming lost to follow-up.

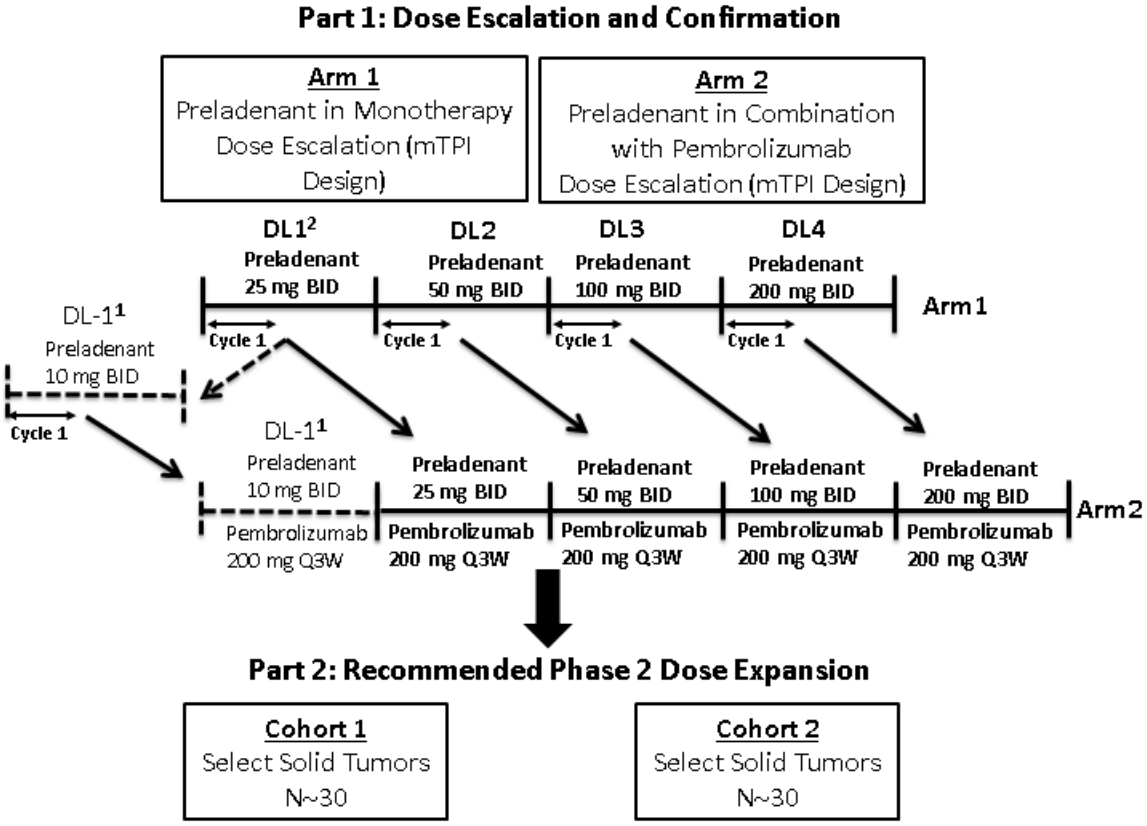
After confirmed progressive disease each subject will be contacted by telephone every 12 weeks (84±7 days) for survival until subject discontinues from the study, becoming lost to follow-up, death, or end of the study, whichever occurs first.

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

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

2.2 Trial Diagram

The study design is presented in Figure 1.



[1.] **DL-1: De-escalating dose**
[2.] **DL1: Starting dose**

Note: Subjects who discontinue preladenant in monotherapy (Arm 1) due to progressive disease may, at the investigator's discretion and after consultation with the Sponsor, cross-over to combination treatment (Arm 2)

Figure 1 Study Design: Part 1: Dose Escalation and Confirmation of MK-3814 as a Single Agent (Arm 1) and in Combination with Pembrolizumab (Arm 2); Part 2: Dose Expansion in 2 Select Solid Tumor Cohorts

3.0 OBJECTIVE(S) & HYPOTHESIS(ES)

In male/female subjects with advanced or metastatic solid tumors in Part 1 (Phase Ib) and with select advanced or metastatic solid tumors in Part 2 (Phase II):

3.1 Primary Objective(s) & Hypothesis(es)

(1) To evaluate the safety and tolerability of dose level-specific preladenant in monotherapy (Part 1) and in combination with pembrolizumab (Parts 1 and 2)

3.2 Secondary Objective(s) & Hypothesis(es)

(1) In Part 1, to determine a Recommended Phase 2 Dose (RP2D) of preladenant in monotherapy and in combination with pembrolizumab

(2) To evaluate ORR based on RECIST 1.1 as assessed by the investigator for dose level-specific preladenant in monotherapy (Part 1) and in combination with pembrolizumab (Parts 1 and 2)

3.3 Exploratory Objectives

(1) To assess the PK profile for dose level-specific preladenant in monotherapy (Part 1) and in combination with pembrolizumab (Parts 1 and 2)

(2) To evaluate the DOR, DCR and PFS based on RECIST 1.1 as assessed by the investigator, and OS, for dose level-specific preladenant in monotherapy (Part 1) and in combination with pembrolizumab (Parts 1 and 2)

(3) To evaluate ORR and PFS based on irRECIST as assessed by the investigator for dose level-specific preladenant in monotherapy (Part 1) and in combination with pembrolizumab (Parts 1 and 2)

(4) To evaluate the correlation between PD-L1 expression levels and tumor response for dose level-specific preladenant in monotherapy (Part 1) and in combination with pembrolizumab (Parts 1 and 2)

(5) To identify molecular (genomic, metabolic and/or proteomic) biomarkers that may be indicative of clinical response/resistance, safety, pharmacodynamic activity, and/or the mechanism of action for dose level-specific preladenant in monotherapy (Part 1) and in combination with pembrolizumab (Parts 1 and 2)

4.0 BACKGROUND & RATIONALE

4.1 Background

Refer to the respective investigator brochures (IBs) for detailed background information on preladenant or pembrolizumab.

4.1.1 Pharmaceutical and Therapeutic Background

Preladenant

Preladenant is a potent and selective competitive antagonist of the human adenosine Type 2a (A2a) receptor, with an inhibition constant (Ki) of 1.1 nM and > 1000-fold selectivity over the other three adenosine receptor subtypes (A1, A2b, and A3) and a variety of other receptors and ion channels.

Safety pharmacology and toxicology studies demonstrated a favorable safety profile for preladenant. In addition, genetic toxicology studies and carcinogenicity studies indicate no evidence of mutagenic or carcinogenic potential (See IB).

Preladenant was originally developed for Parkinson's disease and tested in clinical trials up to Phase III. While a generally acceptable safety and tolerability profile and good pharmacology properties were demonstrated, preladenant development for the Parkinson' disease indication was halted in Phase III due to lack of clinical efficacy.

One of signature features of the solid tumor microenvironment is hypoxia which is a state of cellular oxygen deprivation. It has been shown that hypoxia induces vascular endothelial growth factor (VEGF) production, angiogenesis and diverse epigenetic changes in tumor cells [2]. In addition, hypoxia causes an accumulation of extracellular adenosine, which exerts its biological function through a set of four G protein coupled receptors: A1, A2a, A2b and A3. Adenosine receptor (A2a) is expressed on CD-8+ tumor-infiltrating T lymphocytes (TILs), natural killer cells (NK), regulatory T cells (Tregs) and myeloid derived suppressor cells (MDSCs) and plays important roles in modulating the immune response in the context of inflammation within the tumor microenvironment.

Under normal physiologic conditions extracellular release of adenosine is balanced by rapid cellular uptake. In contrast, inflamed environments and tumors produce high levels of extracellular ATP and adenosine. As tissues are subjected to immune attack, increased cellular turnover and hypoxia trigger release of ATP and adenosine. Levels of extracellular adenosine are also increased by the catabolism of extracellular ATP and ADP by the tandem activity of the ectonucleotidases CD-39 and CD-73. In response to hypoxia-induced HIF-1 generation in tumors and inflamed tissues, CD-39 and CD-73 are up regulated on endothelial, stromal and some solid tumor cells, and on several subsets of immune cells, including T regs, CD-8+ T cells, and B cells [3]. Adenosine/A2aR signaling on endothelial cells upregulates VEGF production and leads to angiogenesis which directly promotes cancer cell proliferation and tumor metastasis. More importantly, adenosine/A2aR signaling on T cells leads to intracellular cAMP level increase and inhibition of AKT activity transmitted from CD-28 co-receptor and TCR activation.

Therefore, adenosine/A2aR represents a non-overlapping inhibitory pathway distinct from that of PD-1/PD-L1 and CTLA-4. Antagonism of A2aR is anticipated to demonstrate synergy with other immune checkpoint inhibitors in T cell activation. Pharmacologic blockade of A2a receptors on effector T cells, Tregs, NK cells, dendritic cells (DCs), MDSCs and tumor-associated macrophages (TAMs) may counteract the immunosuppressive effect of adenosine in tumor microenvironment and enhance multiple phases of the immune response.

Pembrolizumab

Pembrolizumab is a potent humanized immunoglobulin G4 (IgG4) monoclonal antibody (mAb) with high specificity of binding to the programmed cell death 1 (PD-1) receptor, thus inhibiting its interaction with programmed cell death ligand 1 (PD-L1) and programmed cell death ligand 2 (PD-L2).

Based on preclinical in vitro data, pembrolizumab has high affinity and potent receptor blocking activity for PD-1. Pembrolizumab has an acceptable preclinical safety profile and is in clinical development as an i.v immunotherapy for advanced malignancies. KEYTRUDA™ (pembrolizumab) is indicated in several countries for the treatment of patients with melanomas, non-small cell lung cancer (NSCLC), and head and neck squamous cell cancer (HNSCC) (See KEYTRUDA™ Package Circular).

The importance of intact immune surveillance function in controlling outgrowth of neoplastic transformations has been known for decades [4]. Accumulating evidence shows a correlation between tumor-infiltrating lymphocytes in cancer tissue and favorable prognosis in various malignancies. In particular, the presence of CD-8+ T-cells and the ratio of CD-8+ effector T cells/FoxP3+ regulatory T-cells (Tregs) correlates with improved prognosis and long-term survival in solid malignancies, such as ovarian, colorectal, and pancreatic cancer; hepatocellular carcinoma; malignant melanoma; and renal cell carcinoma. Tumor-infiltrating lymphocytes can be expanded ex vivo and reinfused, inducing durable objective tumor responses in cancers such as melanoma [5] [6].

The PD-1 receptor-ligand interaction is a major pathway hijacked by tumors to suppress immune control. The normal function of PD-1, expressed on the cell surface of activated T cells under healthy conditions, is to down-modulate unwanted or excessive immune responses, including autoimmune reactions. PD-1 (encoded by the gene Pdcd1) is an immunoglobulin (Ig) superfamily member related to CD-28 and CTLA-4 that has been shown to negatively regulate antigen receptor signaling upon engagement of its ligands (PD-L1 and/or PD-L2) [7] [8].

The structure of murine PD-1 has been resolved [9]. PD-1 and its family members are type I transmembrane glycoproteins containing an Ig-variable–type (IgV type) domain responsible for ligand binding and a cytoplasmic tail responsible for the binding of signaling molecules. The cytoplasmic tail of PD-1 contains 2 tyrosine-based signaling motifs, an immunoreceptor tyrosine-based inhibition motif, and an immunoreceptor tyrosine-based switch motif. Following T-cell stimulation, PD-1 recruits the tyrosine phosphatases, SHP-1 and SHP-2, to the immunoreceptor tyrosine-based switch motif within its cytoplasmic tail, leading to the dephosphorylation of effector molecules such as CD-3 zeta (CD-3ζ), protein kinase C-theta (PKCθ), and zeta-chain-associated protein kinase (ZAP70), which are involved in the CD-3 T-cell signaling cascade [8] [10] [11] [12]. The mechanism by which PD-1 down-modulates T cell responses is similar to, but distinct from, that of CTLA-4, because both molecules regulate an overlapping set of signaling proteins [13] [14]. As a consequence, the PD-1/PD-L1 pathway is an attractive target for therapeutic intervention in multiple solid tumors.

4.1.2 Rationale for Preladenant in Monotherapy and in Combination with Pembrolizumab

As described before, the adenosine/A2aR pathway, active in the tumor microenvironment, is another checkpoint pathway with a distinct mechanism from that of PD-1 and CTLA-4. Adenosine signaling (triggered by hypoxia and high cell turnover) in the inflammatory setting dampen the immunologic response and protect tissues from associated injury.

A2aR deletion or blockade has been shown to slow or eliminate tumor growth and activate tumor-infiltrating lymphocytes (TILs). Selective deletion of A2aRs on myeloid cells was also found to inhibit solid tumor growth and lung colonization by tumor cells and markedly reduce IL-10 production by TAMs, DCs, and MDSCs, while directly increasing antigen-specific CD-8+ T-cells and natural killer (NK) cell activation [15]. Thus, preladenant in monotherapy is expected to demonstrate clinical activity in a variety of solid tumors where adenosine is secreted in the tumor microenvironment. Emerging data from a Phase 1 clinical study with A2aR inhibitor CPI-444 (see below) suggest clinical activity for A2aR inhibitors as single agents in different tumor types (e.g. 1 partial response (PR) and 3 stable disease (SD) out of 5 subjects with advanced renal cell carcinoma).

Previously, the effectiveness of combining adenosinergic signaling blockade in the context of cytotoxic chemotherapy [3] has been demonstrated, by combining CD-73 blockade with doxorubicin chemotherapy in a murine breast cancer model [16]. The enhanced anti-tumor response, with increased survival in mice with established metastatic breast cancer compared with either agent in monotherapy, was also observed when a specific A2aR compound was used in combination with doxorubicin [3].

The independence of the adenosine/A2aR pathway in regards to other established checkpoint pathways has the potential ability to produce additive effects and to dramatically increase response rates. Preclinical efficacy studies of preladenant in monotherapy have shown partial inhibition of tumor growth in several murine models such as CT-26 or MC-38, with a titration study in MC-38 model showing a dose-dependent response (see IB for preladenant).

Due to the pleotropic effects of the adenosine pathway and its potential to synergize with other immune checkpoint inhibitors, a number of A2aR antagonists and adenosine metabolism key enzymes inhibitors have been pursued in the clinic for cancer immunotherapy. These include: 1) CPI-444, a small molecule A2aR antagonist in Phase 1 (Corvus); AZD4635 (AstraZeneca) and HTL-1071 (Heptares) in Phase 1; Redox, an A2aR inhibitor planned for Phase 1 in combination with CAR-T cells (JUNO); 2) anti-CD-73 antibodies: MEDI-9447 in Phase 1 (MedImmune) and BMS anti-CD-73 antibody; both has been in Phase 1 since June 2016. In addition, a number of small molecules and antibodies against CD-73 and CD-39 are in pre-clinical development.

It is hypothesized that the non-redundant effect of the adenosine/A2aR pathway blockade with PD-1/PDL-1 inhibition will have additive effect in the clinic by disrupting the immune suppressive tumor microenvironment and enhancing TCR-mediated T-cell activity.

4.1.3 Pre-clinical and Clinical Trials

4.1.3.1 Preladenant

Safety pharmacology and toxicology studies have demonstrated a generally favorable safety profile for preladenant (see the IB for further details).

In dogs, hepatic changes and increases in heart rate (28% to 45% in first 8 hours after dosing) and blood pressure (BP; 10% to 12% in the first 8 hours after dosing) support the continued and careful monitoring of these parameters during clinical investigations.

Results of a definitive embryo-fetal development study in rabbits indicate a non-dose-related low incidence of increases in cardiac malformations at all doses of preladenant. However, in a second rabbit embryo-fetal developmental toxicity study at the same doses, the results of the first study were not confirmed. Consequently, the reasons for the cardiac findings in the first study are unknown but may be due to genetic variability. Nevertheless, potential embryo/fetal exposure in women should be avoided.

In addition, genetic toxicology studies and carcinogenicity studies indicate no evidence of mutagenic or carcinogenic potential. In animals and humans, preladenant metabolism includes O-demethylation to an alcohol (SCH 434748) and subsequent oxidation to a carboxylic acid (SCH 446637), as well as N-dealkylation and alterations to the furan ring. Both SCH 434748 and SCH 446637 are also selective, high-affinity A2a receptor antagonists.

A total of 38 clinical trials were conducted with preladenant (see the IB for further details). In Phase 1, 24 clinical studies in healthy volunteers have been completed. In Phase 2, 8 clinical studies have been completed in subjects with drug-induced movement disorders and subjects with idiopathic Parkinson's disease. Four Phase 3 trials in subjects with Parkinson's disease have been also completed.

Approximately 3300 subjects have received preladenant in the Parkinson's disease clinical program. Doses have ranged from 2 to 200 mg/day and have been administered as a single dose or BID for up to 1 year. In general, preladenant was generally well tolerated in these trials (see IB for preladenant).

Adverse events reported by ≥5% of the healthy volunteers in Phase 1 multiple-dose trials include (preladenant vs. placebo): insomnia (24% vs. 3%), headache (15% vs. 3%), dizziness (9% vs. 5%), nausea (9% vs. 1%), abdominal pain (6% vs. 3%), and energy increased (6% vs. 0%). The most common AEs reported in subjects with Parkinson's disease who received preladenant in the double-blind Phase 2 dose-finding trial P04501 were Parkinson's disease (11%), somnolence (9%), dyskinesia (7%), nausea (7%), constipation (7%), headache (7%), and dizziness (6%). Adverse events reported by subjects with Parkinson's disease in Phase 1 trials (n=52) were generally similar to AEs reported in Phase 2 trials.

In later phases of the preladenant clinical program, the following AEs have been noted as risks for preladenant: increases in liver function enzymes and transient increases in blood pressure (BP).

Two Phase 2 trials (P02541 and P03376) were terminated early by the sponsor because of asymptomatic elevated liver enzymes in P02541. In P02541, 3 of 29 subjects had liver function test (LFT) elevations that reached protocol-specified criteria for discontinuation (alanine aminotransferase [ALT] > 3 x upper limit of normal [ULN]). Overall, in 7 of the 8 Phase 2 studies (the 8th being accounted below with the Phase 3 studies), the number of subjects / frequency of ALT or AST elevations ≥ 3x ULN was 7/429 (1.6%) for all doses of preladenant vs 4/145 (2.8%) in the placebo group. These increases were higher in the 25, 50 and 100 mg daily dose than that in the lower dose groups (see preladenant IB).

In the unblinded Phase 2 (P6402) and four Phase 3 trials (P06402, P04938, P07037, P06153, P05664) there were a total of 52 subjects (37 on preladenant at doses) meeting the protocol threshold for adjudication of ≥3x ULN, out of 2699 treated, for an incidence rate of

approximately 2% for ALT increased. Of the 37 preladenant cases, 29 were assessed as drug-related by the investigator. Subjects with increased ALT or AST received 2mg BID, 5mg BID or 10mg BID of preladenant and these elevations were not dose dependent. Although there were other liver enzyme elevations of unknown significance, none of the individuals with ALT elevations had concurrent elevations of any other liver function test to a clinically meaningful degree. Two subjects experienced mild bilirubin concentration fluctuations, but none of the variations exceeded 2 x ULN. None of the subjects enrolled on preladenant clinical trials fulfilled Hy's Law criteria (see preladenant IB).

Adenosine is known to be a vasodilator, and antagonism of the A2a receptor may lead to elevations in BP. Small, non-dose-dependent elevations in BP have been observed in all preladenant treatment groups relative to placebo following the first dose of study medication. These transient mild increases in blood pressure occurred within a few hours after preladenant administration; blood pressure changes were neither cumulative nor dose-related nor associated with clinical sequelae.

4.1.3.2 Pembrolizumab

Therapeutic studies in mouse models have shown that administration of antibodies blocking PD-1/PD-L1 interaction enhances infiltration of tumor-specific CD-8+ T-cells and leads ultimately to tumor rejection, either as a monotherapy or in combination with other treatment modalities. Anti-mouse PD-1 or anti-mouse PD-L1 antibodies have demonstrated anti-tumor responses as a monotherapy in models of squamous cell carcinoma, pancreatic carcinoma, melanoma, and colorectal carcinoma. Blockade of the PD-1 pathway effectively promoted CD-8+ T-cell infiltration into the tumor and the presence of interferon gamma, granzyme B, and perforin, indicating that the mechanism of action involved local infiltration and activation of effector T-cell function in vivo [17] [5] [6] [18] [8] [7]. Experiments have confirmed the in vivo efficacy of PD-1 blockade as a monotherapy as well as in combination with chemotherapy in syngeneic mouse tumor models (see the IB for further details).

Clinical trials have demonstrated efficacy in subjects with advanced melanoma, non-small cell lung cancer, head and neck cancer, bladder cancer, Hodgkin's lymphoma, triple-negative breast cancer, and gastric adenocarcinoma.

4.1.4 Ongoing Clinical Trials

4.1.4.1 Preladenant

There is no current ongoing clinical trial conducted with preladenant.

4.1.4.2 Pembrolizumab

Clinical trials investigating pembrolizumab are on-going in advanced melanoma, non-small cell lung cancer (NSCLC), squamous cell carcinoma of the head and neck, bladder cancer, hematologic malignancies, and in a number of other advanced solid tumor indications. For study details, and safety and efficacy summaries, please refer to the IB.

4.2 Rationale

4.2.1 Rationale for the Trial and Selected Subject Population

Preladenant is an adenosine A(2a) receptor antagonist with a high affinity and very high selectivity for adenosine A(2a) receptors, that has demonstrated enhanced tumor inhibition in combination with PD-1 in CD-73-expressing tumors [19], in preclinical cancer cell lines, and in xenograft animal models.

In Part 1 of the current study, preladenant will be evaluated as a single agent and in combination with pembrolizumab in subjects with advanced solid tumors.

In Part 2, subjects with select advanced tumors will be enrolled in two separate cohorts (~30 subjects per cohort) and will be treated at the RP2D of preladenant in combination with pembrolizumab established in Part 1 (Arm 2).

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

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

4.2.2 Rationale for Dose Selection/Regimen

4.2.2.1 Rationale for Starting Dose and Dose Escalation of Preladenant

A total of 38 clinical trials have been conducted with preladenant in the Parkinson's disease indication. Overall, ~3300 subjects have received preladenant in the neurology clinical development program. Doses have ranged from 2 to 200mg/day and have been administered as a single dose or BID for up to one year. Preladenant was generally well tolerated in these trials (see the IB for further details).

Preclinically, a dose of 25 mpk BID of preladenant has demonstrated efficacy in the CT-26 murine syngeneic tumor model. In combination, the same 25 mpk BID dose of preladenant with a murine anti-PD1 antibody produced additional tumor reduction over monotherapy treatments. Subsequent dose ranging experiments in the same model have indicated that a lower dose of 12.5 mpk may also produce additional efficacy over monotherapy (potentially higher than that observed at 25 mpk). In the RENCA murine syngeneic model, 6.25 and 12.5 mpk combinations have shown added efficacy over monotherapy (while a 25 mpk dose showed little benefit). This indicates a U-shaped dose response curve, which may in part be explained by inhibition of T cell proliferation at high concentration or increased upregulation of PDL-1.

In contrast to these high doses used in preclinical cancer models, preladenant doses of 0.03-3 mpk showed efficacy in rodent models of Parkinson's disease. Thus, while the shape of dose responses in murine cancer models has not always shown monotonic trends, these experiments have indicated that in general higher doses of preladenant may be required for cancer treatment in comparison to Parkinson's disease.

In the Parkinson's disease clinical development program, doses ranging from 2-10 mg BID were tested in Phase 3 studies (based in part on evidence of evidence of Brain RO measured by PET, and preliminary evidence of PD activity at these doses in Phase 2). Consistent with our preclinical observations, it is expected that doses greater than those showing activity in Parkinson's (>10mg) to be required to be effective in oncology program.

The 25 mg dose of preladenant was extensively studied in the Parkinsons program, and was deemed to be a safe starting dose, that would achieve exposures greater than those targeted in the Parkinson's disease Phase 3 trials. A Summary of subjects with 25 mg BID preladenant exposure in prior trials is shown in Table 1.

Table 1 Summary on clinical trials where preladenant was administered at 25 mg BID

Trial ID	Phase	Dosing Regimen	Subject Exposure	Trial Population	Treatment Duration
P03286	1	25 mg BID	25	Healthy Volunteer	5 days
P03291	1	25 mg BID	19	Mild/moderate Parkinson's disease	2 days
P03792	1	25 mg BID	13	Mild/moderate/severe Parkinson's disease	3 days
P04628	2	25 mg BID	9	Schizophrenia with DIMD	14 days
P05145	2	25 mg BID	27	Acute psychosis or akathisias	14 days
P05174	2	25 mg BID	21	Healthy volunteers	3 days

Preliminary projections using preladenant PK and in vitro measurement of Ki and fraction unbound suggest that a starting dose of 25 mg is likely to result in approximately 80% A2a receptor occupancy at trough. While the A2a receptor occupancy levels required for optimum efficacy are unclear, this starting dose minimizes the possibility of treating oncology patients at potentially ineffective doses. Since sporadic LFT elevations and blood pressure increases were noted in the Parkinson's disease program, dose escalation will proceed cautiously based on safety, PK and PD data from previous dose level cohorts. 100 mg of preladenant BID will achieve greater than 92% A2a receptor occupancy (RO). Assuming linear increases in PK from 100 to 200 mg BID, greater than 96% A2a receptor occupancy is expected after 200 mg BID dosing. Higher doses beyond 200 mg BID may be explored based on data collected at previous dose levels, as noted in Section 5.2.1.2.

In summary, the starting dose for this clinical study is 25 mg BID based on: (i) previous experience with preladenant at 25 mg BID in the Phase 1 and 2 clinical trials for the Parkinson's disease indication, which showed a generally well tolerated safety profile at this dose (see Table 1, and IB for preladenant); (ii) the opportunity to administer a dose that is more likely to be efficacious in oncology patients than lower starting doses; (iii) the fact that monotherapy cohorts (Arm 1) for each dose level will be started before each combination cohorts (Arm 2) will ensure that a dose is generally well tolerated prior to evaluating that dose in combination with pembrolizumab.

4.2.2.2 Fixed Dose of Pembrolizumab

An open-label Phase I trial (KEYNOTE 001) has been conducted to evaluate the safety and clinical activity of single agent pembrolizumab (MK-3475). The dose escalation portion of this trial evaluated three dose levels, 1 mg/kg, 3 mg/kg, and 10 mg/kg, administered every 2 weeks (Q2W) in subjects with advanced solid tumors. All three dose levels were well tolerated and no DLTs were observed. This first in human study of pembrolizumab (MK-3475) showed evidence of target engagement and objective evidence of tumor size reduction at all dose levels (1mg/kg, 3mg/kg and 10mg/kg Q2W). No MTD has been identified.

In KEYNOTE 001, two randomized cohort evaluations of melanoma subjects receiving pembrolizumab (MK-3475) at a dose of 2mg/kg versus 10mg/kg Q3W had been completed, and one randomized cohort evaluating of 10mg/kg Q3W versus 10mg/kg Q2W had also been completed. The clinical efficacy and safety data demonstrated a lack of clinically important differences in efficacy response or safety profile at these doses. For example, in Cohort B2, advanced melanoma subjects who had received prior ipilimumab therapy were randomized to receive pembrolizumab (MK-3475) at 2mg/kg versus 10mg/kg Q3W. The ORR was 26% (21/81) in the 2 mg/kg group and 32% (25/79) in the 10mg/kg group (FAS). The proportion of subjects with drug-related AE, grade 3-5 drug-related AE, serious drug-related AE, death or discontinuation due to an AE was comparable between groups or lower in the 10mg/kg group. In Cohort B3, advanced melanoma subjects (irrespective of prior ipilimumab therapy) were randomized to receive pembrolizumab (MK-3475) at 10mg/kg Q2W versus 10mg/kg Q3W. The ORR was 30.9% (38/123) in the 10mg/kg Q2W group and 24.8% (30/121) in the 10 mg/kg Q3W group (APaT). The proportion of subjects with drug-related AE, grade 3-5 drug-related AE, serious drug-related AE, death or discontinuation due to an AE was comparable between groups.

Pharmacokinetic data analysis of pembrolizumab (MK-3475) administered Q2W and Q3W showed slow systemic clearance, limited volume of distribution, and a long half-life (refer to IB). Pharmacodynamic data (IL-2 release assay) suggested that peripheral target engagement is durable (>21days). This early PK/PD data provides scientific rationale for testing a Q3W dosing schedule. Because Q3W dosing is more convenient for subjects, Q3W dosing will be further studied.

The rationale for further exploration of 2 mg/kg and comparable doses of pembrolizumab (MK-3475) in solid tumors is based on: 1) similar efficacy and safety of pembrolizumab (MK-3475) when dosed at either 2 mg/kg or 10mg/kg Q3W in melanoma subjects, 2) the flat exposure-response relationships of pembrolizumab (MK-3475) for both efficacy and safety in the dose ranges of 2 mg/kg Q3W to 10 mg/kg Q3W, 3) the lack of effect of tumor burden or indication on distribution behavior of pembrolizumab (MK-3475) (as assessed by the population PK model) and 4) the assumption that the dynamics of pembrolizumab (MK-3475) target engagement will not vary meaningfully with tumor type.

The choice of the 200mg Q3W as an appropriate dose for the switch to fixed dosing is based on simulations performed using the population PK model of pembrolizumab (MK-3475) showing that the fixed dose of 200mg every 3 weeks will provide exposures that 1) are optimally consistent with those obtained with the 2mg/kg dose every 3 weeks, 2) will maintain individual patient exposures in the exposure range established in melanoma as

associated with maximal efficacy response and 3) will maintain individual subjects exposure in the exposure range established in melanoma that are well tolerated and safe.

A fixed dose regimen will simplify the dosing regimen to be more convenient for physicians and to reduce potential for dosing errors. A fixed dosing scheme will also reduce complexity in the logistical chain at treatment facilities and reduce wastage.

Additionally, recently approved supplemental Biologics License Applications such as that for subjects with advanced HNSCC, mandate the administration of pembrolizumab at the fixed dose of 200mg Q3W.

Therefore, preladenant will be evaluated in combination with pembrolizumab at the fixed dose of 200mg Q3W. Modifications to the dose or dosing regimen of pembrolizumab will not be allowed in this study. Details are provided in Section 5.2.3.2.

4.2.2.3 Starting Dose for This Trial

The starting dose for preladenant in monotherapy (Arm 1) and in combination with pembrolizumab (Arm 2) is 25 mg BID (See Section 4.2.2.1).

4.2.2.4 Maximum Dose/Exposure for This Trial

The maximum pre-planned dose of preladenant for this trial will be 200 mg administered orally twice a day. However, based on safety evaluation and PK and PD data, dose escalation may continue to a MTD (with constant safety monitoring).

The maximum pre-planned dose of preladenant is based on the single agent doses tested in healthy volunteer studies and in Phase 1 studies of the preladenant development program in Parkinson Disease (See Section 4.2.2.1).

4.2.2.5 Rationale for Dose Interval and Trial Design

In healthy volunteer studies and in Phase 1 to 3 clinical studies of the preladenant clinical program in subjects with Parkinson's disease, preladenant was evaluated in monotherapy with doses ranging from 2mg/day to 200mg/day. Doses up to 200mg/day (QD or 100 mg BID) were found to be generally safe and well tolerated in Phase 2 clinical studies.

Pembrolizumab will be evaluated in the combination therapy (Arm 2) at its full single-agent dose (200mg intravenously every 3weeks), and will not be escalated or de-escalated during this trial (See Section 5.2.3.2). This dose was shown to be efficacious as a single-agent and in combination, with an acceptable AE profile.

4.2.3 Rationale for Endpoints

4.2.3.1 Safety Endpoints

The primary objective of this trial is to characterize the safety and tolerability of preladenant in monotherapy and in combination with pembrolizumab in subjects with advanced solid tumors. The primary safety analysis will be based on subjects who experience toxicities as defined by CTCAE Version 4.0 criteria. The primary safety endpoint is the rate of DLTs (see definition in Section 5.2.2). Safety will be assessed by quantifying the toxicities and

grades of toxicities experienced by subjects who received preladenant in monotherapy or in combination with pembrolizumab.

For adverse events, attribution to drug, time-of-onset, duration of the event, its resolution, and any concomitant medications administered will be recorded. AEs that will be analyzed include, but are not limited to, all AEs, SAEs, fatal AEs, and laboratory changes.

Safety data for subjects in Arm 1 who cross-over to combination treatment (Arm 2) due to disease progression will be analyzed separately than that of the subjects enrolled in Arm 1 or Arm 2 from the time they cross-over (Section 8.5.1).

4.2.3.2 Efficacy Endpoints

Objective response rate (ORR) will be used as a secondary endpoint as assessed by the site investigator/local radiology review based on RECIST 1.1, to evaluate efficacy of preladenant in monotherapy or in combination with pembrolizumab in subjects with advanced solid tumors (Part 1) and in subjects with select advanced solid tumors (Part 2).

Exploratory endpoints include OS, and DCR, DOR and PFS as assessed by the investigator/local radiology review based on RECIST 1.1. In addition, ORR and PFS based on irRECIST will be also assessed by the investigator/local radiology review (see Section 7.1.2.6.5).

Secondary and exploratory efficacy endpoints will also be summarized according to tumor types, in Part 1 and in Part 2.

Efficacy data for subjects in Arm 1 who cross-over to combination treatment (Arm 2) due to disease progression will be analyzed separately than that of the subjects enrolled in Arm 1 or Arm 2 from the time they cross over (Section 8.5.2).

Radiological images (e.g. CT, MRI) will be collected for possible review and analysis by blinded, independent central imaging laboratory. The Site Imaging Manual (SIM) contains specific instructions for the acquisition and submission of radiologic images to the central imaging vendor for this study.

The assessment of unidimensional target lesions and response categories per irRECIST are identical to RECIST 1.1. However, the Sponsor has implemented an adaptation related to new lesions, non-target lesions and tumor burden assessment in order to confirm radiographic progression. In this study, irRECIST will be used by site investigators/local radiology review to assess tumor response and progression and to make treatment decisions for subjects with advanced solid tumors. This clinical judgment decision should be based on the subject's overall clinical condition, including performance status, clinical symptoms, and laboratory data. Subjects may continue to receive study treatment until tumor assessment is repeated ≥4 weeks later in order to confirm progressive disease by irRECIST per site assessment.

Immune-related RECIST (irRECIST) is RECIST 1.1 adapted to account for the unique tumor response seen with immuno-therapeutics as described by Nishino, et al. [20]. Immunotherapeutic agents 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

participants can manifest a clinical response after an initial increase in tumor burden or even the appearance of new lesions.

Based on an analysis of patients with melanoma enrolled in Keynote-001, 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. Additionally, the data suggest that RECIST 1.1 may underestimate the benefit of pembrolizumab in approximately 15% of patients. 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.

4.2.3.3 Pharmacokinetic Endpoints

An exploratory objective of this study is to characterize (i) the pharmacokinetic (PK) profile of preladenant administered as a single agent (Arm 1), and when administered in combination with pembrolizumab (Arm 2), and (ii) to characterize the pharmacokinetic profile of pembrolizumab when administered in combination with preladenant (Arm 2). The serum concentrations of these agents will serve as the primary read-out for the PK, and these data will be used to derive PK parameters of the agents when administered alone and in combination. Furthermore, the results of these analyses will be used in conjunction with the pharmacodynamics, and safety and exploratory endpoint data to help assess future dosing strategies for preladenant.

4.2.3.4 Anti-Drug Antibodies (ADA)

Formation of ADAs can potentially confound drug exposures at therapeutic doses, and prime for subsequent infusion-related toxicity. In Arm 2, anti-drug antibody response to pembrolizumab at the beginning of each cycle will be determined to understand drug metabolism, exposure, and safety.

4.2.3.5 Planned Exploratory Biomarker Research (Tumor Biopsies and Blood samples)

Cancer immunotherapies represent an important and novel class of antitumor agents. However, the mechanism of action of these exciting new therapies is not completely understood and much remains to be learned regarding how best to leverage these new drugs in treating patients. Thus, to aid future patients, it is important to investigate the determinants of response or resistance to cancer immunotherapy, as well as determinants of AEs in the course of our clinical trials. These efforts will identify novel predictive/PD biomarkers and generate information that will better guide single-agent and combination therapy with immuno-oncology drugs.

To identify novel biomarkers, biospecimens (ie, blood components, tumor material from archived tumor samples or new biopsy during screening, and new biopsy during study treatment) will be collected to support analyses of cellular components (e.g., protein, DNA, RNA, metabolites) and other circulating molecules (see Section 6.0 for timing of collection).

Investigations may include but are not limited to:

- Germline (blood) genetic analyses (e.g., SNP analyses, whole exome sequencing, whole genome sequencing): This research will evaluate whether genetic variation within a clinical trial population correlates with response to the treatment(s) under evaluation. If genetic variation is found to predict efficacy or AEs, the data might inform optimal use of therapies in the patient population. Furthermore, it is important to evaluate germline DNA variation across the genome in order to interpret tumor-specific DNA mutations.
- Genetic (DNA) analyses from tumor: The application of new technologies, such as next generation sequencing, has provided scientists the opportunity to identify tumor-specific DNA changes (i.e., mutations, methylation status, microsatellite instability etc.). Key molecular changes of interest to immune-oncology drug development include (for example) the mutational burden of tumors and the clonality of T-cells in the tumor microenvironment. Increased mutational burden (sometimes referred to as a 'hyper-mutated' state) may generate neo-antigen presentation in the tumor microenvironment. To conduct this type of research, it is important to identify tumor-specific mutations that occur across all genes in the tumor genome. Thus, genome wide approaches may be used for this effort. Note that in order to understand tumor-specific mutations; it is necessary to compare the tumor genome with the germline genome.
- Tumor and blood RNA analyses: Both genome-wide and targeted messenger RNA (mRNA) expression profiling and sequencing in tumor tissue and in blood may be performed to define gene signatures that correlate to clinical response to treatment with pembrolizumab or other immunotherapies. Pembrolizumab induces a response in tumors that likely reflects an inflamed/ immune phenotype. Specific immune-related gene sets (such as those capturing interferon-gamma transcriptional pathways) may be evaluated and new signatures may be identified. Individual genes related to the immune system may also be evaluated (e.g., IL-10). MicroRNA profiling may also be pursued.
- Proteomics and immunohistochemistry (IHC) using blood or tumor: Tumor and blood samples from this study may undergo proteomic analyses (e.g., PD-L1 IHC). PD-L1 protein level in tumor sections, assessed by IHC, has been shown to correlate with response to pembrolizumab in subjects with NSCLC, and an InVitro Diagnostic (IVD) device has been developed for use with pembrolizumab in NSCLC. Preliminary data indicate that this association may also be true in additional cancer types (i.e., triple-negative breast cancer, head and neck cancer, and gastric cancer). Additional tumor or blood-derived proteins may also correlate with response to pembrolizumab. Tumor tissue may, therefore, be subjected to proteomic analyses using a variety of platforms that could include but are not limited to immunoassays and liquid chromatography/mass spectrometry. This approach could identify novel protein biomarkers that could aid in patient selection for pembrolizumab therapy.

- Other blood derived biomarkers: In addition to expression on tumor tissue, PD-L1 and other tumor derived proteins can be shed from tumors and released into the blood. Assays such as enzyme-linked immunoassay measure such proteins in serum. Correlation of expression with response to pembrolizumab therapy may identify new approaches for predictive biomarkers in blood, representing a major advance from today's reliance on assessing tumor biomarkers. This research would serve to develop such assays for future clinical use.

4.2.3.6 Future Biomedical Research

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

Such research is for biomarker testing to address emergent questions not described elsewhere in the protocol (as part of the main trial) and will only be conducted on specimens from appropriately consented subjects. The objective of collecting/retaining 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.

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 preladenant and pembrolizumab Investigators Brochure (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 or metastatic solid tumors in Part 1 and Male/Female subjects with select advanced or metastatic solid tumors in Part 2 will be enrolled in this trial.

5.1.2 Subject Inclusion Criteria

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

1. Be ≥ 18 years of age on day of signing the informed consent.
2. Be willing and able to provide written informed consent for the trial. 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.
3. Part 1 and Part 2: Have a histologically- or pathologically-documented, locally-advanced or metastatic solid tumor for which standard therapy, either does not exist or has been proven ineffective, intolerable or refused by the subject. Each subject must have received at least one and up to five prior lines of cancer treatment regimens, excluding neo-adjuvant, adjuvant, maintenance treatment and surgery.
4. Have provided archival tumor tissue sample or newly obtained core or excisional biopsy of a tumor lesion not previously irradiated. Formalin-fixed, paraffin embedded (FFPE) tissue blocks are preferred to slides. Newly obtained biopsies are preferred to archived tissue.

   Note: If submitting unstained cut slides, newly cut slides should be submitted to the testing laboratory within 14 days from the date slides are cut (details pertaining to tumor tissue submission can be found in the Procedures Manual).
5. Have measurable disease per RECIST 1.1 as assessed by the local site investigator/radiology. Target lesions situated in a previously irradiated area are considered measurable if progression has been demonstrated in such lesions.
6. Have a performance status of 0 or 1 on the Eastern Cooperative Oncology Group (ECOG) Performance Scale.
7. Be able to swallow and retain oral medication and must not have any clinically significant gastrointestinal abnormalities that may alter absorption.
8. Demonstrate adequate organ function as defined by the following table (Table 2):

Table 2 Adequate Organ Function Laboratory Values

System	Laboratory Value
Hematological	
Absolute neutrophil count (ANC)	≥1,500 /mcL
Platelets	≥100,000 / mcL
Hemoglobin	≥9 g/dL or ≥5.6 mmol/L[a]
Renal	
Serum creatinine **OR** Measured or calculated[b] creatinine clearance (CrCl) or Glomerular Filtration Rate (GFR) in place of CrCl	≤1.5 X upper limit of normal (ULN) **OR** ≥60 mL/min for subject with creatinine levels >1.5x institutional ULN
Hepatic	
Serum total bilirubin **OR** Direct bilirubin	≤ 1.5 X ULN **OR** Direct bilirubin 1≤ ULN for subjects with total bilirubin levels > 1.5 X ULN
AST (SGOT) and ALT (SGPT)	≤ 2.5 X ULN **OR** ≤ 5 X ULN for subjects with liver metastases
Coagulation	
International Normalized Ratio (INR) or Prothrombin Time (PT)	≤1.5 X ULN If subject is receiving anticoagulant therapy only PT is required to be within therapeutic range of intended use of anticoagulants.
Activated Partial Thromboplastin Time (aPTT)	≤1.5 X ULN If subject is receiving anticoagulant therapy only aPTT is required to be within therapeutic range of intended use of anticoagulants

ALT (SGPT) = alanine aminotransferase (serum glutamic pyruvic transaminase);
AST (SGOT) = aspartate aminotransferase (serum glutamic oxaloacetic transaminase);
GFR = glomerular filtration rate; ULN = upper limit of normal.
a Criteria must be met without packed red blood cell (pRBC) transfusion within last 2 weeks. Subjects can be on stable dose of erythropoietin (≥ approximately 3 months).
b Creatinine clearance (CrCl) should be calculated per institutional standard.
Note: This table includes eligibility-defining laboratory value requirements for treatment; laboratory value requirements should be adapted according to local regulations and guidelines for the administration of specific chemotherapies.

9. If a female subject of childbearing potential (see Section 5.7.2) have a negative urine or serum pregnancy test 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. If a female of childbearing potential (Section 5.7.2), 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 preferred contraception for the subject.

11. If a male subject with a female partner(s) of child-bearing potential, 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. Males with pregnant partners must agree to use a condom; no additional method of contraception is required for the pregnant partner (if partner pregnancy is collected, males must also agree to not give/donate sperm).

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

12. Concomitant treatment such as bisphosphonate or denosumab therapy is allowed as long as it is begun at least 2 weeks prior to treatment allocation.

5.1.3 Subject Exclusion Criteria

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

1. Has disease that is suitable for local treatment administered with curative intent.
2. Has received previous treatment with an immunomodulatory agent (e.g. anti-PD-1/PD-L1 or anti-CTLA-4) and was discontinued from that treatment due to a Grade 3 or higher irAE.
3. Has received previous treatment with an A2a receptor antagonist (e.g. CPI-444; HTL1071; PBF-509).
4. Has had chemotherapy, definitive radiation, or biological cancer therapy within 4weeks (2 weeks for palliative radiation) prior to the first dose of study therapy, or has not recovered to CTCAE grade 1 or better from any adverse events that were due to cancer therapeutics administered more than 4 weeks earlier (this includes subjects with previous immunomodulatory therapy with residual immune-related adverse events). Subjects receiving ongoing replacement hormone therapy for endocrine immune-related adverse events will not be excluded from participation in this study.
5. Is currently participating and receiving study therapy or has participated in a study of an investigational agent and has received study therapy or has used an investigational device within 28 days of administration of study therapy.

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

6. Has taken during the 14 days prior to start of study treatment, or is currently taking drugs or grapefruit and star fruit in diet that interferes with CYP3A4 or CYP2C8 as listed in Table 11.
7. Has taken during the 5 days prior to start of study treatment, or is currently taking Proton Pump Inhibitors (PPI).
8. Has a diagnosis of immunodeficiency or is receiving chronic systemic steroid therapy (exceeding 10 mg dose daily of prednisone equivalent) or any other form of immunosuppressive therapy within 7 days prior the first dose of trial drug.

9. Is expected to require any other form of systemic or localized antineoplastic therapy while in study.
10. Has a history of a second malignancy, unless potentially curative treatment has been completed with no evidence of malignancy for 5 years.

    Note: 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, or other *in-situ* cancers.
11. Has clinically active central nervous system (CNS) metastases and/or carcinomatous meningitis. Subjects with previously treated brain or meningeal metastases may participate and be eligible for treatment provided they are stable and asymptomatic (without evidence of progression by MRI scan of the brain separated by at least 4 weeks after treatment), have no evidence of new or enlarging brain metastases, are evaluated within 4 weeks prior to first study drug administration, and are off immunosuppressive doses of systemic steroids at least 2 weeks from enrollment.
12. Has had a severe hypersensitivity reaction to treatment with the monoclonal antibody/components of the study drug.
13. Has an active infection requiring therapy.
14. Has a history of interstitial lung disease.
15. Has a history of (non-infectious) pneumonitis that required steroids or current pneumonitis.
16. Has a known history of active tuberculosis.
17. Has an active autoimmune disease that has required systemic treatment in the past 2 years (i.e. with use of disease modifying agents, corticosteroids or immunosuppressive drugs) except vitiligo or resolved childhood asthma/atopy. Replacement therapy, such as thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency, is not considered a form of systemic treatment and is allowed. Use of non-systemic steroids is permitted (see Section 5.5.2.2).
18. Has received a live-virus vaccine within 30 days of planned treatment start. Seasonal flu vaccines that do not contain live virus are permitted.
19. Has known Human Immunodeficiency Virus (HIV) (HIV 1 or 2 antibodies) and/or known active and acute Hepatitis B or C infections (e.g., positive for HBsAg/HBV DNA or HCV RNA).
20. 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, make administration of the study drugs hazardous or make it difficult to monitor adverse effects such that it is not in the best interest of the subject to participate, in the opinion of the treating Investigator.
21. Has known psychiatric or substance abuse disorders that would interfere with the subject's ability to cooperate with the requirements of the trial.

22. Is pregnant or breastfeeding, or expecting to conceive or father children within the projected duration of the study.
23. Has not fully recovered from any effects of major surgery without significant detectable infection. Surgeries that required general anesthesia must be completed at least 2 weeks before first study drug administration. Surgery requiring regional/epidural anesthesia must be completed at least 72 hours before first study drug administration and subjects should be recovered.

5.2 Trial Treatment(s)

In Part 1 (dose escalation and confirmation phase), an mTPI design with a target DLT rate of approximately 30% will be applied to identify the RP2D of preladenant independently in each treatment arm (preladenant monotherapy [Arm 1] and preladenant in combination with pembrolizumab [Arm 2]).

The starting dose of preladenant will be 25 mg BID and may proceed, based on DLT assessment to a dose of 200 mg BID. Doses lower or higher than the pre-determined doses may be explored based on safety, PK/PD assessment at the pre-determined dose levels.

Table 3 Trial Treatment (21-Day Cycles)

Drug	Dose/Potency	Dose Frequency	Route of Administration	Regimen/ Treatment Period	Use
Arm 1 and Arm 2: Preladenant	DL-1 10 mg DL1 25 mg DL2 50 mg DL3 100 mg DL4 200 mg	Twice a day	Oral	Days 1 to 21 of each cycle	Experimental
Arm 2: Pembrolizumab	200 mg	Every three week	Intravenous infusion	Day 1 of each cycle	Experimental

Part 2: Preladenant will be administered at the RP2D identified in Part 1 of the study, in combination with pembrolizumab at a fixed dose of 200 mg (same fixed dose as in Part 1). Additional lower and/or higher doses of preladenant in combination with pembrolizumab may be explored in Part 2.

Throughout the study (Part 1 and Part 2), the first intake of preladenant will occur at the trial site on Day 1 of each cycle for Arm 1 and Arm 2.

Following the first dose, preladenant will be administered every 12 hours unsupervised at home (e.g. dose 2 on the evening of first dose and then twice daily at approximately the same time each day), until Day 1 of the next cycle.

In combination treatment cohorts (Part 1 Arm 2 and Part 2), the first dose of each cycle will be preladenant followed by pembrolizumab infusion. Pembrolizumab will be administered through an intravenous infusion as described in the Pharmacy Manual. Subsequent dosing of preladenant will be performed in the evening of the same day (Day 1), and then twice daily

by the subject (i.e., unsupervised at his/her home) at approximately the same time each day, until Day 1 of the next cycle.

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

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

5.2.1 Dose Selection

5.2.1.1 Dose Selection (Preparation)

Details on preparation and administration of pembrolizumab are provided in the Pharmacy Manual. Concomitant immunotherapeutic agents will be prepared and administered as per the approved product label(s).

5.2.1.2 Dose Escalation and Confirmation

In Part 1 of the study, an mTPI design [1] with a target DLT rate of approximately 30% will be applied for dose escalation and confirmation to determine a RP2D in each treatment arm (preladenant monotherapy [Arm 1] and preladenant in combination with pembrolizumab [Arm 2]). The final number of subjects enrolled in Part 1 will depend on the empirical safety observations (DLT occurrence), and what dose is ultimately identified as the RP2D using the mTPI design.

Four pre-determined dose levels of preladenant in each arm will be explored independently in Part 1: 25 mg BID, 50 mg BID, 100 mg BID, and 200 mg BID. A 10 mg BID de-escalation dose (DL-1) will be used as an alternative dose level should 25 mg BID prove to be intolerable. Lower and/or higher doses of preladenant may be explored depending on the combined safety, PK/PD data available at each dose level. All dose escalation and de-escalation decisions will be based on the occurrence of DLTs at a given dose and will be made jointly by the investigators and the Sponsor. In Arm 2, the dose of pembrolizumab will remain constant at 200 mg every 3 weeks in Part 1 and Part 2 of the study.

Treatment allocation will be accomplished by non-random assignment. Enrollment in Arm 1 (preladenant in monotherapy) at DL2 will begin once all subjects complete Cycle 1 at DL1 of Arm 1 and a dose escalation decision has been made. Enrollment in Arm 2 (preladenant in combination with pembrolizumab) at DL1 will also begin once all subjects complete Cycle 1 at DL1 of Arm 1 and a dose escalation decision has been made. Thus, the starting dose of preladenant in the combination arm will generally be 1 dose level below the dose being tested concurrently in the preladenant monotherapy arm.

When both treatment arms are open for enrollment, IVRS/IWRS will alternate subject assignment between Arm 1 and Arm 2 starting with Arm 1. For example, once the 50 mg BID dose cohort of Arm 1 (preladenant monotherapy) and the 25 mg BID dose cohort of Arm 2 (preladenant in combination with pembrolizumab) are open for enrollment, the first subject will be allocated to Arm 1, the second subject will be allocated to Arm 2, the third subject will be allocated to Arm 1, etc. Each new dose cohort will open for enrollment

without delay once the 21 day DLT observation period of the previous dose cohort is completed and a dose escalation decision is made.

In Table 4, the number of subjects treated is indicated in the columns and the number of subjects who experienced a DLT is indicated in the rows. Dosing decisions include escalate to the next higher dose (E), stay at the current dose (S), de-escalate to the next lower dose (D), and de-escalate to a lower dose and never test this dose again (i.e., unacceptably toxic dose; DU).

During dose escalation, a minimum of three subjects are required at each dose. Depending on accrual rate, 3, 4, 5 or 6 subjects may be enrolled at each new dose until the last of those subjects completes the 21-day DLT assessment period. For example, the dose escalation rules will proceed as follows if 3 subjects are enrolled: if 0 out of the first three subjects at a given dose level develops a DLT, then the dose can be escalated to the next level without further expansion. If 1 out of the first three subjects at a given dose level develops a DLT, no more than an additional three subjects should be enrolled at this dose level until additional DLT data are available since this dose would be considered unacceptably toxic if all three of the additional subjects experience a DLT (i.e., 4 out of 6 subjects). If two out of the first 3 subjects at a given dose level develop a DLT, the dose will be de-escalated to the next lower level. If 3 out of the first three subjects at a given dose level develop a DLT, this dose will be considered unacceptably toxic, i.e., the dose will be de-escalated and never re-escalated to that dose again. The same principle will be applied whether 3, 4, 5 or 6 subjects are enrolled in the same dose cohort according to Table 4.

The number of subjects who are enrolled at each dose is capped to minimize the exposure to a dose that may be unacceptably toxic (denoted as DU in Table 4). To determine how many more subjects can be enrolled at a dose level, one can count steps in a diagonal direction (down and to the right) from the current cell to the first cell marked DU. In total, three to 14 subjects may be enrolled at a given dose level.

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

The dose of preladenant in the combination arm (Arm 2) may not be escalated to a dose that is higher than the preladenant dose in the preladenant monotherapy arm (Arm 1); however, once dose escalation of preladenant in Arm 1 is stopped, the dose of preladenant in Arm 2 may be escalated up to that dose.

Dose escalation and confirmation in Arm 1 and Arm 2 will end after 14 subjects have been treated at any of the selected doses (which may include the optional doses). The pool-adjacent-violators algorithm [1] will be used to estimate the DLT rates across doses in each treatment arm under the assumption of monotonicity between DLT rates and dose levels. The dose with an estimated DLT rate closest to 30% may be treated as a preliminary RP2D. The totality of the data will be considered before deciding on the dose(s) to carry forward to Part 2 and the escalation schedule may be adjusted based on PK, and safety data emerging throughout the study to determine the RP2D. The RP2D of preladenant in the combination arm (Arm 2) will not exceed, but may equal, the RP2D in the preladenant monotherapy arm (Arm 1).

Note that while 30% was the target toxicity rate used to generate the guidelines in Table 4, the observed rates of subjects with DLTs at the MTD may be slightly above or below 30%.

While during this study there will not be any hypothesis testing, an interim look at the data may be conducted to enable future trial planning and dosing decisions after undergoing first imaging follow-up (see Section 8.7).

Table 4 Dose Escalation and Confirmation Rules Based on the Modified Toxicity Probability Interval Design (mTPI)

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

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

5.2.1.3 Cohort Expansion

In Part 2 of the trial, approximately 30 additional subjects will be treated in each of two cohorts of subjects with select advanced tumors. Subjects in these two cohorts will be treated at the RP2D identified using the mTPI design in Arm 2 of Part 1 (preladenant in combination with pembrolizumab). The dose of pembrolizumab in Arm 2 will remain fixed at 200 mg every 3 weeks.

Each of the select advanced solid tumor cohorts will focus on a specific type of tumor (e.g., Cohort 1: Triple Negative Breast Cancer (TNBC) and Cohort 2: Pancreatic Cancer). The determination of which tumor type chosen will be made at a later time, based on accumulating data from the field. The Sponsor will issue a memo and indicate in the supplemental Statistical Analysis Plan (sSAP) the specific tumor types, based on emerging data in the field.

Part 2 will begin once an RP2D for Arm 2 has been identified. When Part 2 is open for enrollment, IVRS/IWRS will assign subjects to one of two cohorts by tumor type.

In Part 2, a futility check will be performed after the first ~15 evaluable subjects in each of the select solid tumor cohorts. If no responses are observed in a given cohort, enrollment in this cohort may be stopped early (see Section 8.7).

5.2.1.4 Tolerability Evaluation Rules and Dose Escalation

Four dose levels of preladenant are planned in Part 1 (Table 5 and Table 6)

The starting dose (DL1) of preladenant is 25 mg BID Dose escalation will continue as outlined above (Section 5.2.1.2) according to mTPI dose finding rules.

Table 5 Dose Levels for Preladenant Monotherapy (Part 1: Arm 1)

Arm 1	**Preladenant (BID)**	
Dose Levels	**mg per dose**	**mg per day**
DL-1	10	20
DL1	25	50
DL2	50	100
DL3	100	200
DL4	200	400

Table 6 Dose Levels for Preladenant and Pembrolizumab (Part 1: Arm 2)

Arm 2	Preladenant (BID)		Pembrolizumab (Q3W)
Dose Levels	**mg per dose**	**mg per day**	**IV Infusion (mg per dose)**
DL-1	10	20	200
DL1	25	50	200
DL2	50	100	200
DL3	100	200	200
DL4	200	400	200

Each individual subject will be assigned to a single dose level of study therapy. Intra-subject dose escalation is not allowed. Individual patient dose interruptions and/or dose decreases for preladenant may be implemented based on toxicity as described in Section 5.2.3.1. However, dose adjustments should not be made during the DLT observation period without discussion with the Sponsor. In Arm 2, pembrolizumab administration can be delayed or interrupted but will not be de-escalated see Section 5.2.3.2.

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

Subjects may continue on treatment until disease progression, unacceptable toxicity, investigator's decision to withdraw the subject, withdrawal of consent, development of an inter-current condition precluding further administration of study treatment, pregnancy of the subject, failure to comply with dosing evaluations or other study requirements, or administrative reasons requiring cessation of treatment, at which point they will be discontinued from the study.

5.2.2 Definition of Dose-Limiting Toxicities

All toxicities will be graded using NCI CTCAE Version 4.0 based on Investigator assessment (Appendix 12.5).

The DLT window of observation will be during Cycle 1 (Day 1 to Day 21).

The occurrence of any of the following toxicities during Cycle 1 will be considered a DLT, if assessed by the Investigator to be possibly, probably or definitely related to study drug administration:

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 associated with bleeding

3) Grade 3 non-hematologic toxicity (not laboratory) lasting >3 days despite optimal supportive care.

4) Any Grade 3 or Grade 4 non-hematologic laboratory value if:
   - Medical intervention is required to treat the subject, or
   - The abnormality leads to hospitalization, or
   - The abnormality persists for >72 hours.
   - Exceptions:
     - Clinically non-significant, treatable, or reversible laboratory abnormalities including uric acid, etc.

5) Any of the following liver test abnormalities are observed (Hy's Law)
   - ALT or AST > 3X ULN **with** TBL > 2X ULN with no elevation in alkaline phosphatase (AP < 2X ULN)
   - No other reasons can be found to explain the combination of increased AT and TBL, such as viral hepatitis, A,B or C, preexisting or acute liver diseases, or another drug capable of causing the observed injury

6) Febrile neutropenia Grade 3 or Grade 4:
   - Grade 3 is defined as ANC <1000/mm3 with a single temperature of >38.3 degrees C (101 degrees F) or a sustained temperature of ≥38 degrees C (100.4 degrees F) for more than one hour
   - Grade 4 is defined as ANC <1000/mm3 with a single temperature of >38.3 degrees C (101 degrees F) or a sustained temperature of ≥38 degrees C (100.4 degrees F) for more than one hour, with life-threatening consequences and urgent intervention indicated.

7) Prolonged delay (>2 weeks) in initiating cycle 2 due to treatment-related toxicity.

8) Any treatment-related toxicity which causes the subject to discontinue treatment during Cycle 1.

9) Missing >25% of Preladenant doses as a result of drug-related AE(s) during the first cycle.

10) Grade 5 toxicity.

5.2.2.1 Replacement of Subjects in DLT Period

In order to fully evaluate the safety of the combination therapy in this study, all subjects enrolled must meet the criteria for evaluability for Cycle 1. Subjects are considered non-evaluable and will be replaced if:

- They are enrolled but not treated,
- They discontinue from the trial prior to completing all safety evaluations due to reasons other than drug-related AEs,
- They received <90% of the total pembrolizumab infusion in Cycle 1 (e.g., because the infusion had to be discontinued due to an infusion reaction) and did not experience a drug-related event,
- They received ≤75% of preladenant doses intended for the trial during Cycle 1 and did not experience a drug-related AE,
- They must take a prohibited concomitant medication during Cycle 1, unless this medication is used to treat a study drug-related AE,
- They must undergo medical / surgical procedures or have logistical issues not related to study therapy (e.g., elective surgery, unrelated medical events) during Cycle 1.

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

Subjects who experience a DLT in Cycle 1 should be discontinued from treatment. However, if in the opinion of the Investigator, the subject is deriving clinical benefit from the study treatment, the subject may be allowed to continue on the study upon resolution of the DLT to a ≤ Grade 1 adverse event and after discussion with the sponsor.

5.2.3 Guideline for Dose Modification and Treatment Discontinuation

For individual subjects, dose delays and modifications of trial treatment will be based on treatment-related toxicity, laboratory test results prior to treatment administration, and clinical assessments during the previous cycle and on the day of treatment. Guidelines for dose delay and dose modification for Parts 1 and 2 are described below and are applicable to the start of each cycle as well as during the cycle if treatment-related toxicities occur.

5.2.3.1 Preladenant Dose Modifications

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

The Common Terminology Criteria for Adverse Events, version 4.0 (CTCAE 4.0) must be used to grade the severity of adverse events. The investigator may attribute each toxicity event to preladenant alone, or to the combination of preladenant and pembrolizumab, and modify the dose according to Table 7 and Table 8 *(pembro dose mod table added to Section 5.2.3.2)*. If a dose modification for toxicity occurs with preladenant, the dose may not be re-escalated to the dose which preceded the dose modification. Dose modifications are always based on the previous cycle.

Reduction or 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. For example, in the combination arm (Arm 2), if preladenant is held due to an adverse event attributed to that drug, then pembrolizumab may continue to be administered. Appropriate documentation is required regarding which drug the investigator is attributing the adverse event to. If, in the opinion of the investigator, the toxicity is related to the combination of two agents, then both drugs should be held according to recommended dose modifications.

Subjects may have up to 2 dose modifications of preladenant throughout the course of the study, as described in Table 7. If further toxicity occurs or the criteria for resuming treatment are not met, the subject must be discontinued from the agent. If a subject experiences several toxicities and there are conflicting recommendations, follow the most conservative dose adjustment recommended (dose reduction appropriate to the most severe toxicity).

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

Table 7 Preladenant Dose Modification and Treatment Discontinuation Guidelines for Drug-Related Adverse Events

Toxicity	Hold Treatment	Criteria for Restarting Treatment	Dose/Schedule for Restarting Treatment	Criteria for Discontinuation after Consultation with Sponsor
Hematological toxicities:				
• Any Grade 1 hematological toxicity	No	N/A	N/A	N/A
• Any Grade 2 hematological toxicity, or Grade 3 toxicity that persists for ≤ 5 days	Per medical assessment of the Investigator	If treatment held, may be restarted when AE resolves back to baseline or to Grade 1.	Per medical assessment of the investigator: may decrease dose by one dose level.	If AE persists for 12 weeks without resolution following reduction in dose.
• Any Grade 3 hematologic toxicity that persists for > 5 days, or Grade 4 hematological toxicity • Febrile neutropenia • Grade 3 thrombocytopenia of any durations if associated with bleeding	Yes	Treatment may be restarted when AE resolves back to baseline or to Grade 1.	Decrease dose by one dose level.	If AE persists for 12 weeks without resolution following reduction in dosing schedule. Permanent discontinuation should be considered for any severe or life-threatening event
Non-hematological toxicities:				
• Toxicity	Hold Treatment	Criteria for Restarting Treatment	Dose/Schedule for Restarting Treatment	Criteria for Discontinuation after Consultation with Sponsor
• Any Grade 1 non-hematological toxicity • Grade 2 alopecia • Grade 2 fatigue	No	N/A	N/A	N/A
• Any Grade 2 non-hematological toxicity except Grade 2 alopecia and Grade 2 fatigue	Per medical assessment of the investigator	If treatment held, may be restarted when AE resolves back to baseline or to Grade 1.	Per medical assessment of the Investigator: may decrease dose by one dose level.	If AE persists for 12 weeks without resolution following reduction in dose.

Toxicity	Hold Treatment	Criteria for Restarting Treatment	Dose/Schedule for Restarting Treatment	Criteria for Discontinuation after Consultation with Sponsor
• Any Grade 3 or 4 non-hematological toxicity (not including laboratory, unless clinically significant medical intervention is required to treat the subject, or the abnormality leads to hospitalization, or the abnormality persists for >1 week)	Yes	Treatment may be restarted when AE resolves back to baseline or to Grade 1.	Decrease dose by one dose level.	If AE persists for 12 weeks without resolution following reduction in dose. Permanent discontinuation should be considered for any severe or life-threatening event

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

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

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

Dose reductions are not permitted during Cycle 1.

5.2.3.2 Pembrolizumab Withholding

AEs (both non-serious and serious) associated with pembrolizumab exposure may represent an immunologic etiology. These AEs may occur shortly after the first dose or several months after the last dose of treatment. Pembrolizumab must be withheld for drug-related toxicities and severe or life-threatening AEs as per Table 8. Pembrolizumab dose reductions are not permitted during the trial.

In addition, subjects should receive appropriate supportive care measures as deemed necessary by the treating investigator. Suggested supportive care measures, as described in Section 5.6.2, are also included in (Table 8).

Dosing interruptions are permitted after Cycle 1 in the case of medical/surgical events or logistical reasons not related to trial therapy (e.g., elective surgery, unrelated medical events, subject vacation, and/or holidays). Subjects should be placed back on trial therapy within 3 weeks of the scheduled interruption, unless otherwise discussed with the Sponsor. The reason for interruption should be documented in the subject's trial record.

Table 8 Dose Modification and Supportive Care Guidelines for Pembrolizumab for Drug-Related Adverse Events

	Dose Modification Guidelines			Supportive Care Guidelines	
Toxicity	**Hold Treatment for Grade**	**Timing for Restarting Treatment**	**Treatment Discontinuation**	**CTCAE v4.0 Grade**	**Action / Supportive Care Guidelines**
Diarrhea/Colitis	General Considerations across all Grades: Subjects should be carefully monitored for signs and symptoms of enterocolitis (ie, diarrhea, abdominal pain, blood or mucus in stool, with or without fever) and of bowel perforation (ie, peritoneal signs and ileus). 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.				
	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	2	• Monitor for enterocolitis and bowel perforation. Consider GI consultation and endoscopy. • Administer oral corticosteroids. • When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks.
	4	Permanently discontinue	Permanently discontinue	3-4	• Monitor for enterocolitis and bowel perforation. Consider GI consultation and endoscopy. • Treat with IV 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.
AST, ALT or Increased Bilirubin	2	Toxicity resolves to Grade 0-1	Toxicity does not resolve within 12 weeks of last dose	2	• Monitor liver function tests more frequently until returned to baseline values (consider weekly). • Treat with IV or oral corticosteroids.
	≥3	Permanently discontinue (see exception below)[a]	Permanently discontinue	3-4	• Treat with IV 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.

	Dose Modification Guidelines			Supportive Care Guidelines	
Toxicity	**Hold Treatment for Grade**	**Timing for Restarting Treatment**	**Treatment Discontinuation**	**CTCAE v4.0 Grade**	**Action / Supportive Care Guidelines**
Type 1 diabetes mellitus (if new onset) including diabetic ketoacidosis (DKA) or Hyperglycemia (≥Grade 3) if associated with ketosis (ketonuria) or metabolic acidosis (DKA)	T1DM or 3-4 hyper-glycemia	Hold pembrolizumab for new onset Type 1 diabetes mellitus or Grade 3-4 hyperglycemia associated with evidence of beta cell failure	Resume pembrolizumab when subjects are clinically and metabolically stable	T1DM or 3-4 hyper-glycemia	• Insulin replacement therapy is recommended for T1DM and for Grade 3-4 hyperglycemia associated with metabolic acidosis or ketonuria. • Evaluate subjects with serum glucose and a metabolic panel, urine ketones, glycosylated hemoglobin, and C-peptide.
Hypophysitis	2-4	Toxicity resolves to Grade 0-1. Therapy with pembrolizumab 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	2	• 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.
				3-4	• 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.
Hyperthyroidism	General Considerations across all Grades: Thyroid disorders can occur at any time during treatment. Monitor subjects for changes in thyroid function (at start of treatment, periodically during treatment and as indicated based on clinical evaluation) and for clinical signs and symptoms of thyroid disorders.				
				2	• In hyperthyroidism, non-selective beta-blockers (e.g. propranolol) are suggested as initial therapy.
	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	3-4	• 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.
	4	Permanently discontinue	Permanently discontinue		
Hypothyroidism		Therapy with pembrolizumab can be continued while thyroid replacement therapy is instituted	Therapy with pembrolizumab can be continued while thyroid replacement therapy is instituted	2-4	• Treat with thyroid hormone replacement therapy (levothyroxine or liothyroinine), as indicated per standard of care.

	Dose Modification Guidelines			Supportive Care Guidelines	
Toxicity	**Hold Treatment for Grade**	**Timing for Restarting Treatment**	**Treatment Discontinuation**	**CTCAE v4.0 Grade**	**Action / Supportive Care Guidelines**
Infusion Reaction	General Considerations across all Grades: Signs and symptoms usually develop during or shortly after drug infusion and generally resolve completely within 24 hours of completion of infusion.				
				1[d]:	• Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator. • No premedication at subsequent dosing.

	2[b]	Toxicity resolves to Grade 0-1		2[e]	• **Stop Infusion and monitor symptoms**.
					• Additional appropriate medical therapy may include, but is not limited to:
					  • IV fluids
					  • Antihistamines
					  • NSAIDS
					  • Acetaminophen
					  • Narcotics
					• Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator.
					• If symptoms resolve within 1 hour of stopping drug infusion, the infusion may be restarted at 50% of the original infusion rate (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.
					• Subject may be premedicated 1.5h (± 30 minutes) prior to infusion of pembrolizumab with:
					  • Diphenhydramine 50 mg PO (or equivalent dose of antihistamine).
					  • Acetaminophen 500-1000 mg PO (or equivalent dose of antipyretic).

	3-4	Permanently discontinue	Permanently discontinue	3[f] or 4[g]	• **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

	Dose Modification Guidelines			Supportive Care Guidelines	
Toxicity	**Hold Treatment for Grade**	**Timing for Restarting Treatment**	**Treatment Discontinuation**	**CTCAE v4.0 Grade**	**Action / Supportive Care Guidelines**
					opinion of the investigator. • Hospitalization may be indicated. • **Subject is permanently discontinued from further trial treatment administration.**
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	2	• 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.
	3-4 or Recurrent 2	Permanently discontinue	Permanently discontinue	3-4 or Recurrent 2	• Immediately treat with IV 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	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	2	• Treatment with corticosteroids. • When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks.
	3-4	Permanently discontinue	Permanently discontinue	3-4	• 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.
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		

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 subjects 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 subject should be discontinued.

[b] If symptoms resolve within 1 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.

[c] Subjects 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.

[d] Mild reaction; infusion interruption not indicated; intervention not indicated

[e] Requires infusion interruption but responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDS, narcotics, IV fluids); prophylactic medications indicated for < =24 hrs.

[f] Prolonged (ie, not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae (e.g., renal impairment, pulmonary infiltrates)

[g] Life-threatening; pressor or ventilatory support indicated

5.2.4 Timing of Dose Administration

All trial treatments will be administered on an outpatient basis.

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

Table 9 Treatment Schedule for Preladenant Monotherapy in each Arm for each Treatment Cycle

Treatment Arm 1 (Part 1)	**Day 1**		**Days 2 – 21**	
	am	**pm**	**am**	**pm**
Preladenant	X*	X	X	X
* The AM dose of preladenant on Day 1 of each cycle is witnessed at the site.				

Table 10 Treatment Schedule for Preladenant and Pembrolizumab in each Arm for each Treatment Cycle

Treatment Arm 2 (Part 1 and Part 2)	**Day 1**		**Days 2 – 21**	
	am	**pm**	**am**	**pm**
Preladenant	X*	X	X	X
Pembrolizumab	X			
* The AM dose of preladenant on Day 1 of each cycle is witnessed at the site.				

During the study (in Part 1 and Part 2, and in Arm 1 and Arm 2), starting on Day 1 of Cycle 1, preladenant will be administered orally BID (twice a day) approximately every 12 hours on each day of a 21-day treatment cycle. Preladenant may be administered up to 4 hours before or after the scheduled time for preladenant oral intake. All capsules comprising a dose should be taken within approximately 15 minutes (See Pharmacy Manual).

In Arm 2 (Part 1 and Part 2), on Day 1 of each 21-day cycle, after preladenant administration in the morning, pembrolizumab will be administered at a fixed dose of 200 mg as a 30-minute IV infusion.

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

Trial treatment of pembrolizumab may be administered up to three days before or after the scheduled Day 1 of each cycle due to administrative reasons (up to three days after treatment allocation is permitted).

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

5.2.5 Trial Blinding

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

5.3 Randomization or Treatment Allocation

Treatment allocation will occur centrally using an interactive voice response system / integrated web response system (IVRS/IWRS). There are 2 treatment arms. Subjects will be allocated to 1 of 2 treatment arms: preladenant monotherapy (Arm 1) or preladenant in combination with pembrolizumab (Arm 2) using an IVRS/IWRS in Part 1.

In Part 1 of the study, treatment will be allocated by non-random assignment. Enrollment into the preladenant + pembrolizumab combination treatment arm (Arm 2) will begin once all subjects complete 1 cycle of preladenant monotherapy in Arm 1 and complete the DLT evaluation, and a dose finding decision has been made. This ensures that the starting dose of preladenant in the combination arm will be at least 1 level below the dose being tested in the preladenant monotherapy arm. When both treatment arms are open for enrollment, IVRS/IWRS will alternate subject assignment between Arm 1 and Arm 2 starting with Arm 1. For example, once the 50 mg BID dose cohort of Arm 1 (preladenant monotherapy) and the 25 mg BID dose cohort of Arm 2 (preladenant + pembrolizumab) are open for enrollment, the first subject will be allocated to Arm 1, the second subject will be allocated to Arm 2, the third subject will be allocated to Arm 1, etc. Each new dose cohort will open for enrollment without delay once the 21-day DLT observation period of the previous dose cohort is completed and a dose escalation decision is made. When Part 2 is open for enrollment, IVRS/IWRS will assign subjects to one of two cohorts by tumor type.

Subjects participating in this trial will be allocated 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 Medications

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

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

Bisphosphonate or denosumab therapy is allowed as long as it is begun at least 2 weeks prior to treatment allocation.

5.5.2 Prohibited Concomitant Medications

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

- Antineoplastic systemic chemotherapy or biological therapy
- Immunotherapy not specified in this protocol (with the exception of denosumab as noted above in Section 5.5.1)
- Chemotherapy not specified in this protocol
- Investigational agents other than preladenant and pembrolizumab
- Radiation therapy
    - Note: Radiation therapy to a symptomatic solitary lesion or to the brain may be allowed at the Investigator's discretion.
- Live vaccines within 30 days prior to the first dose of trial treatment and while participating in the trial. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, chickenpox, yellow fever, rabies, BCG, and typhoid vaccine. Seasonal influenza vaccines for injection are generally killed virus vaccines and are allowed; however, intranasal influenza vaccines (e.g. FluMist®) are live attenuated vaccines and are not allowed.
- Systemic glucocorticoids for any purpose other than to modulate symptoms from an event of clinical interest of suspected immunologic etiology (see Section 5.5.2.2). The use of physiologic doses of corticosteroids may be approved after consultation with the Sponsor.
    - Note: Inhaled steroids are allowed for management of asthma.

Subjects who, in the assessment by the investigator, require the use of any of the aforementioned treatments for clinical management, should be removed from the trial. Subjects may receive other medications that the Investigator deems to be medically necessary. Section 5.1.3 - Subject Exclusion Criteria describes other medications that are prohibited in this trial.

5.5.2.1 Prohibited Concomitant Medications for Preladenant

Specific restrictions for preladenant administration (Arm 1 and Arm 2) during the course of the trial are listed. These are based on the current known metabolism of the drugs as described. Restrictions may be removed if indicated by emergent data from drug-drug interaction trials. Any medications/therapies no longer contraindicated will be communicated

to the site by an administrative letter. The following medications/therapies are not permitted from 2 weeks prior to Day 1 through 2 weeks after the study treatment period.

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

- Inhibitors/inducers/substrates of CYP3A4 and substrates for CYP2C8 enzymes.

Preladenant is a competitive and irreversible metabolism-dependent inhibitor of cytochrome P450 (CYP) 3A4, a substrate of CYP3A4, and a direct competitive inhibitor of CYP2C8. As such, concomitant use of other drugs that are identified in Table 11 as strong inducers, strong or moderate inhibitors, or substrates (characterized with a narrow therapeutic range) of CYP3A4 or CYP2C8, is prohibited while the subject is enrolled in this study.

If the use of a CYP3A4 or CYP2C8 medication listed in Table 11 is medically necessary, and an alternate therapeutic agent is not available, then the subject must discontinue treatment with preladenant.

Preladenant may potentially inhibit the activity of other CYP3A4 or CYP2C8 substrates that are not identified as prohibited in Table 11. Caution and close drug monitoring is strongly advised when preladenant is administered concomitantly with other CYP3A4 or CYP2C8 substrates. See Table 11 for more detailed information regarding adverse effects of CYP3A4 substrates with a narrow therapeutic range.

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

CYP3A4 inhibitors/inducers/substrates are listed below. The subject must not take the treatments listed in Table 11 during the trial after the start of the study treatment. Since this list is not comprehensive, the investigator should use his/her medical judgment when a subject presents with a medication not on the list or call the Sponsor Clinical Director for clarification.

Table 11 Medications, Supplements, and Other Substances Prohibited During the Trial

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

CYP = cytochrome P450.

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

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

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

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

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

- Proton-pump inhibitors

The subject must not take proton-pump inhibitors (PPI) during the trial from 5 days before the start of the study treatment to 5 days following the last administration of preladenant. The investigator should use his/her medical judgment when a subject presents with a PPI treatment or call the Sponsor Clinical Director for clarification.

Of note, antacids, such as calcium carbonate or aluminum hydroxide-based product, will be allowed during the study, and are recommended to be taken either 4 hours before or after dosing of preladenant.

5.5.2.2 Prohibited Concomitant Medications for Pembrolizumab

Systemic glucocorticoids > 10 mg for any purpose other than to modulate symptoms from an adverse event are not allowed. However, the use of physiologic doses of corticosteroids may be approved after consultation with the Sponsor:

- Inhaled steroids as part of a stable regimen for the treatment of asthma/chronic obstructive pulmonary disease [COPD] are permitted.
- Use of physiologic doses of corticosteroids (≤10 mg daily of prednisone equivalent) as replacement therapy for endocrinopathies may be approved after consultation with the Sponsor.
- Non-immune suppressing doses of steroids in patients with stable CNS metastases may be approved after consultation with the Sponsor.
- Additionally, a short limited course of steroids may be used to treat medical conditions and/or adverse events during the study after sponsor notification and consultation.
- Use of prophylactic corticosteroids to avoid allergic reactions (e.g. IV contrast dye) is permitted.
- Use of non-systemic steroids is permitted.

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

There are no prohibited therapies during the Post-Treatment Follow-up Phase**.**

5.6 Rescue Medications & Supportive Care

5.6.1 Supportive Care Guidelines for Preladenant

Medications required to treat AEs or concurrent illnesses other than those prohibited in Table 11 are allowed during the study. Contraceptive medications as described in Section 5.1 are allowed.

Bisphosphonates are allowed for subjects with lytic bone metastases.

Antiemetics, including serotonin-receptor antagonists, metoclopramide, prochlorperazine, or thiethylperazine are allowed. Aprepitant is a CYP3A4 inhibitor and should not be used in the study.

Asymptomatic increases in liver enzymes have been noted in human subjects receiving preladenant. Liver function will be monitored throughout the clinical study as recommended by the FDA Guidance for Industry Drug-Induced Liver Injury: Premarketing Clinical Evaluation [21].

Administration of preladenant to healthy volunteers and subjects with Parkinson's disease have been associated with transient non-dose-related increases in systolic and diastolic BP. Blood Pressure monitoring will be conducted during the clinical study as appropriate to further evaluate these changes and to support subject safety. Acute and symptomatic rises in BP should be treated according to the standard of care.

Every medication taken by the subject during the trial and the reason for use must be recorded in the eCRF. Note that the use of any concomitant medication must relate to the documented medical history, prophylaxis, or an adverse event of the subject. Subjects will be permitted to receive appropriate supportive care measures as deemed necessary by the treating physician.

Please refer to preladenant investigator brochure (IB) for detailed information.

5.6.2 Supportive Care Guidelines for Pembrolizumab

Subjects should receive appropriate supportive care measures as deemed necessary by the treating investigator. Suggested supportive care measures for the management of adverse events with potential immunologic etiology are outlined along with the dose modification guidelines in Section 5.2.3.2, Table 8. 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 pembrolizumab.

Note: If after the evaluation the event, it is determined not to be related, the Investigator does not need to follow the treatment guidance. Refer to Table 8, Section 5.2.3.2 for guidelines regarding dose modification and supportive care.

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

Please refer to pembrolizumab IB for detailed information.

5.7 Diet/Activity/Other Considerations

5.7.1 Diet

Foods that are CYP3A inhibitors must not be consumed during the study. Grapefruit and star fruit are known to be CYP3A inhibitors, and should not be consumed for 2 weeks before the first dose of preladenant and for the entire duration of the study. Consumption of CYP3A4 inhibitors, such as grapefruit juice, may significantly increase the levels of preladenant and cause increased toxicity. St. John's Wort is a CYP3A inducer, and the consumption of St. John's Wort or products containing St. John's Wort may reduce the levels of preladenant. A partial list of CYP3A inhibitors is provided in Section 5.5.2.1.

5.7.2 Contraception

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

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).

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

- 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

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

OR

- 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 treatment and for 120 days after the last dose. Subjects must comply with one of the following:

- practice abstinence from heterosexual activity.

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

OR

- 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

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

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

5.7.3 Pregnancy

If a subject inadvertently becomes pregnant while on treatment with preladenant and/or pembrolizumab, the subject will be immediately discontinued from study treatment. The site will contact the subject at least monthly and document the subject's status until the pregnancy has been completed or terminated. The outcome of the pregnancy will be reported to the Sponsor without delay and within 24 hours if the outcome is a serious adverse reaction (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 must be reported to the Sponsor and followed as described in Section 7.2.

5.7.4 Use in Nursing Women

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

5.8 Subject Withdrawal/Discontinuation Criteria

5.8.1 Discontinuation of Treatment

Discontinuation of treatment does not represent withdrawal from the trial.

As certain data on clinical events beyond treatment discontinuation may be important to the study, they must be collected through the subject's last scheduled follow-up, even if the subject has discontinued treatment. Therefore, all subjects who discontinue trial treatment prior to completion of the treatment period will still continue to participate in the trial as specified in Section 6.0 - Trial Flow Chart and Section 7.1.5. – Visit Requirements .

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

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

- The subject or subject's legally acceptable representative requests to discontinue treatment.
- Non-compliance with trial treatment or procedure requirements.
- A confirmed positive serum pregnancy test.
- Confirmed radiographic disease progression outlined in Section 7.1.5 (exception if the Sponsor approves treatment continuation).
    - A subject with confirmed radiologic progression may continue to receive study treatment, after consultation with the Sponsor, if the investigator deems the subject is receiving clinical benefit or value from treatment.
- Unacceptable adverse experiences as described in Section 7.2.
- Intercurrent illness other than another malignancy as noted above that prevents further administration of treatment.
- Investigator's decision to discontinue treatment.
- Recurrent Grade 2 pneumonitis.
- Progression or recurrence of any malignancy, or any occurrence of another malignancy that requires active treatment.
- Completion of 35 treatments with preladenant and/or pembrolizumab.

    Note: 35 cycles (approximately. 2 years) are calculated from the first dose

- Administrative reasons.

For subjects who are discontinued from treatment but continue to be monitored in the trial, all visits and procedures, as outlined in the trial flowchart, should be completed.

Subjects who discontinue preladenant in the monotherapy arm due to disease progression may at the Investigator's discretion and after consultation with the Sponsor, cross-over to combination treatment. The subject will receive the dose of preladenant that has been determined to be safe in the combination arm (e.g., 1 dose level below the dose being tested) at the time of treatment cross-over. The preladenant dose will not exceed the dose the subject received in the monotherapy arm. The first dose of combination treatment will not occur until the 21-day Cycle 1 of preladenant monotherapy treatment finishes.

Specific details regarding procedures to be performed are provided in the Arm 2 Study Flowchart in Section 6.0.

For subjects who are discontinued from treatment but continue to be monitored in the trial, all visits and procedures, as outlined in the trial flowchart, should be completed.

5.8.2 Withdrawal from the Trial

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

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

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

5.9 Subject Replacement Strategy

In order to adequately evaluate the safety of the doses administered in this study, all subjects enrolled must meet the criteria for evaluability for Cycle 1. Subjects are considered non-evaluable and will be replaced if:

- They are allocated 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 pembrolizumab infusion in Cycle 1 (e.g., if the infusion had to be discontinued due to an infusion reaction) and did not experience a DLT

Subjects who are not evaluable will be replaced unless accrual to the cohort has stopped. Non-evaluable subjects will not be counted toward the total number of subjects in the cohort 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.

A subject who discontinues from trial treatment or withdraws from the trial during or after Cycle 2 (See Section 5.2.2.1 for subject replacement during Cycle 1) will not be replaced.

5.10 Beginning and End of the Trial

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

5.11 Clinical Criteria for Early Trial Termination

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

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

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

6.0 TRIAL FLOW CHART

6.1 Flowchart

Preladenant in Monotherapy (Arm 1 ; Part 1)												
		Treatment Phase						**Tumor Assessment**	**End of Treatment**	**Post-treatment Follow-Up Phase**		
	Screening	Cycle 1			Cycle 2-4		Cycles 5 and all Subsequent Cycles	Every 9 weeks	Discontinuation	Safety Follow-up		Survival Follow-Up[11]
	Up to 28 days Prior to Day 1 Cycle 1	Day 1	Day 8	Day 15	Day 1	Day 15	Day 1		At Treatment Discontinuation	30 days after the last dose	90 days after the last dose	Every 12 weeks post discontinuation
Scheduling Window (Days) [1]	-28 to -1	+3	±3	±3	±3	±3	±3	±7		+7	+7	±7
Administrative Procedures												
Informed Consent [2]	X											
Informed Consent for Optional Future Biomedical Research [2, 24]	X											
Inclusion/Exclusion Criteria[2]	X											
Subject Identification Card [3]	X											
Medical History [2]	X											
Prior Oncology Treatment History [2]	X											
Prior Medications [2, 4]	X											
Concomitant Medications [2, 4]	X	X	X	X	X	X	X		X	X		
Clinic Procedures/Assessments												
Physical Examination[5]	X	X			X		X		X[5]	X		
12-Lead Electrocardiogram [5, 6]	X											
Vital Signs [5, 7]	X	X	X	X	X		X		X	X		
ECOG Performance Status [5]	X	X			X		X		X	X		
Dispense preladenant [8]		X			X		X					
Adverse Events Reporting [9]	X	X	X	X	X	X	X		X	X	X	

Preladenant in Monotherapy (Arm 1 ; Part 1)												
		Treatment Phase						**Tumor Assessment**	**End of Treatment**	**Post-treatment Follow-Up Phase**		
	Screening	Cycle 1			Cycle 2-4		Cycles 5 and all Subsequent Cycles	Every 9 weeks	Discontinuation	Safety Follow-up		Survival Follow-Up[11]
	Up to 28 days Prior to Day 1 Cycle 1	Day 1	Day 8	Day 15	Day 1	Day 15	Day 1		At Treatment Discontinuation	30 days after the last dose	90 days after the last dose	Every 12 weeks post discontinuation
Scheduling Window (Days) [1]	-28 to -1	+3	±3	±3	±3	±3	±3	±7		+7	+7	±7
Tumor Imaging and RECIST 1.1 Response Assessment [10]	X							X	X			
Survival Status [11]												X
Laboratory Procedures/Assessments												
Archival or Newly Obtained Tumor Tissue Collection for Biomarker Analysis and Molecular Profiling [12]	X											
Blood for Genetic Analyses [13]		X										
Hematology [5, 14]	X	X	X	X	X	X	X		X	X		
Blood for RNA Analyses[15]		X			X		X		X			
Blood for Stimulation Assay[16]		X			X							
PBMC for Biomarker Analysis[17]	X			X[17]		X[17]						
Serum for Cytokine Analysis [18]		X			X		X					
Plasma Collection for Proteomic Analysis [19]		X	X	X	X		X					
Urinalysis [5, 20]	X											
Chemistry [5, 21]	X	X	X	X	X	X	X		X	X		

Preladenant in Monotherapy (Arm 1 ; Part 1)												
		Treatment Phase						**Tumor Assessment**	**End of Treatment**	**Post-treatment Follow-Up Phase**		
	Screening	Cycle 1			Cycle 2-4		Cycles 5 and all Subsequent Cycles	Every 9 weeks	Discontinuation	Safety Follow-up		Survival Follow-Up[11]
	Up to 28 days Prior to Day 1 Cycle 1	Day 1	Day 8	Day 15	Day 1	Day 15	Day 1		At Treatment Discontinuation	30 days after the last dose	90 days after the last dose	Every 12 weeks post discontinuation
Scheduling Window (Days) [1]	-28 to -1	+3	±3	±3	±3	±3	±3	±7		+7	+7	±7
Prothrombin Time (PT)/International Normalized Ratio (INR) and Activated Partial Thromboplastin Time (aPTT)[22]	X											
Serum or Urine Pregnancy Test – if applicable [23]	X	X										
On-treatment Tumor Biopsy [24]						X						
Pharmacokinetics Evaluations												
Blood for preladenant PK assay [25]		X	X	X	X		X					

AE = adverse event; ALT = alanine aminotransferase; AST = aspartate aminotransferase; BUN = blood urea nitrogen; CR = complete response; CT = computed tomography; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; min = minute; PGt = pharmacogenetic; PK = pharmacokinetic; PR = interval between the P wave and the QRS wave; QRS = interval from onset of the Q wave to end of the S wave; QT = interval from onset of the QRS complex to end of the T-wave; QTcF = QT interval corrected for heart rate; SAE = serious adverse event; SGOT = serum glutamic oxaloacetic transaminase; SGPT = serum glutamic pyruvic transaminase.

1. Visits should occur within the prespecified days window (e.g. +/- 3d).
2. Screening procedures to be performed within 28 days prior Cycle 1 Day1 (C1D1), unless otherwise noted. Informed consent may be obtained more than 28 days prior to C1D1 to allow for tumor tissue collection pre-treatment.
3. Subject Identification Card must be given to Subject at the start of study and must be collected when the Subject is no longer participating in any portion of the study.
4. Record medications taken 28 days prior to C1D1 and all medications taken up to and including 30 days after the last dose of study drug or the End-of-Treatment (whichever is later). Refer to Inclusion/Exclusion criteria for prohibited medications and washout periods.
5. Must be performed within 3 days prior to Day 1 of each cycle unless otherwise noted to coincide with the clinical and laboratory procedures. Physical examination, ECOG Performance Status, ECG, Vital Signs must be performed within 3 days prior to C1D1. It is not necessary to repeat C1D1 testing if the Screening testing was performed within 3 days prior to C1D1. Full Physical Examination will be performed at the Screening Visit and at the Treatment Discontinuation Visit. Directed Physical Examination will be done at all other visits.
6. Perform standard 12-lead ECG reporting ventricular rate, PR and QRS duration and QT/QTcF intervals prior to any blood collections or other study procedures.
7. Vital signs include blood pressure, pulse rate, and respiratory rate while sitting; temperature, height (at screening only), and weight.
8. After Cycle 1, preladenant may be dispensed up to 3 days prior to the cycle start to coincide with the physical exam. Study drug may only be dispensed after the treating physician has confirmed the subject will continue on to the next cycle. Each cycle is 21 days. Subjects may receive treatment for up to 35 cycles.
9. Adverse events and serious adverse events will be recorded from the time of treatment allocation. All adverse events and serious adverse events that occur after the consent form is signed but before treatment allocation must be reported by the Investigator if they cause the subject to be excluded from the trial, or are the result of a protocol-specified intervention, including but not limited to washout or discontinuation of usual therapy or a study procedure. After treatment discontinuation, each subject will be followed for 90 days for adverse event and serious adverse event monitoring, 30 days if the subject initiates new anticancer therapy less than 30 days after study treatment discontinuation, or the day new anticancer therapy is initiated if between 30 days and 90 days after study treatment discontinuation. Subjects with an ongoing AE of Grade >1 at the time of treatment discontinuation will be followed until resolution of the AE to Grade 0-1, until considered stable by the treating physician, or until beginning a new anticancer therapy, whichever occurs first.
10. Baseline radiology images by CT (or MRI) of chest, abdomen, and pelvis, and all known tumor sites (if evaluable by imaging) must be obtained within 28 days prior to C1D1 and must be repeated every 9 weeks (±7 days) from C1D1 (See SIM). Imaging must be obtained at the End of Treatment visit at discontinuation unless done within the previous 4 weeks. Images are to be submitted to the central imaging vendor for potential future central analysis.
11. After confirmed disease progression subjects will be contacted by telephone every 12 weeks for survival until withdrawal of consent to participate in the study, becoming lost to follow-up, death, or end of the study, whichever occurs first.
12. Tumor tissue (archival or newly obtained biopsy) will be required at Screening upon signing the informed consent for the study. This sample will be assessed to collect information on biomarkers for all subjects enrolled in the study. Tumor tissue will be sent to central laboratory for biomarker analysis and leftover tissue may be saved for future biomedical research (FBR) if the subject signs the FBR consent.
13. This blood sample will be drawn for planned analysis of the association between genetic variants in DNA and drug response. If the IRB/IEC does not approve of the planned analysis of the association between DNA variation and drug response, or if there is a local law or regulation prohibiting the same, data analysis will be limited. Leftover extracted DNA will be stored for future biomedical research if the subject signs the FBR consent.
14. Hematology tests include complete blood count with 5-part differential and platelets. Hematology does not need to be repeated on C1D1 if Screening samples were obtained within 3 days of C1D1.
15. Blood sample for RNA analysis should be obtained predose of administration of preladenant on Day 1 of Cycle 1, Cycle 2, Cycle 5 and at the Treatment Discontinuation Visit. Leftover extracted RNA will be stored for future biomedical research if the subject signs the FBR consent.
16. Procedures for collection of PD samples and precise time points are described in the Procedures Manual. Blood sample for Stimulation Assay should be obtained predose, 2hr and 4hr post-dose of administration of preladenant on Day1 of Cycle 1 and Cycle 2.
17. Procedures for collection of PD samples and precise time points are described in the Procedures Manual. PBMC samples for Biomarker Analysis should be obtained at screening, and predose of administration of preladenant on Day 15 of Cycle 1, Cycle 2 and Cycle 3.

18. Procedures for collection of PD samples and precise time points are described in the Procedures Manual. Serum Sample for cytokine analysis should be obtained at predose of administration of preladenant on Day 1 of each cycle for all treatment cycles.
19. Procedures for collection of PD samples and precise time points are described in the Procedures Manual. Plasma Collection for Proteomic Analysis should be obtained at each time point when preladenant PK samples are collected. Samples need to be obtained at pre-dose, 1 hour, 2 hours, 4 hours and 8 hours after drug administration of preladenant (+/- 10 minutes) on Day 1 of Cycle 1 and Cycle 2; Prior to dosing on Cycle 1 Day 8; Prior to dosing on Cycle 1 Day 15; Prior to dosing on Cycle 4 Day 1; And, Prior to dosing on Cycle 8 Day 1. If the sample day falls on a weekend or a holiday, please consult the Sponsor for alternate sample collection times.
20. Urine dipstick or microscopic urinalysis may be performed according to site SOP. Urine dipstick includes pH, protein, glucose, leukocyte-esterase, ketones, and nitrite. Mandatory microscopic urinalysis will be performed if the dipstick results are abnormal. Microscopic analysis includes white blood cell count, red blood cell count, epithelial cells and casts.
21. Serum Chemistry tests include sodium, potassium, calcium, phosphate, chloride, bicarbonate/CO2 (if performed in region), BUN or Urea , creatinine (Cystatin C if abnormal), SGOT (AST), SGPT (ALT), total proteins, total bilirubin (direct bilirubin if abnormal), albumin, alkaline phosphatase, glucose, uric acid, amylase, lipase, Lactate Dehydrogenase (LDH) and γ-glutamyltransferase (GGT). Serum chemistry does not need to be repeated on C1D1 if screening samples were obtained within 3 days of C1D1.
22. Coagulation factors (PT/INR and aPTT) should be tested as part of the screening procedures for all subjects. Furthermore, any subject receiving anticoagulant therapy should have coagulation factors monitored closely throughout the trial.
23. For women of reproductive potential, a urine pregnancy test will be performed at Screening and within 72 hours prior to the first dose of study treatment. If a urine pregnancy test cannot be confirmed as negative, a serum pregnancy test is required and should be negative. Additional pregnancy testing should be conducted as per local regulations where applicable.
24. On-treatment tumor biopsy will be performed on Day 15 of Cycle 2 (+/- 7 Days). Tumor tissue will be sent to designated laboratory for biomarker analysis and leftover tissue may be saved for future biomedical research if the subject signs the FBR consent.
25. Procedures for collection of PK samples and precise time points are described in the Procedures Manual. Samples for preladenant and its metabolites pharmacokinetic (PK) testing should be collected prior to dosing, and 1 hour, 2 hours, 4 hours and 8 hours after drug administration of preladenant (+/- 10 minutes) on Cycle 1 Day 1 and Cycle 2 Day 1; Prior to dosing on Cycle 1 Day 8; Prior to dosing on Cycle 1 Day 15; Prior to dosing on Cycle 4 Day 1; And, Prior to dosing on Cycle 8 Day 1. If the sample day falls on a weekend or a holiday, please consult the Sponsor for alternate sample collection times.

Preladenant in Combination with Pembrolizumab (Arm 2 ; Part 1 and Part 2) and (cross-over subjects)												
		Treatment Phase						**Tumor Assessment**	**End of Treatment**	**Post-treatment Follow-Up Phase** [9]		
	Screening	Cycle 1			Cycle 2-4		Cycles 5 and all Subsequent Cycles	Every 9 weeks	Discontinuation	Safety Follow-up		Survival Follow-Up[12]
	Up to 28 days Prior to Day 1 Cycle 1	Day 1	Day 8	Day 15	Day 1	Day 15	Day 1		At Treatment Discontinuation	30 days after the last dose	90 days after the last dose	Every 12 weeks post discontinuation
Scheduling Window (Days) [1]	-28 to -1	+3	±3	±3	±3	±3	±3	±7		+7	+7	±7
Administrative Procedures												
Informed Consent [2]	X											
Informed Consent for Optional Future Biomedical Research [2, 27]	X											
Inclusion/Exclusion Criteria[2]	X											
Subject Identification Card [3]	X											
Medical History [2]	X											
Prior Oncology Treatment History [2]	X											
Prior Medications [2, 4]	X											
Concomitant Medications [2, 4]	X	X	X	X	X	X	X		X	X		
Clinic Procedures/Assessments												
Physical Examination[5]	X	X			X		X		X[5]	X		
12-Lead Electrocardiogram [5, 6]	X											
Vital Signs [5, 7]	X	X	X	X	X		X		X	X		
ECOG Performance Status [5]	X	X			X		X		X	X		
Dispense Preladenant [8]		X			X		X					
Pembrolizumab infusion[9]		X			X		X					
Adverse Events Reporting [10]	X	X	X	X	X	X	X		X	X	X	

Preladenant in Combination with Pembrolizumab (Arm 2 ; Part 1 and Part 2) and (cross-over subjects)												
		Treatment Phase						**Tumor Assessment**	**End of Treatment**	**Post-treatment Follow-Up Phase** [9]		
	Screening	Cycle 1			Cycle 2-4		Cycles 5 and all Subsequent Cycles	Every 9 weeks	Discontinuation	Safety Follow-up		Survival Follow-Up[12]
	Up to 28 days Prior to Day 1 Cycle 1	Day 1	Day 8	Day 15	Day 1	Day 15	Day 1		At Treatment Discontinuation	30 days after the last dose	90 days after the last dose	Every 12 weeks post discontinuation
Scheduling Window (Days) [1]	-28 to -1	+3	±3	±3	±3	±3	±3	±7		+7	+7	±7
Tumor Imaging and RECIST 1.1 Response Assessment [11]	X							X	X			
Survival Status [12]												X
Laboratory Procedures/Assessments												
Archival or Newly Obtained Tumor Tissue Collection for Biomarker Analysis and Molecular Profiling [13]	X											
Blood for Genetic Analyses [14]		X										
Hematology [5, 15]	X	X	X	X	X	X	X		X	X		
Blood for RNA Analyses[16]		X			X		X		X			
Blood for Stimulation Assay[17]		X			X							
PBMC for Biomarker Analysis[18]	X			X[18]		X[18]						
Serum for Cytokine Analysis [19]		X			X		X					
Plasma Collection for Proteomic Analysis [20]		X	X	X	X		X					
Urinalysis [5, 21]	X											
Chemistry [5, 22]	X	X	X	X	X	X	X		X	X		

Preladenant in Combination with Pembrolizumab (Arm 2 ; Part 1 and Part 2) and (cross-over subjects)												
		Treatment Phase						**Tumor Assessment**	**End of Treatment**	**Post-treatment Follow-Up Phase** [9]		
	Screening	Cycle 1			Cycle 2-4		Cycles 5 and all Subsequent Cycles	Every 9 weeks	Discontinuation	Safety Follow-up		Survival Follow-Up[12]
	Up to 28 days Prior to Day 1 Cycle 1	Day 1	Day 8	Day 15	Day 1	Day 15	Day 1		At Treatment Discontinuation	30 days after the last dose	90 days after the last dose	Every 12 weeks post discontinuation
Scheduling Window (Days) [1]	-28 to -1	+3	±3	±3	±3	±3	±3	±7		+7	+7	±7
Prothrombin Time (PT)/International Normalized Ratio (INR) and Activated Partial Thromboplastin Time (aPTT)[23]	X											
Serum or Urine Pregnancy Test – if applicable [24]	X	X										
Thyroid Function (T3 or FT3, FT4 and TSH) [25]	X	X			X		X		X	X		
Anti-pembrolizumab Antibodies [26]		X			X		X			X		
On-treatment Tumor Biopsy [27]						X						
Pharmacokinetics Evaluations												
Blood for Preladenant PK assay [28]		X	X	X	X		X					
Blood for Pembrolizumab PK assay [29]		X			X		X			X		

AE = adverse event; ALT = alanine aminotransferase; AST = aspartate aminotransferase; BUN = blood urea nitrogen; CR = complete response; CT = computed tomography; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; min = minute; PGt = pharmacogenetic; PK = pharmacokinetic; PR = interval between the P wave and the QRS wave; QRS = interval from onset of the Q wave to end of the S wave; QT = interval from onset of the QRS complex to end of the T-wave; QTcF = QT interval corrected for heart rate; SAE = serious adverse event; SGOT = serum glutamic oxaloacetic transaminase; SGPT = serum glutamic pyruvic transaminase.

1 Visits should occur within the prespecified days window (e.g. +/- 3d).

2. Screening procedures to be performed within 28 days prior Cycle 1 Day1 (C1D1), unless otherwise noted. Informed consent may be obtained more than 28 days prior to C1D1 to allow for tumor tissue collection pre-treatment.

3. Subject Identification Card must be given to Subject at the start of study and must be collected when the Subject is no longer participating in any portion of the study.

4. Record medications taken 28 days prior to C1D1 and all medications taken up to and including 30 days after the last dose of study drug or the End-of-Treatment (whichever is later). Refer to Inclusion/Exclusion criteria for prohibited medications and washout periods.

5. Must be performed within 3 days prior to Day 1 of each cycle unless otherwise noted to coincide with the clinical and laboratory procedures. Physical examination, ECOG Performance Status, ECG, Vital Signs must be performed within 3 days prior to C1D1. It is not necessary to repeat C1D1 testing if the Screening testing was performed within 3 days prior to C1D1. Full Physical Examination will be performed at the Screening Visit and at the Treatment Discontinuation Visit. Directed Physical Examination will be done at all other visits..

6. Perform standard 12-lead ECG reporting ventricular rate, PR and QRS duration and QT/QTcF intervals prior to any blood collections or other study procedures.

7. Vital signs include blood pressure, pulse rate, and respiratory rate while sitting; temperature, height (at screening only), and weight.

8. After Cycle 1, Preladenant may be dispensed up to 3 days prior to the cycle start to coincide with the physical exam. Study drug may only be dispensed after the treating physician has confirmed the subject will continue on to the next cycle. Each cycle is 21 days. Subjects may receive treatment for up to 35 cycles.

9. Pembrolizumab will be administered via IV infusion on Day 1 of each cycle. See Table 6 for dosing instructions. Each cycle is 21 days. Subjects may receive treatment for up to 35 cycles.

10. Adverse events and serious adverse events will be recorded from the time of treatment allocation. All adverse events and serious adverse events that occur after the consent form is signed but before treatment allocation must be reported by the Investigator if they cause the subject to be excluded from the trial, or are the result of a protocol-specified intervention, including but not limited to washout or discontinuation of usual therapy or a study procedure. After treatment discontinuation, each subject will be followed for 90 days for adverse event and serious adverse event monitoring, 30 days if the subject initiates new anticancer therapy less than 30 days after study treatment discontinuation, or the day new anticancer therapy is initiated if between 30 days and 90 days after study treatment discontinuation. Subjects with an ongoing AE of Grade >1 at the time of treatment discontinuation will be followed until resolution of the AE to Grade 0-1, until considered stable by the treating physician, or until beginning a new anticancer therapy, whichever occurs first.

11. Baseline radiology images by CT (or MRI) of chest, abdomen, and pelvis, and all known tumor sites (if evaluable by imaging) must be obtained within 28 days prior to C1D1 and must be repeated every 9 weeks (±7 days) from C1D1. Confirmatory imaging are required for all responses (CR and PR) seen by imaging at the study site should be obtained at least 4-5 weeks after the documented response. Imaging must be obtained at the End of Treatment visit at discontinuation unless done within the previous 4 weeks. Images are to be submitted to the central imaging vendor for potential future central analysis.

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

13. Tumor tissue (archival or newly obtained biopsy) will be required at Screening upon signing the informed consent for the study. This sample will be assessed to collect information on biomarkers for all subjects enrolled in the study. Tumor tissue will be sent to central laboratory for biomarker analysis and leftover tissue may be saved for future biomedical research (FBR) if the subject signs the FBR consent.

14. This blood sample will be drawn for planned analysis of the association between genetic variants in DNA and drug response. If the IRB/IEC does not approve of the planned analysis of the association between DNA variation and drug response, or if there is a local law or regulation prohibiting the same, data analysis will be limited. Leftover extracted DNA will be stored for future biomedical research if the subject signs the FBR consent.

15. Hematology tests include complete blood count with 5-part differential and platelets. Hematology does not need to be repeated on C1D1 if Screening samples were obtained within 3 days of C1D1.

16. Blood sample for RNA analysis should be obtained predose of administration of preladenant on Day 1 of Cycle 1, Cycle 2, Cycle 5 and at the Treatment Discontinuation Visit. Leftover extracted RNA will be stored for future biomedical research if the subject signs the FBR consent.

17. Procedures for collection of PD samples and precise time points are described in the Procedures Manual. Blood sample for Stimulation Assay should be obtained predose, 2hr and 4hr post-dose of administration of preladenant on Day1 of Cycle 1 and Cycle 2.
18. Procedures for collection of PD samples and precise time points are described in the Procedures Manual. PBMC samples for Biomarker Analysis should be obtained at screening, and predose of administration of preladenant on Day 15 of Cycle 1, Cycle 2 and Cycle 3.
19. Procedures for collection of PD samples and precise time points are described in the Procedures Manual. Serum Sample for cytokine analysis should be obtained at predose of administration of preladenant on Day 1 of each cycle for all treatment cycles.
20. Procedures for collection of PD samples and precise time points are described in the Procedures Manual. Plasma Collection for Proteomic Analysis should be obtained at each time point when preladenant PK samples are collected. Samples need to be obtained at pre-dose, 1 hour, 2 hours, 4 hours and 8 hours after drug administration of preladenant (+/- 10 minutes) on Day 1 of Cycle 1 and Cycle 2; Prior to dosing on Cycle 1 Day 8; Prior to dosing on Cycle 1 Day 15; Prior to dosing on Cycle 4 Day 1; And, Prior to dosing on Cycle 8 Day 1. If the sample day falls on a weekend or a holiday, please consult the Sponsor for alternate sample collection times.
21. Urine dipstick or microscopic urinalysis may be performed according to site SOP. Urine dipstick includes pH, protein, glucose, leukocyte-esterase, ketones, and nitrite. Mandatory microscopic urinalysis will be performed if the dipstick results are abnormal. Microscopic analysis includes white blood cell count, red blood cell count, epithelial cells and casts.
22. Serum Chemistry tests include sodium, potassium, calcium, phosphate, chloride, bicarbonate/CO2 (if performed in region), BUN or Urea, creatinine (Cystatin C if abnormal), SGOT (AST), SGPT (ALT), total proteins, total bilirubin (direct bilirubin if abnormal), albumin, alkaline phosphatase, glucose, uric acid, amylase, lipase, Lactate Dehydrogenase (LDH) and γ-glutamyltransferase (GGT). Serum chemistry does not need to be repeated on C1D1 if screening samples were obtained within 3 days of C1D1.
23. Coagulation factors (PT/INR and aPTT) should be tested as part of the screening procedures for all subjects. Furthermore, any subject receiving anticoagulant therapy should have coagulation factors monitored closely throughout the trial.
24. For women of reproductive potential, a urine pregnancy test will be performed at Screening and within 72 hours prior to the first dose of study treatment. If a urine pregnancy test cannot be confirmed as negative, a serum pregnancy test is required and should be negative. Additional pregnancy testing should be conducted as per local regulations where applicable.
25. Samples for thyroid function testing should be collected at screening, on Day 1 of Cycle 1 and on Day 1 of Cycle 2. Following Cycle 2, testing will be performed on Day 1 of every other cycle (i.e. Cycles 1, 2, 4, 6, etc.), at discontinuation, and at the 30 days Safety Follow-up Visit. Analysis of T3 or FT3, FT4 and TSH will be performed by the local study site laboratory (or by central vendor if testing is not available at the local study site laboratory).
26. ADA samples for pembrolizumab will be collected within 24 hours before infusion in cycles 1, 2, 4, 8 and every 4 cycles thereafter, 30 days after discontinuation of study drug (or until the subject starts new anti-cancer therapy). Please refer to the procedure manual for detailed sampling timepoints.
27. On-treatment tumor biopsy will be performed on Day 15 of Cycle 2 (+/- 7 Days). Tumor tissue will be sent to designated l laboratory for biomarker analysis and leftover tissue may be saved for future biomedical research if the subject signs the FBR consent.
28. Procedures for collection of PK samples and precise time points are described in the Procedures Manual. Samples for preladenant and its metabolites pharmacokinetic (PK) testing should be collected prior to dosing, and 1 hour, 2 hours, 4 hours and 8 hours after drug administration of preladenant (+/- 10 minutes) on Cycle 1 Day 1 and Cycle 2 Day 1; Prior to dosing on Cycle 1 Day 8; Prior to dosing on Cycle 1 Day 15; Prior to dosing on Cycle 4 Day 1; And, prior to dosing on Cycle 8 Day 1. If the sample day falls on a weekend or a holiday, please consult the Sponsor for alternate sample collection times.
29. Procedures for collection of PK samples and precise time points are described in the Procedures Manual. Pre-dose (trough) PK samples for pembrolizumab will be collected within 24 hours before infusion in cycles 1, 2, 4, 8 and every 4 cycles thereafter, 30 days after discontinuation of study drug (or until the subject starts new anti-cancer therapy). Post-dose (peak) PK samples will be drawn within 30 minutes after end of pembrolizumab infusion in cycles 1 and 8.

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/IEC requirements, applicable laws and regulations and Sponsor requirements.

7.1.1.1.2 Consent and Collection of Specimens for Future Biomedical Research

The investigator or 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 as per Section 5.1.2 and 5.1.3.

7.1.1.3 Subject Identification Card

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

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

7.1.1.4 Medical History

A medical history will be obtained by the Investigator or qualified designee. Medical history will collect 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 this trial will be recorded separately and should not be listed in medical history (see Section 7.1.1.5.1).

7.1.1.5 Disease Details and Treatments

7.1.1.5.1 Oncology Disease Details

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

7.1.1.5.2 Prior Oncology Treatment History

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

7.1.1.6 Prior and Concomitant Medications Review

7.1.1.6.1 Prior Medications

The Investigator or qualified designee will review prior medication use, including any protocol-specified washout requirement, and record prior medication taken by the subject within 28 days before starting the trial. Treatment for the disease for which the subject has enrolled in this trial will be recorded separately and not listed as a prior medication (see Section 7.1.1.5.2).

7.1.1.6.2 Concomitant Medications

The investigator or qualified designee will record medication, if any, taken by the subject during the trial through the Post-Treatment Safety Follow-Up visit, 30 days after the last dose of study drug.

After the Safety Follow-Up visit, all medications related to reportable SAEs and ECIs as defined in Section 7.2, should be recorded.

All new anti-cancer therapy initiated after the study start must be recorded in the eCRF. If a subject initiates another anti-cancer therapy other than the assigned study treatment(s), the study treatment(s) should be discontinued and the subject will move into the survival follow-up phase; if a subject initiates a new anti-cancer therapy within 30 days after the last dose of the trial treatment, the 30 day Safety Follow-up visit should occur before the first dose of the new therapy.

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 treatment allocation. Each subject will be assigned only one screening number. Screening numbers must not be re-used for different subjects.

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

7.1.1.8 Assignment of Treatment/Randomization Number

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

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

7.1.1.9 Trial Compliance (Medication)

Preladenant will be taken orally twice a day by the subject at the dose allocated through an IVRS/IWRS for the currently enrolling cohort. During on-site visits, administration of preladenant will be witnessed by the investigator and/or trial staff. The administration, the dose, the time of administration, as well as any immediate reactions at the time of intake will be documented in the eCRF.

For non-visit days, preladenant will be taken at home. When a subject attends a study visit, he/she will bring any unused capsules. Compliance will be assessed via tablet counts of returned medication and/or subject report, and will be reinforced at each visit. Subjects will be instructed to return preladenant containers with them at the time of clinic visits (See Pharmacy Manual).

Pembrolizumab will be administered at the fixed dose of 200 mg by IV infusion on Day 1 of each 21-day cycle. The Pharmacy Manual contains specific instructions for the preparation and administration of the infusion solution. Administration of pembrolizumab will be witnessed by the investigator and/or trial staff. The total volume of pembrolizumab infused will be compared with the total volume prepared to determine compliance with each dose administered (See Pharmacy Manual).

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

7.1.2 Clinical Procedures/Assessments

7.1.2.1 Adverse Event 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 (Section 6) and more frequently if clinically indicated. Adverse events will be graded and recorded throughout the trial and during the follow-up period according to NCI CTCAE Version 4.0 (see Appendix 12.5). Toxicities will be characterized in terms including seriousness, causality, toxicity grading, and action taken with regard to trial treatment.

Please refer to Section 7.2 for detailed information regarding the assessment and recording of AEs.

7.1.2.2 Physical Examination

7.1.2.2.1 Full Physical Examination

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

A full physical examination should be repeated at the timepoints outlined in the Trial Flow Chart (Section 6.0). After the first dose of study treatment, new clinically significant abnormal findings should be recorded as AEs.

7.1.2.2.2 Directed Physical Examination

For visits that do not require a full physical examination (Section 6.0), the Investigator or qualified designee will perform a directed physical examination as clinically indicated prior to the administration of the trial treatment. After the first dose of study treatment, new clinically significant abnormal findings should be recorded as AEs.

7.1.2.3 Height, Weight, and Vital Signs

Height will be measured at screening only.

Weight will be measured at the timepoints outlined in the Trial Flow Chart (Section 6.0).

The Investigator or qualified designee will measure vital signs at the time points outlined in the Trial Flow Chart (Section 6.0). Vital signs include body temperature, pulse, respiratory rate, and blood pressure. Specifically, during on-site visits, blood pressure will be carefully monitored throughout the day.

7.1.2.4 Electrocardiogram

A standard 12-lead electrocardiogram (ECG) will be performed using local standard procedures once at screening. Clinically significant abnormal findings should be recorded in the medical history. Additional ECGs may be performed as clinically necessary.

7.1.2.5 Eastern Cooperative Oncology Group (ECOG) Performance Scale

The Investigator or qualified designee will assess ECOG status (see Section 12.4) at screening, prior to the administration of each dose of trial treatment administered at the clinic, and during the Follow-Up Period as specified in the Trial Flow Chart (Section 6.0).

7.1.2.6 Tumor Imaging and Assessment of Disease

Tumor imaging should be acquired by computed tomography (CT, strongly preferred). Magnetic resonance imaging (MRI) should be used when CT is contraindicated or for imaging of the brain. The same imaging technique regarding modality and use of contrast should be used in a subject throughout the trial to optimize the visualization of existing and new tumor burden. The process for image collection and transmission to the central imaging vendor (CIV) can be found in the Site Imaging Manual (SIM).

Although RECIST 1.1 references to maximum of 5 target lesions in total and 2 per organ, the Sponsor allows maximum of 10 target lesions in total and 5 per organ, if clinically relevant to enable a broader sampling of tumor burden. All scheduled images for all study subjects from the sites will be submitted to the CIV. In addition, additional imaging (including other modalities) that are obtained at an unscheduled time point to determine disease progression, as well as imaging obtained for other reasons but captures radiologic progression, should be submitted to the CIV as well.

7.1.2.6.1 Initial Tumor Imaging

Initial tumor imaging at Screening must be performed within 28 days prior to the date of randomization. The site trial team must review screening images to confirm the subject has measurable disease per RECIST 1.1.

Subjects with previously treated brain metastases may participate provided they have stable brain metastases, i.e. without evidence of progression by imaging (confirmed by magnetic resonance imaging (MRI) if MRI was used at prior imaging, or confirmed by computed tomography (CT) imaging if CT used at prior imaging) for at least 4 weeks prior to the first dose of trial treatment. Any neurologic symptoms must have returned to baseline and subjects must have no evidence of new or enlarging brain metastases, and have not used steroids for brain metastases for at least 7 days prior to trial initiation as per local site assessment. This exception does not include carcinomatous meningitis, as subjects with carcinomatous meningitis are excluded regardless of clinical stability.

7.1.2.6.2 Tumor Imaging During Trial

The first on-trial imaging assessment should be performed at 9 weeks (63 days ±7 days]) from the date of randomization. Subsequent tumor imaging should be repeated every 9 weeks or more frequently if clinically indicated. Imaging timing should follow calendar days and should not be adjusted for delays in cycle starts. Imaging should continue to be performed until disease progression, the start of new anti-cancer treatment, withdrawal of consent, or death, whichever occurs first.

Per RECIST 1.1, partial and complete response should be confirmed by a repeat tumor imaging assessment not less than 4 weeks from the date the response was first documented. The tumor imaging to confirm a response may be performed, at the earliest 4 weeks after the first indication of a response, or at the next scheduled scan (i.e., 9 weeks later), whichever is clinically indicated. Subjects will then return to regular scheduled imaging every 9 weeks, starting with the next scheduled imaging time point. Subjects who obtain a confirmation scan do not need to undergo the next scheduled tumor imaging if it is <4 weeks later; tumor imaging may resume at the subsequent scheduled imaging time point.

Per irRECIST (Section 7.1.2.6.5), disease progression should be confirmed by the site at least 4 weeks after site-assessed first radiologic evidence of PD in clinically stable subjects. Subjects who have unconfirmed disease progression may continue on treatment at the discretion of the site Investigator until progression is confirmed by the site provided they have met the conditions detailed in Section 7.1.2.6.5. Subjects who obtain a confirmation scan do not need to undergo the next scheduled tumor imaging if it is <4 weeks later; tumor imaging may resume at the subsequent scheduled imaging time point if clinically stable. Subjects who have confirmed disease progression as assessed by the site, will discontinue trial treatment. Exceptions are detailed in Section 7.1.2.6.5.

7.1.2.6.3 End of Treatment and Follow-up Treatment Imaging

In subjects who discontinue trial treatment, tumor imaging should be performed at the time of treatment discontinuation (±4-week window). If a previous scan was obtained within 4 weeks prior to the date of discontinuation, then a scan at treatment discontinuation is not mandatory. In subjects who discontinue trial treatment due to documented disease progression, this is the final required tumor imaging.

In subjects who discontinue trial treatment without documented disease progression, every effort should be made to continue monitoring their disease status by tumor imaging using the same imaging schedule used while on treatment (every 9 weeks) to monitor disease status

until the start of a new anticancer treatment, disease progression, death, or the end of the trial, whichever occurs first.

7.1.2.6.4 RECIST 1.1 Assessment of Disease

All images will be submitted to a central imaging vendor for potential analysis at the end of the study. RECIST 1.1 will be only used by the central imaging vendor for potential retrospective analysis of the primary measure for assessment of tumor response and date of disease progression.

7.1.2.6.5 irRECIST Assessment of Disease

irRECIST is RECIST 1.1 adapted as described below to account for the unique tumor response seen with immunotherapeutic drugs. irRECIST will be used by the site Investigator/local radiology reviewers to assess tumor response and progression, and make treatment decisions. This data will be collected in the clinical database.

When feasible, subjects should not be discontinued until progression is confirmed by the local site Investigator/radiology assessment. This allowance to continue treatment despite initial radiologic 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 nontarget lesion(s)
- Development of new lesion(s)

In subjects who have shown initial evidence of radiological PD by RECIST 1.1, it is at the discretion of the Investigator whether to continue a subject on trial medication until repeat imaging is obtained (using irRECIST for subject management (see Table 12). This clinical judgment decision by the site Investigator should be based on the subject's overall clinical condition, including performance status, clinical symptoms, and laboratory data. Subjects may receive trial medication and the 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

Any subject deemed clinically unstable should be discontinued from trial treatment at site-assessed first radiologic evidence of PD and is not required to have repeat imaging for PD confirmation.

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).

Disease progression will be considered to be "not confirmed" at repeat imaging if ALL of the following occur (as assessed by irRECIST):

- Target lesion sum of diameters 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 lesion progression since last evaluation

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

Disease progression will be considered to be "confirmed" at repeat imaging if ANY of the following occur (as assessed by irRECIST):

- Target lesion sum of diameters 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 lesion progression since last evaluation

If repeat imaging confirms PD due to any of the scenarios listed above, subjects will be discontinued from study therapy.

NOTE: If a subject has confirmed radiographic progression (i.e., 2 scans at least 4 weeks apart demonstrating progressive disease) per irRECIST, but the subject is achieving a clinically meaningful benefit, and there is no further increase in the tumor burden at the confirmatory tumor imaging, an exception to continue treatment may be considered following consultation with the Sponsor. In this case, if treatment is continued, tumor imaging should continue to be performed following the intervals as outlined in Section 6.0 and be submitted to the central imaging vendor.

Additional details about irRECIST are provided in the Sponsor TIP Sheet for RECIST 1.1 and irRECIST.

Table 12 Imaging and Treatment after First Radiologic Evidence of Progressive Disease

	Clinically Stable		Clinically Unstable	
	Imaging	**Treatment**	**Imaging**	**Treatment**
First radiologic evidence of PD by RECIST 1.1	Repeat imaging at >4 weeks at site to confirm PD	May continue trial treatment at the local site Investigator's discretion while awaiting confirmatory tumor imaging by site by irRECIST.	Repeat imaging at >4 weeks to confirm PD per physician discretion only	Discontinue treatment
Repeat tumor imaging confirms PD by irRECIST at the local site	No additional imaging required	Discontinue treatment (exception is possible upon consultation with Sponsor)	No additional imaging required	Not applicable
Repeat tumor imaging shows SD, PR or CR by irRECIST at the local site	Continue regularly scheduled imaging assessments	Continue trial treatment at the local site investigator's discretion	Continue regularly scheduled imaging assessments	May restart trial treatment if condition has improved and/or clinically stable per investigator's discretion. Next tumor image should occur according to the regular imaging schedule
CR=complete response; irRECIST=immune-related response evaluation criteria in solid tumors; PD=progressive disease; PFS=progression-free survival; PR=partial response; SD=stable disease				

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 Study Procedures Manual. Refer to the Trial Flow Chart (Section 6.0) for the schedule of laboratory assessments.

7.1.3.1 Laboratory Safety Evaluations (Hematology, Chemistry and Urinalysis)

Laboratory tests for hematology, chemistry and urinalysis are specified in Table 13.

Table 13 Laboratory Tests

Hematology	Chemistry	Urinalysis	Other
Hematocrit	Albumin	Blood	Pregnancy test (serum or urine)a
Hemoglobin	Alkaline phosphatase	Glucose	PT/INR
Platelet count	Alanine aminotransferase	Protein	aPTT
WBC (total and differential)e	Aspartate aminotransferase	Specific gravity	Total T3 or free T3, FT4, and TSHb,d
RBC	Bicarbonate/CO2c	Microscopic exam, if abnormal results are noted	
Absolute lymphocyte count	Calcium		
Absolute neutrophil count	Chloride Creatinine (Cystatin C if abnormal) Glucose Phosphorus Potassium Sodium Total bilirubin Direct bilirubin Total protein GGT Blood urea nitrogen Uric acid Amylase Lipase LDH		

a Perform on women of childbearing potential only 72 hours prior to Day 1 of Cycle 1. Pregnancy tests must be repeated prior to every cycle if required or as specified per local regulatory guidance.
b T3 is preferred; if not available free T3 may be tested.
c If this test is not done as part of local standard of care, this test does not need to be performed.
d If the local laboratory is unable to perform these tests, the site should submit the sample to the central laboratory for testing. Details are provided in the Procedure Manual.
e Report % or absolute results per standard of practice. Report the results in the same manner throughout the trial.

aPTT=activated partial thrombin time; FT4=free thyroxine; GGT=gamma-glutamyl transferace; INR=insulin receptor; PT=prothrombin time; RBC=red blood cells; T3=triothyronine; TSH=thyroid stimulating hormone (thyrotropin); WBC=white blood cells.

Laboratory tests for screening should be performed within 3 days prior to the first dose of trial treatment. An exception is hepatitis and thyroid serologies, which may be performed within 28 days prior to first dose. After Cycle 1, pre-dose laboratory safety tests can be conducted up to 72 hours prior to dosing unless otherwise noted on the flow charts.

Laboratory test results must be reviewed by the Investigator or qualified designee and found to be acceptable prior to administration of each dose of trial treatment. Unresolved abnormal laboratory values that are drug-related AEs should be followed until resolution. Laboratory tests do not need to be repeated after the end of treatment if laboratory results are within the normal range.

7.1.3.2 Pregnancy Test

All women who are being considered for participation in the trial, and who are not surgically sterilized or postmenopausal, must be tested for pregnancy within 72 hours of each cycle of trial treatment and 30 days post-treatment. If a urine test is positive or not evaluable, a serum test will be required. Subjects must be excluded/discontinued from the trial in the event of a positive or borderline-positive test result.

7.1.3.3 Pharmacokinetic/Pharmacodynamic Evaluations

7.1.3.3.1 Blood Collection for PK Assessment for Preladenant

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

7.1.3.3.2 Blood Collection for PK and ADA Assessment for Pembrolizumab

To further evaluate pembrolizumab immunogenicity and exposure of the proposed dosing regimen, sample collections for analysis of antidrug antibodies (ADA) and PK are currently planned as shown in the Trial Flow Chart (Section 6.0). Blood samples will be obtained to measure PK of serum pembrolizumab. The pembrolizumab serum maximum concentration (Cmax) and minimum concentration (Ctrough) at planned visits and times will be summarized.

If ongoing ADA and/or PK results continue to be consistent with existing ADA and/or PK data from other pembrolizumab clinical trials, it may be decided to discontinue or reduce further sample collection in this trial. Should this occur, it will be communicated by an administrative memo.

Pharmacokinetic data will also be analyzed using nonlinear mixed effects modeling. Based on PK data obtained in this trial as well as PK data obtained from other studies, a population PK analysis will be performed to characterize PK parameters (clearance [CL], volume of distribution [V]) and evaluate the effect of extrinsic and intrinsic factors to support proposed dosing regimen. Pharmacokinetic data will also be used to explore the exposure response relationships for pembrolizumab antitumor activity/efficacy as well as safety in the proposed patient population, if feasible. The results of these analyses, if performed, will be reported separately.

7.1.3.3.3 Blood Collection for RNA, Plasma and Serum Biomarker Analysis

Blood should be collected pre-dose at the timepoints outlined in Section 6.0 – Trial Flow Chart. Leftover RNA, plasma, and serum will be stored at the end of the trial for FBR if the subject has consented (see Section 4.2.3.5).

Further details are provided in the Procedures Manual.

7.1.3.4 Planned Genetic Analysis Sample Collection (On-Treatment Tumor Biopsy)

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

On-treatment tumor biopsy should be performed on Cycle 2 Day 15 (+/- 7 days). Samples will be collected for planned analysis of associations between genetic variants in germline/tumor DNA and drug response.

If a documented law or regulation prohibits (or local IRB/Independent Ethics Committee [IEC] does not approve) sample collection for these purposes, then such samples should not be collected at the corresponding sites.

Leftover DNA extracted from planned genetic analysis samples will be stored for future biomedical research only if subject signs the Future Biomedical Research consent.

7.1.3.5 Future Biomedical Research Samples

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

- DNA for future research.
- Remaining RNA.
- Remaining plasma and serum from biomarker analyses.
- Remaining main study tumor.

7.1.4 Other Procedures

7.1.4.1 Withdrawal/Discontinuation

Subjects who discontinue 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 End of Treatment visit should be performed at the time of discontinuation. Any adverse events which are present at the time of discontinuation/withdrawal should be followed in accordance with the safety requirements outlined in Section 7.2 - Assessing and Recording Adverse Events. .

7.1.4.1.1 Withdrawal From Future Biomedical Research

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

In the event that the medical records for the main trial are no longer available (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 withdrawal cannot be processed.

7.1.4.1.2 Lost to Follow-up

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

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

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

7.1.4.2 Subject Blinding/Unblinding

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

7.1.4.3 Domiciling

Subjects will report to the clinical research unit (CRU) prior to dosing on Day 1 of each 21-day cycle to allow for completion of all pre-treatment procedures as outlined in the Trial Flow Chart (Section 6.0).

7.1.4.4 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 laboratory evaluations and trial assessments.
- Imaging equipment – calibration and maintenance of imaging equipment as required for study objectives per local regulations.
- ECG equipment – as required for study assessments.

- Infusion equipment – as required for pembrolizumab administration.
- Refrigerators and freezers – as required to store study treatments and laboratory samples.

Additional guidance regarding critical equipment is provided in the Procedures Manual, Pharmacy Manual, and Site Imaging Manual.

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 Visit

Within 28 days prior to treatment randomization, potential subjects will be evaluated to determine that they fulfill the entry requirements as set forth in Section 5.1. Visit requirements are outlined in the Trial Flow Chart (Section 6.0). Screening procedures may be repeated.

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:

Use the bullets below that apply to the trial.

- Laboratory tests are to be performed within 3 days prior to the first dose of trial treatment. An exception is hepatitis testing which may be done up to 28 days prior to the first dose of trial treatment.
- Evaluation of ECOG is to be performed within 3 days prior to the first dose of trial treatment.
- For women of reproductive potential, a urine or serum pregnancy test will be performed within 72 hours prior to the first dose of trial treatment. If urine pregnancy results cannot be confirmed as negative, a serum pregnancy test will be required (performed by the local trial site laboratory).
- Archival tumor sample collection is not required to be obtained within 28 days prior to the first dose of trial treatment. Newly obtained tumor tissue may be obtained within 90 days of treatment initiation.

Subjects may be rescreened after initially failing to meet the inclusion/exclusion criteria. Results from assessments during the initial screening period are acceptable in lieu of a repeat screening test if performed within the specified time frame and the corresponding inclusion/exclusion criteria is met. Subjects who are rescreened will retain their original screening number.

7.1.5.2 Treatment Period Visits

Visit requirements are outlined in the Trial Flow Chart (Section 6.0). Specific procedure-related details are provided in Section 7.1 – Trial Procedures.

7.1.5.3 Post-Treatment Visits

7.1.5.3.1 End of Treatment – Discontinuation Visit

The Discontinuation Visit should occur at the time study treatment is discontinued for any reason. If the Discontinuation Visit occurs 30 days from the last dose of study treatment, at the time of the mandatory Safety Follow up Visit, the Discontinuation visit procedures and any additional Safety Follow-up procedures should be performed. Visit requirements are outlined in Section 6.0- Trial Flow Chart. Additional details regarding subject withdrawal and discontinuation are presented in Section 5.7– Subject Withdrawal/Discontinuation.

7.1.5.3.2 Safety Follow-up Visit

When subjects discontinue study treatment, safety follow-up visit will be required. The Post-Treatment Safety Follow-Up visit should occur approximately 30 days after the last dose of study treatment. If a subject initiates a new anticancer therapy within 30 days after the last dose of study treatment, the Post-Treatment Safety Follow-Up visit should occur before the first dose of the new therapy.

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

Subjects who discontinue treatment for reasons other than confirmed disease progression will have post-treatment follow-up for disease status until disease progression, initiating a new anticancer therapy, withdrawing consent for trial participation, or becoming lost to follow-up, whichever occurs first. Subjects with an AE of Grade > 1 will be followed until the resolution of the AE to Grade 0-1 or until the beginning of a new anti-cancer therapy, whichever occurs first.

7.1.5.3.3 Imaging Follow-up Visits

Subjects who discontinue treatment for reasons other than verified PD should continue with imaging assessments per the protocol defined schedule until: 1) PD is verified or further confirmed by the investigator, 2) initiation of a new anti-cancer treatment, 3) death, 4) withdrawal of consent or 5) study conclusion or early termination, whichever occurs first.

7.1.5.3.4 Survival Follow-up Visits

Subjects, who experience confirmed disease progression or start a new anti-cancer therapy, will move into the Survival Follow-Up Phase and should be contacted by telephone every 12 weeks to assess for survival status until death, withdrawal of consent, or the end of the study, whichever occurs first.

The Sponsor may request survival status be assessed at additional time points during the course of the study. For example, these additional time points may be requested prior to an efficacy interim analysis, and/or final analysis. All subjects who are not known to have died prior to the request for these additional survival status time points will be contacted at that time.

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

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.

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

All adverse events that occur after the consent form is signed but before treatment allocation/randomization must be reported by the investigator if they cause the subject to be excluded from the trial, or are the result of a protocol-specified intervention, including but not limited to washout or discontinuation of usual therapy, diet, placebo treatment or a procedure. From the time of treatment allocation/randomization through 90 days following cessation of treatment, or 30 days following cessation of trial treatment if the subject initiates new anticancer therapy, whichever is earlier, all adverse events must be reported by the investigator. Such events will be recorded at each examination on the Adverse Event case report forms/worksheets. The reporting timeframe for adverse events meeting any serious criteria is described in section 7.2.3.1. The investigator will make every attempt to follow all subjects with non-serious adverse events for outcome.

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

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

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

For this trial, an overdose of preladenant will be defined as any dose exceeding the prescribed dose for preladenant by ≥20% of the indicated dose. An overdose of pembrolizumab will be defined as any dose of 1000 mg or greater (≥5 times the indicated dose).

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

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

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

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

7.2.2 Reporting of Pregnancy and Lactation to the Sponsor

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

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

(Important Medical Events). If the pregnancy continues to term, the outcome (health of infant) must also be reported.

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

7.2.3 Immediate Reporting of Adverse Events to the Sponsor

7.2.3.1 Serious Adverse Events

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

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

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

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

Refer to Table 14 for additional details regarding each of the above criteria.

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

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

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

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

7.2.3.2 Events of Clinical Interest

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

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

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

Events of clinical interest for this trial include:

1. an overdose of Sponsor's product, as defined in Section 7.2.1 - Definition of an Overdose for This Protocol and Reporting of Overdose to the Sponsor, that is not associated with clinical symptoms or abnormal laboratory results.

2. an elevated AST or ALT lab value that is greater than or equal to 3X the upper limit of normal and an elevated total bilirubin lab value that is greater than or equal to 2X the upper limit of normal and, at the same time, an alkaline phosphatase lab value that is less than 2X the upper limit of normal, as determined by way of protocol-specified laboratory testing or unscheduled laboratory testing.*

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

7.2.3.3 Protocol-Specific Exceptions to Serious Adverse Event Reporting

Efficacy endpoints as outlined in this section will not be reported to the Sponsor as described in Section 7.2.3.

Specifically, the suspected/actual events covered in this exception include any event that is disease progression of the cancer under study.

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

7.2.4 Evaluating Adverse Events

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

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

For studies in which multiple agents are administered as part of a combination regimen, the investigator may attribute each adverse event causality to the combination regimen or to a single agent of the combination. In general, causality attribution should be assigned to the combination regimen (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 event to the single agent.

Table 14 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 strategies and procedures for the primary and key secondary analyses of the study. Exploratory and other non-confirmatory analyses will be outlined in a separate supplemental Statistical Analysis Plan (sSAP).

If, after the study has begun, changes are made to primary and/or secondary objectives, or the statistical methods related to those objectives, then the protocol will be amended (consistent with ICH Guideline E9). Changes to exploratory or other non-confirmatory analyses made after the protocol has been finalized, but prior to the conduct of any analyses, will be documented in the sSAP as needed and referenced in the Clinical Study Report (CSR) for the study. Post hoc exploratory analyses will be clearly identified in the CSR.

8.1 Statistical Analysis Plan Summary

This section contains a brief summary of the statistical analyses for this trial. Full details are in the Statistical Analysis Plan (SAP), Section 8.2 through 8.12.

Trial Design Overview	Phase 1b/II trial of preladenant as monotherapy and preladenant in combination with pembrolizumab in subjects with advanced solid tumors. The trial applies an mTPI design for dose escalation and confirmation of RP2Ds, followed by an expansion phase to further examine safety and exploratory efficacy in select tumor types.
Analysis Populations	Safety (Primary): All-Subjects-as-Treated (ASaT) Efficacy (Secondary & Exploratory): Full Analysis Set (FAS)
Primary Endpoint(s)	Safety: Dose-limiting toxicities (DLTs)
Key Secondary Endpoints	ORR in subjects treated with preladenant as monotherapy and preladenant in combination with pembrolizumab
Statistical Methods for Key Efficacy/Immunogenicity/ Pharmacokinetic Analyses	The point estimate and 95% confidence interval (CI) for ORR will be evaluated separately in subjects treated with preladenant as monotherapy and subjects treated with preladenant in combination with pembrolizumab, using exact binomial distribution.
Treatment Assignment	Subjects will be allocated to receive single agent preladenant or preladenant co-administered with pembrolizumab centrally through an IVRS/IWRS. In Part 1, subjects will be allocated by non-random assignment. Allocation will alternate between the 2 arms when both arms are open for enrollment. In Part 2, subjects will be allocated to each cohort by tumor type. . The trial is open-label.
Statistical Methods for Key Safety Analyses	Summary statistics (counts, percentages, means, standard deviations, etc.) will be provided for the safety endpoints as appropriate. The pool-adjacent-violators algorithm [22] that forces the DLT rate estimates to be non-decreasing with dose levels and pools adjacent violators for weighted estimates by sample size will be used to estimate the DLT rates across doses. The estimates of the DLT rates among subjects treated at the RP2Ds of preladenant when used as monotherapy and when used in combination with pembrolizumab and the 80% Bayesian credible intervals for the estimates will be provided.

Interim Analyses	Data will be examined on a continuous basis to allow for dose escalation and confirmation decisions using the mTPI design in Part 1. An interim futility check will be performed for each of the select solid tumor cohorts in Part 2.
Multiplicity	No multiplicity adjustment is planned for this Phase 1b/II trial.
Sample Size and Power	The overall sample size for this trial depends on the observed DLT profiles of preladenant as monotherapy and preladenant in combination with pembrolizumab. A target sample size of 112 subjects will be used for trial planning purposes.

8.2 Responsibility for Analyses/In-House Blinding

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

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

8.3 Hypotheses/Estimation

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

8.4 Analysis Endpoints

8.4.1 Efficacy/Immunogenicity/Pharmacokinetic Endpoints

Overall response rate is a secondary endpoint of the trial. Overall response rate is defined as the proportion of subjects in the analysis population who experience complete response (CR) or partial response (PR) using RECIST 1.1 criteria as assessed by investigator review. Other efficacy endpoints (e.g., DOR, PFS) are exploratory endpoints in this trial and will be defined in the sSAP.

Pharmacokinetic endpoints include serum concentrations of preladenant and pembrolizumab and derived PK parameters.

8.4.2 Safety Endpoints

The primary safety endpoint is the rate of DLTs. A description of safety measures is provided in Section 5.2.2 and Section 7.2.

8.5 Analysis Populations

8.5.1 Safety Analysis Population

The All-Subjects-as-Treated (ASaT) population will be used for the analysis of safety data in this study. The ASaT population consists of all subjects who received at least one dose of study treatment. In case of treatment administration errors, subjects will be analyzed according to the treatment they actually received. For DLT evaluation, ASaT subjects that were observed for safety for 21 days after the first dose of assigned treatment or experienced a DLT prior to 21 days after the first dose of assigned treatment will be used. The replacement subjects will also be considered evaluable if the above specified criteria are met.

At least one laboratory or vital sign measurement obtained subsequent to at least 1 dose of study treatment is required for inclusion in the analysis of each specific parameter. To assess change from baseline, a baseline measurement is also required. Safety data from subjects who experienced disease progression in the monotherapy arm and crossed over into the combination arm will be presented separately.

8.5.2 Efficacy Analysis Populations

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

8.6 Statistical Methods

8.6.1 Statistical Methods for Efficacy Analyses

For the secondary endpoint of ORR, the point estimate and 95% CI will be evaluated separately in subjects treated with preladenant as monotherapy and subjects treated with preladenant in combination with pembrolizumab, using an exact method based on binomial distribution (Clopper-Pearson interval). Of note, patients enrolled in Part 1 in the combination arm (Arm 2) and treated at the same dose level as that selected for Part 2, will be pooled together with patients enrolled in Part 2 for efficacy analysis if they have the same tumor type.

8.6.2 Statistical Methods for Safety Analyses

Safety and tolerability will be assessed by clinical review of all relevant parameters including AEs, SAEs, laboratory tests, vital signs, ECG measurements, and physical examinations.

Adverse events will be summarized by counts and frequencies for each dose level and treatment arm. Patients enrolled in Part 1 in the combination arm (Arm 2) and treated at the same dose level as that selected for Part 2, will also be pooled together with patients enrolled in Part 2 for safety analysis if they have the same tumor type. Laboratory tests, vital signs, and other safety endpoints will be summarized as appropriate.

Dose limiting toxicities will be listed, and further summarized by dose level and treatment arm. The pool adjacent-violators-algorithm [22], which forces the DLT rate estimates to be non-decreasing with dose levels and pools adjacent violators for weighted estimates by sample size, will be used to estimate the DLT rates across doses in each treatment arm. The estimates of the DLT rates among subjects treated at the MTDs (or MADs) and the 80% Bayesian credible intervals based on a prior distribution of Beta (1,1) for the estimates will be provided.

8.6.3 Summaries of Baseline Characteristics, Demographics, and Other Analyses

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

8.7 Interim Analyses

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

An interim futility check will be performed for each of the select solid tumor cohorts in Part 2. If there are no responders among approximately the first 15 evaluable patients that have at least 1 post-baseline scan assessment in a given cohort, that cohort may be stopped early for futility. If the true response rate is 10%, there is an 80% chance to observe at least one responder among 15 patients.

8.8 Multiplicity

There will be no multiplicity control in this trial.

8.9 Sample Size and Power Calculations

During Part 1 (dose escalation and confirmation), approximately 52 subjects (26 subjects in each treatment arm) are expected to be enrolled. For each testing dose level in each treatment arm, 3 to 6 subjects may be enrolled, however based on the occurrence of DLTs, up to 14 subjects may be enrolled. The actual sample size of Part 1 will depend on the safety profiles of preladenant in each treatment arm, and may be increased if the RP2D is not reached and additional dose levels are required.

In Part 2 (expansion phase) approximately 60 subjects (30 subjects in each cohort) are expected to be enrolled. The key efficacy endpoint will be the objective response rate based on the investigator assessment per RECIST 1.1. Table 15 shows the ORR estimate and at least 95% CI (Clopper-Pearson interval) in each cohort.

Table 15 Estimate and 95% CI of ORR in Each Cohort

Sample Size	Number of Responses (PR/CR)	Observed ORR	95% CI of ORR
30	3	10%	(2.1%, 26.5%)
	4	13.3%	(3.8%, 30.7%)
	5	16.7%	(5.6%, 34.7%)
	6	20%	(7.7%, 38.6%)
	7	23.3%	(9.9%, 42.3%)
	8	26.7%	(12.3%, 45.9%)
	9	30%	(14.7%, 49.4%)
	10	33.3%	(17.3%, 52.8%)

A target sample size of 112 subjects will be used for trial planning purposes.

8.10 Subgroup Analyses

Subgroup analyses of the efficacy endpoint ORR will be conducted by treatment arm, dose level, and tumor type.

Additional subgroup analyses for Part 2 may be conducted as needed, for example, age, race,

8.11 Compliance (Medication Adherence)

Drug accountability data for study treatment will be collected during the tria1 (see Section 7.1.1.9). Any deviation from protocol-directed administration will be reported.

8.12 Extent of Exposure

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

9.0 LABELING, PACKAGING, STORAGE AND RETURN OF CLINICAL SUPPLIES

9.1 Investigational Product

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

Clinical Supplies will be provided by the Sponsor as summarized in Table 16.

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 16 Product Descriptions

Treatment Group	Product Name and Dosage Form	Dose	Potency	Total Dosage Forms	Additional Information
Part1					
Arm 1	MK-3814 capsule	Cohort DL-1 10mg BID	5mg capsule	2 capsules twice a day	Provided centrally by the Sponsor
		Cohort DL1 25mg BID	25mg capsule	1 capsule twice a day	Provided centrally by the Sponsor
		Cohort DL2 50mg BID	25mg capsule	2 capsules twice a day	Provided centrally by the Sponsor
		Cohort DL3 100mg BID	25mg capsule	4 capsules twice a day	Provided centrally by the Sponsor
		Cohort DL4 200mg BID	25mg capsule	8 capsules twice a day	Provided centrally by the Sponsor

Treatment Group	Product Name and Dosage Form	Dose	Potency	Total Dosage Forms	Additional Information
		Cohort DL-1 10mg BID	5mg capsule	2 capsules twice a day	Provided centrally by the Sponsor
		Cohort DL1 25mg BID	25mg capsule	1 capsule twice a day	Provided centrally by the Sponsor
		Cohort DL2 50mg BID	25mg capsule	2 capsules twice a day	Provided centrally by the Sponsor
		Cohort DL3 100mg BID	25mg capsule	4 capsules twice a day	Provided centrally by the Sponsor
	MK-3814 capsule	Cohort DL4 200mg BID	25mg capsule	8 capsules twice a day	Provided centrally by the Sponsor
Arm 2	MK-3475 vial	All cohorts 200mg/dose	100mg/4mL vial	2 vials	Provided centrally by the Sponsor
Part 2					
Arm 2 only (cohort 1 and cohort 2)	MK-3814 capsule	RP2D TBD BID	TBD capsule	TBD twice a day	Provided centrally by the Sponsor
	MK-3475 vial	RP2D 200 mg/dose	100 mg/4mL vial	2 vials	Provided centrally by the Sponsor

9.2 Packaging and Labeling Information

Clinical supplies will be affixed with a clinical label in accordance with regulatory requirements.

Subjects will receive open label supplies of MK-3814 and MK-3475 consistent with their treatment arm and dose cohort.

9.3 Clinical Supplies Disclosure

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

9.4 Storage and Handling Requirements

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

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

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

9.5 Discard/Destruction/Returns and Reconciliation

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

9.6 Standard Policies

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

10.0 ADMINISTRATIVE AND REGULATORY DETAILS

10.1 Confidentiality

10.1.1 Confidentiality of Data

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

10.1.2 Confidentiality of Subject Records

By signing this protocol, the investigator agrees that the Sponsor (or Sponsor representative), IRB/ERC, or regulatory authority representatives may consult and/or copy trial documents in order to verify worksheet/case report form data. By 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/IEC 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 Protocol/CSR CI during the anticipated review process, thorough understanding of clinical trial methods, appropriate enrollment of subject cohort, timely achievement of trial milestones). The Protocol CI must be a participating trial investigator.

10.4 Compliance with Trial Registration and Results Posting Requirements

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

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

10.5 Quality Management System

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

10.6 Data Management

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

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

10.7 Publications

This trial is intended for publication, even if terminated prematurely. Publication may include any or all of the following: posting of a synopsis online, abstract and/or presentation at a scientific conference, or publication of a full manuscript. The Sponsor will work with the authors to submit a manuscript describing trial results within 12 months after the last data become available, which may take up to several months after the last subject visit in some cases such as vaccine trials. However, manuscript submission timelines may be extended on OTC trials. For trials intended for pediatric-related regulatory filings, the investigator agrees

to delay publication of the trial results until the Sponsor notifies the investigator that all relevant regulatory authority decisions on the trial drug have been made with regard to pediatric-related regulatory filings. Merck will post a synopsis of trial results for approved products on www.clinicaltrials.gov by 12 months after the last subject's last visit for the primary outcome, 12 months after the decision to discontinue development, or product marketing (dispensed, administered, delivered or promoted), whichever is later.

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

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

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

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

11.0 LIST OF REFERENCES

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12.0 APPENDICES

12.1 Merck Code of Conduct for Clinical Trials

Merck*
Code of Conduct for Clinical Trials

I. Introduction

A. Purpose

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

B. Scope

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

II. Scientific Issues

A. Trial Conduct

1. Trial Design

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

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

2. Site Selection

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

3. Site Monitoring/Scientific Integrity

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

B. Publication and Authorship

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

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

III. Subject Protection

A. IRB/ERC review

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

B. Safety

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

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

C. Confidentiality

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

D. Genomic Research

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

IV. Financial Considerations

A. Payments to Investigators

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

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

B. Clinical Research Funding

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

C. Funding for Travel and Other Requests

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

V. Investigator Commitment

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

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

12.2 Collection and Management of Specimens for Future Biomedical Research

1. Definitions

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

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

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

d. DNA: Deoxyribonucleic acid.

e. RNA: Ribonucleic acid.

2. Scope of Future Biomedical Research

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

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

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

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

3. Summary of Procedures for Future Biomedical Research

a. Subjects for Enrollment

All subjects enrolled in the clinical trial will be considered for enrollment in the Future Biomedical Research 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 the visit designated in the trial flow chart. If delayed, present consent at next possible Subject Visit. Consent forms signed by the subject will be kept at the clinical trial site under secure storage for regulatory reasons.

A template of each trial site's approved informed consent will be stored in the Sponsor's clinical document repository.

c. eCRF Documentation for Future Biomedical Research Specimens

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

d. Future Biomedical Research Specimen(s)

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

4. Confidential Subject Information for Future Biomedical Research

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

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

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

5. Biorepository Specimen Usage

Specimens obtained for the Sponsor will be used for analyses using good scientific practices. Analyses utilizing the Future Biomedical Research specimens may be performed by the Sponsor, or an additional third party (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 ask that their biospecimens not be used for Future Biomedical Research. Subjects may withdraw consent at any time by contacting the principal investigator for the main trial. If medical records for the main trial are still available, the investigator will contact the Sponsor using the designated mailbox (clinical.specimen.management@merck.com).

Subsequently, the subject's specimens will be flagged in the biorepository and restricted to main study use only. If specimens were collected from study participants specifically for Future Biomedical Research, these specimens will be removed from the biorepository and destroyed. Documentation will be sent to the investigator confirming withdrawal and/or destruction, if applicable. It is the responsibility of the investigator to inform the subject of completion of the withdrawal and/or destruction, if applicable. Any analyses in progress at the time of request for withdrawal/destruction or already performed prior to the request being received by the Sponsor will continue to be used as part of the overall research trial data and results. No new analyses would be generated after the request is received.

In the event that the medical records for the main trial are no longer available (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 withdrawal of consent and/or destruction cannot be processed.

7. Retention of Specimens

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

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

8. Data Security

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

9. Reporting of Future Biomedical Research Data to Subjects

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

If important research findings are discovered, the Sponsor may publish results, present results in national meetings, and make results accessible on a public website in order to rapidly report this information to doctors and subjects. Subjects will not be identified by

name in any published reports about this study or in any other scientific publication or presentation.

10. Future Biomedical Research Study Population

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

11. Risks Versus Benefits of Future Biomedical Research

Risks include those associated with venipuncture to obtain the whole blood specimen. This specimen will be obtained at the time of routine blood specimens drawn in the main trial.

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

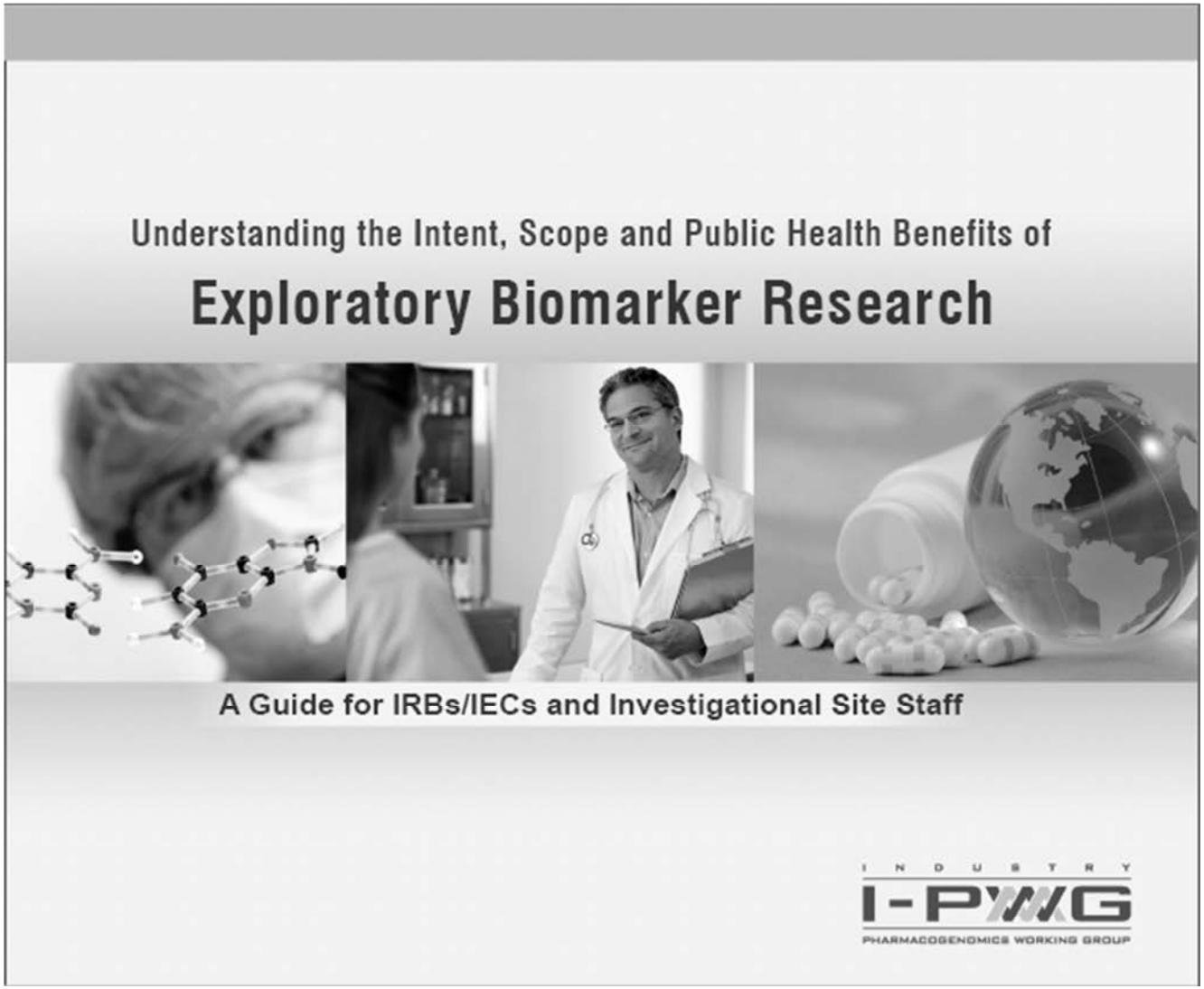
12. Questions

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

13. References

1. National Cancer Institute: http://www.cancer.gov/dictionary/?searchTxt=biomarker
2. International Conference on Harmonization: DEFINITIONS FOR GENOMIC BIOMARKERS, PHARMACOGENOMICS, PHARMACOGENETICS, GENOMIC DATA AND SAMPLE CODING CATEGORIES - E15; http://www.ich.org/LOB/media/MEDIA3383.pdf
3. Industry Pharmacogenomics Working Group. Understanding the Intent, Scope and Public Health Benefits of Exploratory Biomarker Research: A Guide for IRBs/IECs and Investigational Site Staff. Available at http://i-pwg.org/
4. Industry Pharmacogenomics Working Group. Pharmacogenomics Informational Brochure for IRBs/IECs and Investigational Site Staff. Available at http://i-pwg.org/

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



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

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

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

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

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

2. Why is Biomarker Research Important?

Importance to Patients and Public Health

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

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

Importance to Drug Development

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

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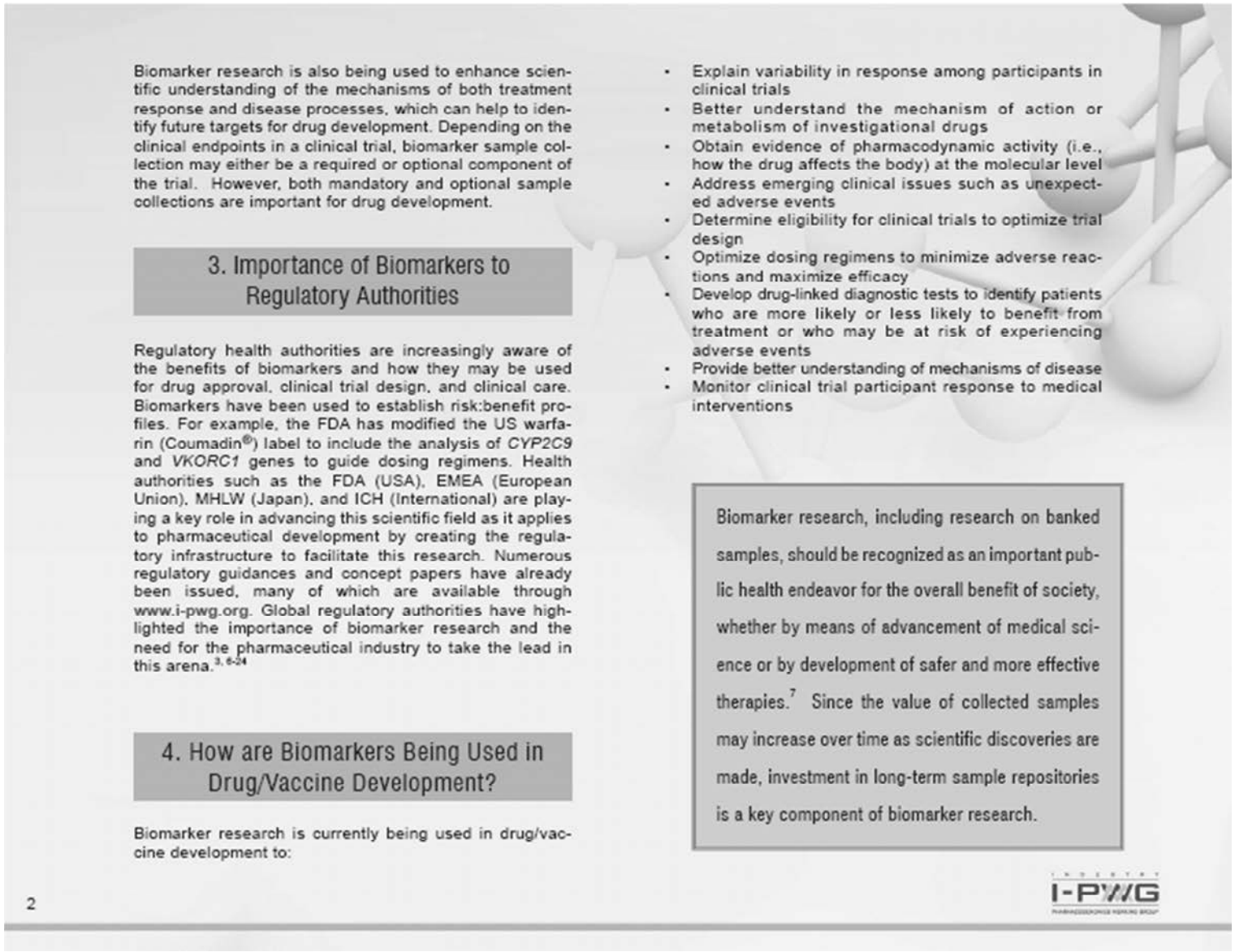
Biomarker research is also being used to enhance scientific understanding of the mechanisms of both treatment response and disease processes, which can help to identify future targets for drug development. Depending on the clinical endpoints in a clinical trial, biomarker sample collection may either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

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

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

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

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

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

6. Biomarker Samples from Clinical Trials: An Invaluable Resource

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

7. Informed Consent for Collection & Banking of Biomarker Samples

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

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

Optional vs. Required Subject Participation

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

Consent for Future Research Use

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

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

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

Withdrawal of consent / sample destruction – The informed consent form should inform participants of their right to withdraw their consent / request destruction of their samples. This should include the mechanisms for exercising that right and any limitations to exercising that right. For example, participants should be informed that it is not possible to destroy samples that have been anonymized.[3] In addition, according to industry standards and regulatory guidance, participants should be informed that data already generated prior to a consent withdrawal request are to be maintained as part of the study data.[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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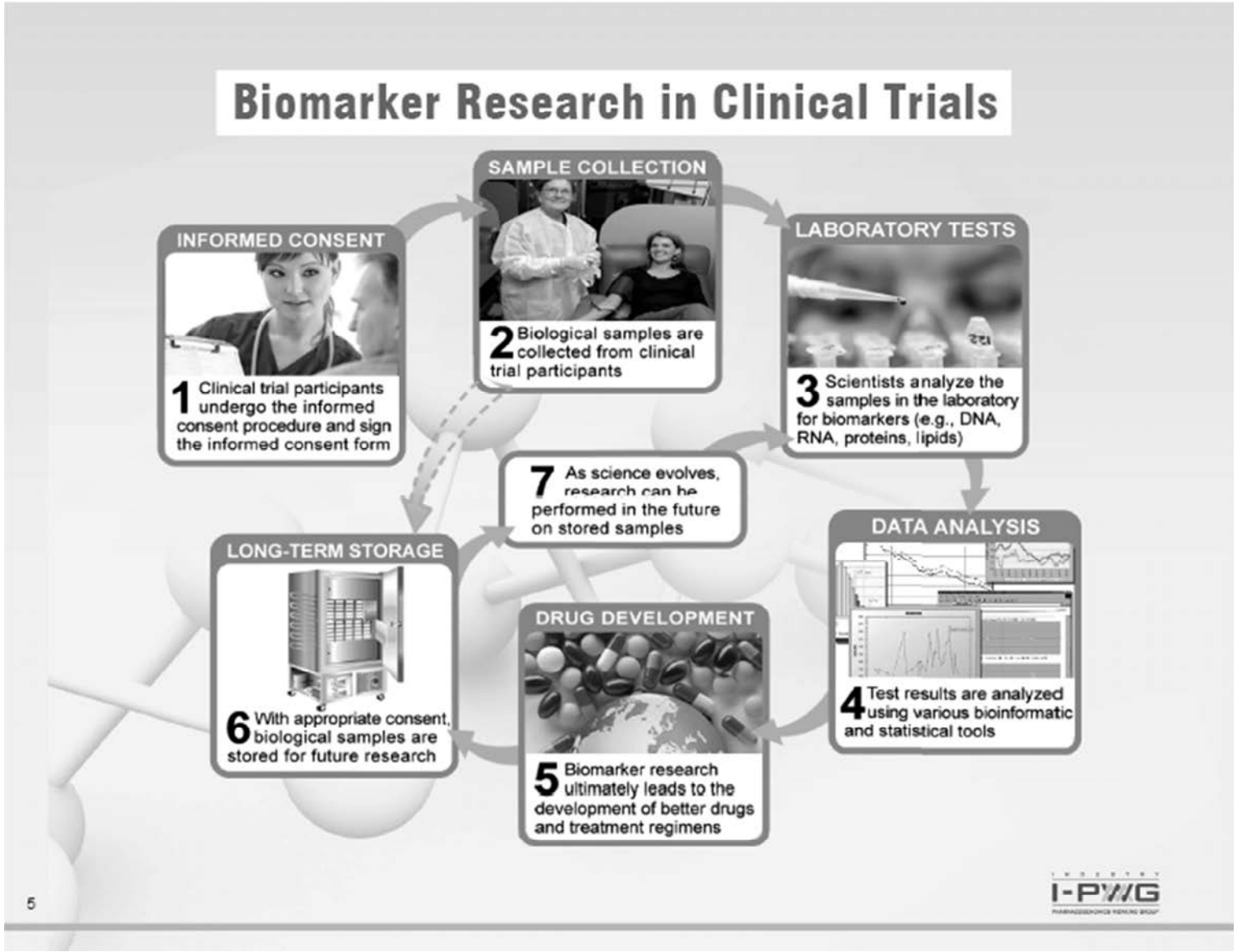
Biomarker Research in Clinical Trials
SAMPLE COLLECTION
2 Biological samples are collected from clinical trial participants
LABORATORY TESTS
3 Scientists analyze the samples in the laboratory for biomarkers (e.g., DNA, RNA, proteins, lipids)
INFORMED CONSENT
1 Clinical trial participants undergo the 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
5
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8. Biomarker Sample Collection in Different Countries

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

9. Return of Research Results to Study Participants

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

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

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

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

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

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

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

10. Benefits and Risks Associated with Biomarker Research

Benefits

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

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

Risks

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

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

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

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

11. Privacy, Confidentiality, and Patient Rights

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

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

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

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

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

12.Where to Get More Information?

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

13. What is I-PWG?

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

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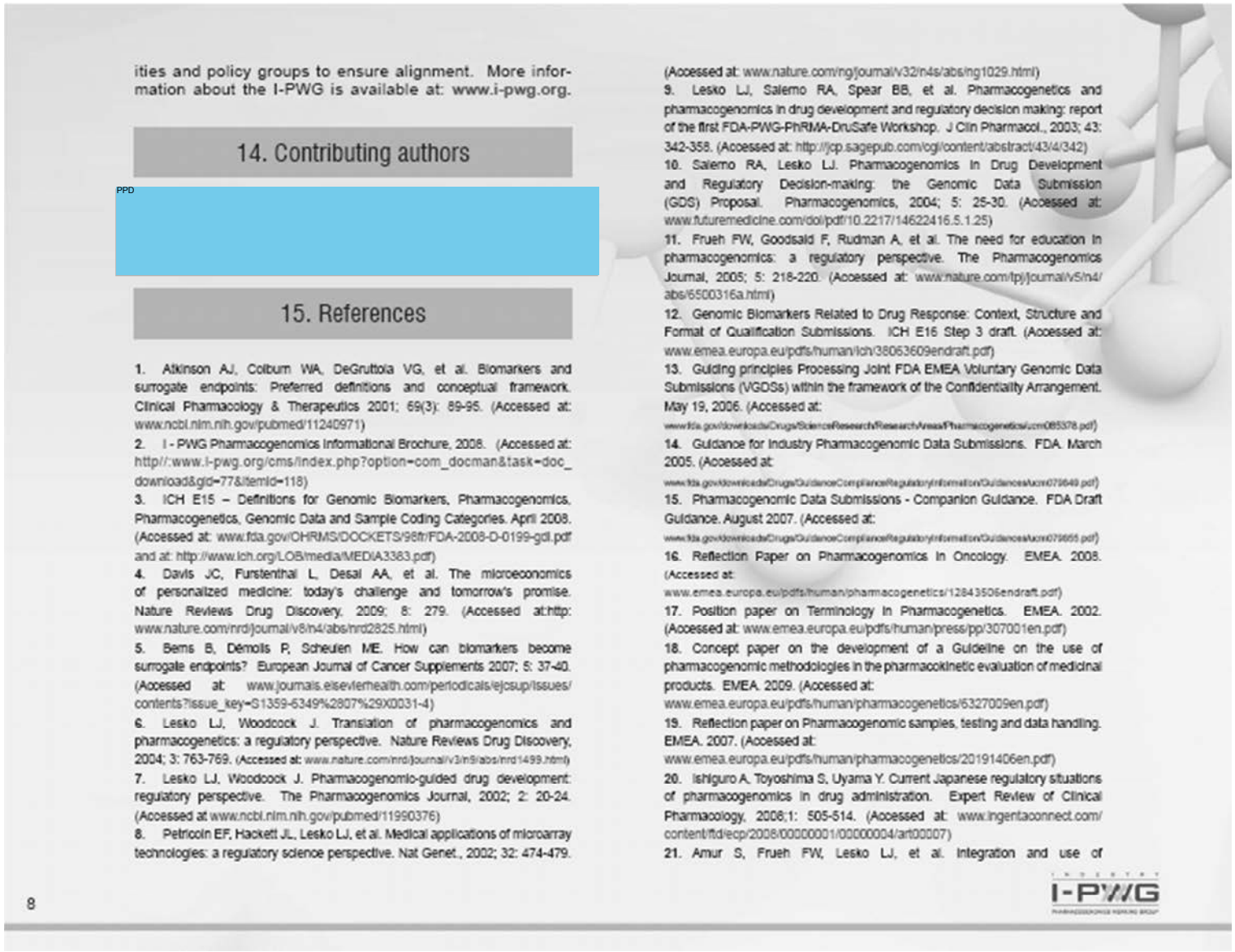

ities and policy groups to ensure alignment. More information about the I-PWG is available at: www.i-pwg.org.

14. Contributing authors

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12.4 ECOG Performance Status

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

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

12.5 National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events V4.0 (CTCAE)

The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized for adverse event reporting.

(http://ctep.cancer.gov/reporting/ctc.html).

12.6 List of Abbreviations

Abbreviation/Term	Definition
A2AR	Adenosine Type 2a Receptor
ADA	Anti-Drug Antibody
ADP	Adenosine Diphosphate
AE	Adverse Event
ALT	Alanine aminotransferase
ANC	Absolute Neutrophil Count
aPTT	Activated Partial Thromboplastin Time
ASaT	All Subjects as Treated
AST	Aspartate aminotransferase
ATP	Adenosine Triphosphate
AUC	Area Under the Curve
BCG	Bacille Calmette Guerin
BID	Two times a day
BUN	Blood Urea Nitrogen
CEA	Carcinoembryonic Antigen
CFR	Code of Federal Regulations
CI	Coordinating Investigator
Cmax	Maximum Concentration in blood
CNS	Central Nervous System
CO2	Carbon Dioxide
COPD	Chronic obstructive pulmonary disease
CR	Complete Response
CRC	Colorectal Cancer
CRU	Clinical research unit
CrCl	Creatinine Clearance
CRF	Case Report Form
CRU	Clinical Research Unit
CSR	Clinical Study Report
CT	Computed Tomography
CTCAE	Common Toxicity Criteria for Adverse Events
CTLA-4	Cytotoxic T-lymphocyte-associated antigen-4
Ctrough	Trough concentration in blood
DCs	Dendritic Cells
DCR	Drug Control Rate
DL	Dose Level
DLT	Dose Limiting Toxicity
dMMR	deficient Mismatch Repair (MMR)
DNA	Deoxyribonucleic Acid
DOR	Duration of Response
ECG	Electrocardiogram
ECI	Events of Clinical Interest
ECOG	Eastern Cooperative Oncology Group
EDC	Electronic Data Capture
ERC	Ethics Review Committee
FAS	Full Analysis Set
FBR	Future Biomedical Research
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act
FDAMA	Food and Drug Administration Modernization Act
FFPE	Formalin fixed paraffin embedded

Abbreviation/Term	Definition
FSH	Follicle Stimulating hormone
FT3	Triiodothyronine
FT4	Free Thyroxine
GCP	Good Clinical Practice
GFR	Glomerular Filtration Rate
GGT	Gamma Glutamyl Transferase
GI	Gastrointestinal
HBsAg	Hepatitis B surface Antigen
HCV	Hepatitis C Virus
HIV	Human Immunodeficiency Virus
HNSCC	Head and neck squamous cell cancer
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonization
Ig	Immunoglobulin
IHC	Immunohistochemistry
INR	International Normalized Ratio
irAE	Immune-related Adverse Event
IRB	Institutional Review Board
irORR	Immune related Overall Response Rate
irRECIST	Immune-related Response Evaluation Criteria in Solid Tumors
ITIM	Immunoreceptor Tyrosine-based Inhibition Motif
ITSM	Immunoreceptor Tyrosine-based Switch Motif
ITT	Immunoglobulin Tail Tyrosine
IUD	IntraUterine Device
IV	IntraVenous
IVD	InVitro Diagnostic
IVRS	Interactive Voice Response System
IWRS	Integrated Web Response System
Kg	Kilogram
LDH	Lactate Dehydrogenase
mAb	Monoclonal Antibody
MDSCs	Myeloid Derived Suppressor Cells
mL	Milligram
MMR	Mismatch Repair
MRI	Magnetic Resonance Imaging
mRNA	Messenger Ribonucleic Acid
MTD	Maximum Tolerated Dose
mTPI	modified Toxicity Probability Interval
NK Cells	Natural Killer Cells
NSCLC	Non-Small Cell Lung Cancer
ORR	Overall Response Rate
OS	Overall Survival
PD	Progressive Disease
PD-L1	Programmed Cell Death-1
PFS	Progression Free Survival
PK/PD	Pharmacokinetic/Pharmacodynamic
pMMR	Proficient Mismatch Repair
p.o	Administered orally
PPI	Proton Pump Inhibitor
PR	Partial response

Abbreviation/Term	Definition
PT	Preferred Term
Q2W	Once Every 2 weeks
Q3W	Once Every 3 weeks
RCC	Renal Cell Cancer
RECIST	Response Evaluation Criteria in Solid Tumors
RO	Receptor occupancy
RP2D	Recommended Phase II Dose
SAP	Statistical analysis plan
SAE	Serious Adverse Event
SD	Stable disease
sSAP	Supplemental statistical analysis plan
T3	Triiodothyronine
T4	Thyroxine
TAMs	Tumor-Associated Macrophages
TBNC	Triple negative breast cancer
TILs	Tumor-infiltrating T Lymphocytes
Tregs	Regulatory T cells
TSH	Thyroid Stimulating Hormone
TQT	Thorough QT/QTc
ULN	Upper Limit Of Normal
VEGF	Vascular Endothelial Growth Factor
WBC	White Blood Cells
ZAP70	Zeta-chain-associated protein kinase
β-hCG	B-Human Chorionic Gonadotropin

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	