PROTOCOL 2125-204

Study Title	A Phase 1/2 Study to Assess the Safety and Efficacy of Intratumoral IMO-2125 in Combination with Ipilimumab or Pembrolizumab in Patients with Metastatic Melanoma
Investigational Drug:	IMO-2125
IND Number:	125515
EudraCT Number	2017-003329-14
Sponsor:	Idera Pharmaceuticals, Inc. 505 Eagleview Blvd., Suite 212 Exton, PA 19341 and 167 Sidney Street Cambridge, MA 02139
Protocol Number:	2125-204
Protocol Version:	8.0
Date:	27 March 2018

INVESTIGATOR STATEMENT

I have read the protocol, including all appendices and the Investigator's Brochure, and I agree that it contains all necessary details for me and my staff to conduct this study as described. I will personally oversee the conduct of this study as outlined herein and will make a reasonable effort to complete the study within the time designated.

I will provide all study personnel under my supervision with copies of the protocol and access to all information provided by Idera Pharmaceuticals, Inc. I will discuss this material with them to ensure that they are fully informed about IMO-2125, the safety parameters, and the conduct of the study in general. I am aware that, before commencement of this study, the institutional review board responsible for such matters must approve this protocol in the clinical facility where it will be conducted. I agree to make all reasonable efforts to adhere to the attached protocol.

I, or my designee, agree to be present at all site-initiation visits and Investigator meetings. In addition, I will ensure the presence of all relevant study personnel under my supervision at these visits and meetings.

I agree to provide all patients with informed consent forms, as required by government and International Council for Harmonisation regulations. I further agree to report to Idera Pharmaceuticals, Inc. any adverse experiences in accordance with the terms of this protocol and FDA (or applicable regulatory agency) regulations.

_____

Principal Investigator Name (print)

_____ _____

Signature Date

Protocol Approval Page

Study Title	A Phase 1/2 Study to Assess the Safety and Efficacy of Intratumoral IMO-2125 in Combination with Ipilimumab or Pembrolizumab in Patients with Metastatic Melanoma
Protocol Number:	2125-204
Protocol Version:	8.0
Date:	27 March 2018

I, the undersigned, have read and approve this protocol and agree on its content.

Shah Rahimian

03/27/2018

Shah Rahimian, MD
Sr. Medical Director, Medical Lead (Oncology)
Idera Pharmaceuticals, Inc. Sponsor Representative

Date

Version History

Ver. No.	Approval Date	Comment
1.0	23 June 2015	Initial submission
2.0	08 September 2015	Revisions based on Food and Drug Administration review and MD Anderson Cancer Center Clinical Research Committee review
3.0	11 January 2016	Revisions made in order to align patient management with the labeled safety guidance for ipilimumab (Yervoy®, USPI) and current pivotal study designs for other agents in metastatic melanoma, as well as administrative updates and updates for clarity.
4.0	10 May 2016	Revisions made to include IMO-2125 + pembrolizumab (Keytruda®, USPI) as a new treatment arm and to modify the secondary and exploratory objectives/endpoints Additional clarity around the rationale for study design and administrative changes have also been provided.
5.0	30 November 2016	• Removed Phase 2 randomization and the concurrent start of the two Phase 2 treatment arms to expedite the initiation of the Phase 2 ipilimumab + IMO-2125 treatment arm. • Allowed enrollment of additional Phase 1 cohorts at previously studied doses of IMO-2125 to facilitate selection of the RP2D(s). • In Phase 2, switched from irRC to irRECIST for objective response assessments. • Modification to enrollment criteria to provide a more homogeneous population for the primary efficacy analysis. • Added optional tumor biopsy at Week 1.
6.0	29 March 2017	• Extended the IMO-2125 treatment period to 9 doses to further evaluate the safety and clinical effects of IMO-2125 in patients with metastatic melanoma. Delayed responses to treatment (>12 weeks after the start of treatment) have been noted in advanced melanoma patients treated with immunotherapy agents (Wolchok, 2009). To further evaluate safety and potential clinical responses to treatment with IMO-2125, Protocol Amendment 2125-204 Version 6.0 extends the IMO-2125 treatment period. • Updated PK schedule. • Introduced the possible addition of cohorts for new immunotherapy combinations. Immunotherapy for the treatment of metastatic melanoma is a rapidly advancing field. There are new immunotherapy agents currently under investigation with some recently approved for marketed use. To expand the potential options for IMO-2125 development, the Sponsor may enroll patients in additional Phase 1 cohorts to investigate IMO-2125 in combination with other immunotherapies. • Corrections to irRC response assessments in Appendix 2 (Section 21.2).

7.0	01 September 2017	• Allows for enrollment of patients who have received prior ipilimumab, (including the ipilimumab/PD-1 inhibitor combination) now that preliminary safety and efficacy objectives have been achieved in the more restricted ipilimumab-naïve population • Increases the cohort size for the Phase 2 IMO-2125 + ipilimumab to improve the precision of the ORR estimate in the primary efficacy population. • Updates pembrolizumab dosing to use the 200 mg fixed dose to be consistent with the current labeling as of July 2017. • Updates the list for selection priority of the injected tumors. • Updates Section 9.2.1 to include an optional biopsy of the non-injected lesion at Week 2. • Clarifies that the concomitant medications reporting period starts at 30 days before the patient signs consent (Section 10.7.1). • Adds disease control rate (DCR) endpoint. • Clarifies that the assessment of exploratory endpoints will be based on assessments at Week 23 not Week 29. • Correction to the type of two-stage design for Phase 2 in the Synopsis and Section 16. • Additional updates in Section 16 (Statistical Analysis Methods) corresponding with the other updates.
8.0	27 March 2018	• Update Idera Medical Monitor contact. • Change response criteria used in the primary efficacy endpoint in the Phase 2 portion of the trial. • Add patient reported outcomes (PRO) assessments and corresponding statistical analysis text. • Inclusion of liquid-fill presentation of IMO-2125 as an option for use in the study. • Clarify post-treatment contraception use. • Clarify PK and cytokine sampling schedules. Please note the additional cytokine sample times on Day 1, 4 hours post-dose and pre-dose on Cycle 1 Week 2, to better characterize the IMO-2125 activity. • Add descriptions of immune-related AEs to be evaluated by Sponsor. • Allow Idera to collect scans for potential central independent review.

EMERGENCY CONTACT INFORMATION

Reporting of Serious Adverse Events (SAEs)

Any SAE must be entered in the Medidata RAVE Electronic Data Capture (EDC) system **within 24 hours.**

If the EDC system is not accessible, SAEs must then be captured on the back-up paper SAE form and reported **by fax within 24 hours** to:

CRO: SynteractHCR, Inc.
Fax: 760-268-6500
Phone: 760-268-8200
Email: safetyfax@synteracthcr.com

See Section 11.1 (Adverse Events) for definition and reporting procedure for SAEs.

Sponsor Medical Monitor:

Shah Rahimian, MD
Sr. Medical Director, Medical Lead (Oncology)
Phone: 484-348-1642
Cell: 814-691-7377
Email: srahimian@iderapharma.com

1. SYNOPSIS

Name of Sponsor/Company: Idera Pharmaceuticals, Inc.

Name of Investigational Product: IMO-2125

Title of Study: A Phase 1/2 Study to Assess the Safety and Efficacy of Intratumoral IMO-2125 in Combination with Ipilimumab or Pembrolizumab in Patients with Metastatic Melanoma

Study period: End of study will be approximately 1 year after the last patient in Phase 2 has commenced study treatment.	**Phase of development:** Phase 1/2

Rationale: IMO-2125 is a synthetic phosphorothioate oligonucleotide that acts as a direct agonist of Toll-like receptor (TLR) 9, stimulates both the innate and adaptive immune systems, and induces the expression of an array of endogenous cytokines and chemokines, including interleukin (IL)-1β, IL-6, IL-12, interferon (IFN)-α, IFN-γ, interferon gamma-induced protein (IP)-10, tumor necrosis factor (TNF)-α, and monocyte chemoattractant protein-1 (MCP-1). Of note, activation of TLR9 by IMO-2125 induces high levels of IFN-α from plasmacytoid dendritic cells (pDCs). This extensive profile of cytokines and chemokines results in the activation of both innate and adaptive immunity. Local innate immune activation through IMO-2125, administered by intratumoral injection may lead to enhanced induction and infiltration of tumor-specific CD8+ T cells and synergize with systemic therapies based on cytotoxic T lymphocyte antigen-4 (CTLA-4)/programmed cell death-1 (PD-1) blockade, resulting in superior anti-melanoma activity. Ipilimumab is a monoclonal antibody that binds to CTLA-4 and is used in the treatment of metastatic melanoma that cannot be treated surgically. Pembrolizumab is a PD-1-blocking antibody indicated for the treatment of patients with unresectable or metastatic melanoma. In combination, IMO-2125 with either ipilimumab or pembrolizumab may offer a novel therapy to benefit patients with metastatic melanoma.

Objectives:

Primary: The primary objective of Phase 1 is to characterize the safety and determine a recommended Phase 2 dose (RP2D) of IMO-2125 when administered in combination with ipilimumab or when administered in combination with pembrolizumab in patients with metastatic melanoma. The maximum tolerated dose (MTD) and RP2D for IMO-2125 may differ between the combination of IMO-2125 and ipilimumab and the combination of IMO-2125 and pembrolizumab.

The primary objective of Phase 2 is to assess preliminary clinical activity of IMO-2125 in combination with ipilimumab or in combination with pembrolizumab at the respective RP2D(s) in patients with metastatic melanoma that is not responsive to PD-1 inhibitor therapy, using Response Evaluation Criteria in Solid Tumors (RECIST) v1.1.

Secondary: The secondary objectives of Phase 1 are to determine the plasma pharmacokinetics (PK) of single-dose IMO-2125 and repeat-dose IMO-2125 administered by intratumoral injection in combination with ipilimumab or pembrolizumab. An additional secondary objective of Phase 1 is to describe any preliminary antitumor activity.

The secondary objectives of Phase 2 are to further assess the safety and tolerability of IMO-2125 in combination with ipilimumab or in combination with pembrolizumab in patients with metastatic melanoma and to assess treatment response using immune-related Response

Evaluation Criteria in Solid Tumors (irRECIST) and RECIST v1.1, overall survival (OS), OS at 6 and 12 months, progression-free survival (PFS), PFS at 6 and 12 months, durable response rate (DRR), duration of response (DoR), and disease control rate (DCR).

Exploratory: The exploratory objectives of Phase 1 and 2 are to assess patient reported outcomes (PRO), pre- and post-treatment blood biomarkers, pre- and post-treatment tumor biopsies for immunologic assessment, and explore any potential association between these biomarker measures and antitumor activity. In addition, anti-IMO-2125, anti-ipilimumab, and anti-pembrolizumab antibody formation will be assessed.

Endpoints

Primary: The primary endpoint of Phase 1 is to characterize the safety of IMO-2125 when administered in combination with ipilimumab or when administered in combination with pembrolizumab.

The primary endpoint in Phase 2 is clinical activity, defined as objective response as assessed by the Investigator using RECIST v1.1.

Secondary:

The secondary endpoints in Phase 1 are:

- PK assessments for IMO-2125;
- ORR assessed using irRC and RECIST v1.1

The secondary endpoints in Phase 2 include:

- Safety and tolerability (type and frequency of AEs, clinical laboratory values, electrocardiograms [ECGs], and vital sign measurements) for each combination;
- Duration of response using RECIST v1.1;
- ORR and duration of response using irRECIST;
- PFS, defined as time from the initiation of treatment to disease progression by irRECIST and RECIST v1.1, or death from any cause;
- PFS at 6 and 12 months;
- OS, defined as time from initiation of treatment to death from any cause;
- OS at 6 and 12 months;
- Durable response rate by irRECIST and RECIST v1.1, defined as the rate of complete response (CR) plus partial response (PR) lasting at least 180 days continuously and beginning within the first 12 months of study;
- Disease control rate by irRECIST and RECIST v1.1, defined as the rate of CR, PR, or stable disease (SD).

Exploratory: The pre- and post-treatment exploratory endpoints of Phase 1 and 2 include, but are not limited to, PRO using the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-CORE 30 (EORTC QLQ-C30), blood biomarkers (e.g., IFN-γ and other plasma cytokines) and tumor markers to assess any potential association between immune responses to IMO-2125 at the Week 8 tumor biopsy with tumor response in both injected and

uninjected tumor lesions at Week 13 or at Week 23 (depending on the protocol version under which the patients were enrolled).

Study design: This is a two arm, open-label Phase 1/2 study to assess the safety, tolerability, PK, immunogenicity, and efficacy of IMO-2125 when administered in combination with ipilimumab or in combination with pembrolizumab. Patients with metastatic melanoma who have experienced symptomatic or confirmed radiographic progression during or after treatment with an anti-PD-(L)1 agent (alone or in combination) will be eligible. Prior BRAF or MEK inhibitor treatment is not required. The study will be conducted in two parts: a dose-escalation portion (Phase 1) to evaluate safety and tolerability of multiple dose levels and a Phase 2 portion to assess preliminary efficacy.

Phase 1: The Phase 1 portion of the study will explore escalating dose levels of IMO-2125 (from 4 to 32 mg with de-escalation to 2 mg allowed for each IMO-2125 combination). For each cohort, IMO-2125 will be administered as a once-weekly intratumoral injection for 3 consecutive weeks in Cycle 1, followed by intratumoral injections on Weeks 5, 8, 11, 17, 23, and 29 (Day 1 of Cycles 2 through 7). Both ipilimumab and pembrolizumab will be administered as per the USPI every 3 weeks beginning Day 1 of Cycle 1 Week 2. Continued pembrolizumab dosing following the study period is permitted at the discretion of the Investigator for patients in the IMO-2125 + pembrolizumab treatment arm. The dosing schedule is summarized for Phase 1 and Phase 2 in the table below.

Schedule of dosing for Phase 1 and Phase 2

	Cycle															
	1				**2**			**3**			**4**			**5**	**6**	**7**
Study week	1	2	3	4	5	6	7	8	9	10	11	12	13	17	23	29
IMO-2125 + ipilimumab																
IMO-2125	X	X	X	-	X	-	-	X	-	-	X	-	-	X	X	X
Ipilimumab	-	X	-	-	X	-	-	X	-	-	X	-	-	-	-	-
IMO-2125 + pembrolizumab																
IMO-2125	X	X	X	-	X	-	-	X	-	-	X	-	-	X	X	X
Pembrolizumab	-	X	-	-	X	-	-	X	-	-	X	X[1]				

Note: On weeks when the combinations are administered, administration of ipilimumab or pembrolizumab will be first, followed by IMO-2125. IMO-2125 administration must occur within a ±2 day window of the scheduled dosing day.

[1] For patients in the IMO-2125 + pembrolizumab treatment arm, continued pembrolizumab dosing per the approved product label is permitted at the discretion of the Investigator.

Patients assigned to 11 weeks of IMO-2125 under previous versions of the protocol who have not yet reached the end of the Treatment Period may receive the Week 17, 23, and 29 injections at the discretion of the treating Investigator.

Each cohort will be monitored for the occurrence of dose-limiting toxicities (DLTs). The DLT evaluation period will be Cycle 1 (Weeks 1 through 4). If a patient discontinues study participation before the DLT evaluation period is finished due to reasons other than experiencing a DLT, that patient must be replaced so that the cohort may be properly evaluated.

There are 3 patients planned per cohort. During Phase 1, the Sponsor will assign patients to a

treatment arm (IMO-2125 + ipilimumab or IMO-2125 + pembrolizumab) by cohort. The Sponsor will maintain a prioritization schedule for cohort assignment in a separate document. A Cohort Review Committee (CRC) will be convened prior to each dose level escalation to review the available data and provide recommendations on study conduct. After completing the DLT evaluations for all planned IMO-2125 doses in either combination, supplemental cohorts of up to 5 patients each may be enrolled with either combination at doses up to and including the MTD. CRC review is not required for initiation of these supplemental cohorts but safety review meetings will still take place monthly throughout Phase 1 of the study. After completion of either Phase 1 treatment arm and determination of the RP2D for that arm, the Phase 2 portion for the completed treatment arm may be initiated. It is not necessary for Phase 1 to be completed in both treatment arms before Phase 2 is started. After Phase 2 in either treatment arm is initiated, the Sponsor will assign the treatment arm, cohort, and phase for patients.

Dose-limiting toxicity evaluations and CRC reviews for any additional immunotherapy combination cohorts will be done as described for the ipilimumab and pembrolizumab combinations.

Phase 2: The Phase 2 portion of the study will assess preliminary efficacy, using investigator-assessed RECIST v1.1, of IMO-2125 + ipilimumab, IMO-2125 + pembrolizumab, and any additional combinations that are studied in Phase 1. The dose level of IMO-2125 to be administered for each treatment arm will be the RP2D for the combination, as determined in Phase 1.

Phase 2 will enroll at least 60 patients treated at the IMO-2125 + ipilimumab RP2D. This will include at least 21 patients in the primary IMO-2125 + ipilimumab efficacy-evaluable population and up to 20 patients in the secondary IMO-2125 + ipilimumab efficacy-evaluable population.

In the IMO-2125 + pembrolizumab Phase 2 cohort, enrollment will continue until 21 patients in the IMO-2125 + pembrolizumab efficacy-evaluable population have been treated at the IMO-2125 + pembrolizumab RP2D.

Phase 1 patients treated at RP2D for either combination will contribute to these totals. A two-stage design will be used to test for clinically and statistically relevant clinical activity. A treatment arm will stop if an interim futility analysis shows there is insufficient evidence of a clinically relevant response rate after 10 patients (Stage 1).

If a patient discontinues treatment before completing at least one efficacy evaluation for reasons other than toxicity, then that patient will be replaced, with the replacement assigned to the same treatment arm and dose level as the patient who dropped out early.

Combination therapy in Phase 2 will continue using the same schedule as Phase 1, as presented in the schedule of dosing table.

Assessments will be conducted as defined in the Schedule of Evaluations (Table 1 and Table 2).

Number of patients (planned): The study will enroll approximately 90 to 100 patients. It is estimated that approximately 30 patients will be treated in the dose-finding portion of Phase 1 and approximately 60 to 70 additional patients will be treated in the Phase 2 portion of the study.

Diagnosis and main criteria for inclusion and exclusion:

These criteria apply to both the Phase 1 dose-escalation portion and the Phase 2 portion of this study.

Inclusion criteria

1) Patients must have histologically confirmed metastatic melanoma with measurable, stage III (lymph node or in transit lesions) or stage IVA, IVB, or IVC disease.
2) Patients must have symptomatic or radiographic progression during or after treatment with a PD-(L)1 inhibitor administered either as monotherapy or in combination.
    a. The interval between last PD-(L)1 directed treatment and start of study treatment should be at least 21 days.
    b. Prior BRAF or MEK inhibitor treatment is not required. However, for patients with known BRAF status:
        i. Those with BRAF wild type may have had a maximum of two previous systemic regimens for the treatment of melanoma.
        ii. Those with a BRAF mutation may have had a maximum of three previous systemic regimens for the treatment of melanoma.
    c. Prior ipilimumab is permitted.
    d. Previous treatment with either a PD-1 inhibitor (for patients enrolling on the IMO-2125 + pembrolizumab combination) or CTLA-4 inhibitor (for patients enrolling on the IMO-2125 + ipilimumab combination) should not have been accompanied by DLT for which permanent discontinuation is recommended (per USPI).
        i. Patients with a history of Grade ≥2 gastrointestinal symptoms (e.g., diarrhea, colitis) during prior checkpoint inhibitor treatment should be discussed with the Idera Medical Monitor during the Screening Period before starting study treatment.
3) Phase 1 patients must have at least two measurable tumor lesions ≥ 1.0 cm that are accessible to biopsy. Phase 2 patients must have at least one measurable lesion (per RECIST v1.1) which may be the same site that is used for the intratumoral injections.
4) Patients must be ≥18 years of age.
5) Patients must have Eastern Cooperative Oncology Group (ECOG) Performance Status ≤2.
6) Patients must meet the following laboratory criteria:
    a. Absolute neutrophil count (ANC) ≥ 1.5 x 10^9/L (1500/mm^3)
    b. Platelet count ≥75 x 10^9/L (75,000/mm^3)
    c. Hemoglobin ≥8.0 g/dL (4.96 mmol/L)
    d. Serum creatinine ≤1.5 x upper limit of normal (ULN) or calculated creatinine clearance ≥60 mL/minute
    e. Aspartate aminotransferase (AST) ≤2.5 x ULN; alanine aminotransferase (ALT) ≤2.5 x ULN; AST/ALT <5 x ULN if liver involvement
    f. Serum bilirubin ≤1.5 x ULN, except in patients with Gilbert's Syndrome who must have a total bilirubin <3 mg/dL

7) Women of childbearing potential (WOCBP) and men must agree to use effective contraceptive methods from Screening throughout the study treatment period and until at least 90 days after the last dose of IMO-2125, 3 months after the last dose of ipilimumab, or at least 4 months after the last dose of pembrolizumab.

   Non-childbearing potential is defined as a woman who meets ***either*** of the following criteria: a) postmenopausal state defined as no menses for 12 months without an alternative medical cause, or b) documented hysterectomy, bilateral tubal ligation, or bilateral oophorectomy.

   Effective contraception methods are defined as ***one*** of the following:

   a. True abstinence, defined as refraining from heterosexual intercourse, when this is in line with the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods), declaration of abstinence for the duration of a trial, and withdrawal are not acceptable methods of contraception.
   b. Condoms and spermicide
   c. Diaphragm and spermicide
   d. Oral or implanted hormonal contraceptive (e.g., Implanon™)
   e. An intra-uterine device (IUD)

8) WOCBP must have a negative pregnancy test (serum or urine) prior to the first dose of study treatment.
9) Patients must be willing and able to sign the informed consent and comply with the study protocol.
10) Patients must have an anticipated life expectancy >3 months.

Exclusion criteria

1) Patients who have received prior therapy with a TLR agonist, excluding topical agents. Patients who have received experimental vaccines or other investigational immune therapies should be discussed with the Medical Monitor to confirm eligibility.
2) Patients who have received systemic treatment with IFN-α within the previous 6 months prior to enrolling into this study.
3) Patients with known hypersensitivity to any oligodeoxynucleotide.
4) Patients with active autoimmune disease requiring disease-modifying therapy.
5) Patients requiring concurrent systemic steroid therapy higher than physiologic dose (7.5 mg/day of prednisone).
6) Patients with any form of active primary or secondary immunodeficiency.
7) Patients with another primary malignancy that has not been in remission for at least 3 years. The following are exempt from the 3 year limit: non-melanoma skin cancer, curatively treated localized prostate cancer with non-detectable prostate-specific antigen, cervical carcinoma in situ on biopsy or a squamous intraepithelial lesion on Papanicolaou (Pap) smear, and thyroid cancer (except anaplastic).
8) Patients with active systemic infections requiring antibiotics or active hepatitis A, B, or C.

9) Patients who are hepatitis B surface antigen positive.
10) Patients with a known diagnosis of human immunodeficiency virus (HIV) infection.
11) WOCBP who are pregnant or breast-feeding.
12) Patients who have had prior anaphylactic or other severe infusion reaction associated with human antibody administration.
13) Patients with known central nervous system, meningeal, or epidural disease. Patients with stable brain metastases following definitive local treatment are eligible if steroid requirement is less than 7.5 mg/day of prednisone (or equivalent).
14) Patients with impaired cardiac function or clinically significant cardiac disease such as:
    a. New York Heart Association Class III or IV cardiac disease, including preexisting clinically significant ventricular arrhythmia, congestive heart failure, or cardiomyopathy
    b. Unstable angina pectoris ≤6 months prior to study participation
    c. Acute myocardial infarction ≤6 months prior to study participation
    d. Other clinically significant heart disease (i.e., Grade ≥3 hypertension, history of labile hypertension, or poor compliance with an anti-hypertensive regimen)
15) Ocular melanoma.

Investigational product, dosage, and mode of administration:

In Phase 1, the starting dose of IMO-2125 will be 4 mg (Dose Level +1) for the ipilimumab combination, and 8 mg (Dose Level +2) for the pembrolizumab combination (with de-escalation to 2 mg allowed for each combination). IMO-2125 dose level escalation or de-escalation for each combination will be done independently of the other combinations, as appropriate, when the respective targets are functionally distinct.

IMO-2125 will be administered by intratumoral injection for all doses and ipilimumab or pembrolizumab will be administered per the labeled guidance using commercial supplies. Administration of ipilimumab or pembrolizumab will precede IMO-2125 when administered in the same week; IMO-2125 dosing must occur on the scheduled dosing day (±2 day window). Note that tumor biopsies should be done prior to study treatment administration. If a full dose can no longer be practically administered into the designated tumor for injection, another tumor may be selected. In the event that complete tumor regression occurs in all accessible lesions prior to completion of therapy, any remaining IMO-2125 doses should be administered into the tumor bed, except in the case of visceral lesions where remaining doses should be given s.c. to minimize procedural risks.

Dose escalation: Up to five dose levels for IMO-2125 are initially planned (as shown in the table below).

Dose Level	IMO-2125	Ipilimumab	Pembrolizumab
-1	2 mg	3 mg/kg	200 mg
+1	4 mg	3 mg/kg	200 mg
+2	8 mg	3 mg/kg	200 mg
+3	16 mg	3 mg/kg	200 mg
+4	32 mg	3 mg/kg	200 mg

In Phase 1, the study will enroll patients in planned cohorts of 3, beginning at Dose Level +1 for the ipilimumab treatment arm and beginning at Dose Level +2 for the pembrolizumab treatment arm once safety of the IMO-2125 + ipilimumab combination has been established for that level. A charter will be used to guide the CRC's decision-making.

Additionally, if, due to observed toxicity, it proves difficult to provide IMO-2125 for 3 consecutive weeks in Cycle 1, the decision may be taken by the CRC to add cohorts where alternative schedules of IMO-2125 administration will be explored.

The MTD will be determined from the assessment of DLTs during the first treatment cycle of each cohort. Using a prior beta(1,1) distribution of the DLT rate δ_i for each dose level i, the MTD is defined as the highest dose level for which the mean of the posterior distribution of toxicity is closest to but less than 25% among all the evaluated doses i for which $Pr(\delta_i > 0.25 \mid data) < 0.80$.

The RP2D(s) will be selected from dose level(s) at or below the MTD. Additional dose levels may be studied if the MTD(s) have not been reached and pharmacodynamic activity is deemed to be inadequate. At the time of completion of the Phase 1 portion of the study, an analysis of the data will be performed.

Assuming a prior beta(0.6, 1.4) distribution for the overall toxicity rate for a treatment, a Phase 2 arm will terminate if the $Pr(\delta_t > 0.25 \mid data) > 0.80$, where δ_t is the DLT rate attributable to the treatment.

Dose-limiting toxicities: Toxicity will be evaluated according to the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) v4.03 toxicity criteria. Dose-limiting toxicities are defined in Section 8.1.5 and should be referenced throughout the Phase 1 and 2 portions of the study. The DLT evaluation period will be Cycle 1 (Weeks 1 through 4).

For the purposes of dose level escalation and determination of the MTD(s), only DLTs (as defined below) that occur during the first cycle of treatment will be considered in the decisions regarding dose level escalation; however, DLTs or other clinically significant toxicities that occur throughout the observation period will be considered when determining the RP2D(s) for use in this trial and in subsequent clinical trials.

During Cycle 1 of the dose escalation portion, if two of the three patients in a cohort experience the same Grade 2, treatment-related AE, then subsequent increases in dose level will proceed in increments less than 100%. If more than one cohort is treated at the same dose level and greater than 67% of patients treated at that dose level experience the same Grade 2 treatment-related AE, dose level escalation will proceed in increments less than 100% (see table of planned dose level escalation above). In such a case, specific dose level increments will be decided by the CRC.

Protocol-defined hematologic DLTs include:

- CTCAE Grade 4 neutropenia ≥7 days;
- CTCAE Grade 3 or 4 neutropenia with fever ≥38.5°C;
- CTCAE Grade 3 thrombocytopenia with bleeding;
- CTCAE Grade 4 thrombocytopenia ≥7 days.

Protocol-defined non-hematologic DLTs include:

- Grade ≥3 vomiting or nausea ≥ 14 days despite the use of optimal anti-emetic treatments;
- Grade ≥3 diarrhea ≥14 days despite the use of optimal anti-diarrheal treatments which should include infliximab as per institutional guidelines;
- Serum creatinine >3.0 x ULN;
- AST or ALT >5 x ULN; in patients with liver metastasis who entered the study with Grade 2 elevation of AST or ALT, an AST or ALT increase ≥ 50% relative to baseline and lasting ≥1 week;
- Bilirubin ≥3.0 x ULN;
- Bilirubin ≥2.0 x ULN with ALT >3 x ULN in patients without liver metastases;
- Other non-hematologic toxicities of Grade ≥3, except for the following:
  - AEs related to underlying disease;
  - CTCAE Grade 3 fatigue <14 days;
  - Alopecia;
  - Isolated, asymptomatic elevations in biochemistry laboratory values lasting ≤14 days. This includes electrolyte abnormalities that respond to medical intervention.

Ipilimumab-related DLTs:

- Grade ≥4 immune-mediated dermatitis (except skin reaction at site of injection);
- Grade ≥3 immune-mediated endocrinopathy (with the exception of Grade 3 autoimmune thyroiditis that resolves to Grade 1 or baseline within 28 days of onset);
- Grade ≥3 immune-mediated enterocolitis;
- Grade ≥3 immune-mediated hepatitis with the exception of Grade 3 immune-mediated hepatitis that resolves to Grade 1 or baseline within 28 days of onset;
- Grade ≥3 immune-mediated neuropathy, pancreatitis, meningitis, nephritis, and pneumonitis that are considered to be possibly, probably, or definitely related to study therapy as determined by the Investigator;
- Any persistent IMO-2125-related toxicity that leads to a delay of scheduled (per standard of care) ipilimumab >14 days.

Pembrolizumab-related DLTs:

- Grade ≥3 pneumonitis or recurrent Grade 2 pneumonitis;
- Grade ≥3 nephritis;
- Grade ≥3 infusion-related reactions;
- Inability to reduce corticosteroid dose to 10 mg or less of prednisone or equivalent per day within 12 weeks;
- Any Grade ≥3 treatment-related AE that recurs.

If at any time during the study, a patient experiences a DLT as outlined above, the toxicity in question must be assessed for attribution based on the known toxicity profiles for ipilimumab, pembrolizumab, and IMO-2125. If assessment can be clearly attributed to one of the drugs in the

combination, then dosing should be interrupted and the toxicity should be followed until resolution, stabilization, or return to baseline. Treatment with the other agent may continue during this time period. If attribution cannot be clearly ascribed to one agent versus the other, then both IMO-2125 and ipilimumab (or pembrolizumab) should be stopped and the toxicity should be followed until resolution, stabilization, or return to baseline. If treatment is to be resumed, then re-initiation criteria must be met. If the DLT was clearly related to IMO-2125 or if attribution cannot be clearly determined, then IMO-2125 must be administered at a lower dose level (a minimum reduction of at least one dose level). If the DLT recurs after a dose level reduction, then treatment should be discontinued.

Patients who experience a non-laboratory, IMO-2125-related DLT must be evaluated weekly, at a minimum, until resolution to Grade ≤1 or baseline and then at least monthly until return to baseline or stabilization of the event, whichever comes first. For abnormal laboratory values that qualify as DLTs, patients will be followed twice weekly until values return to Grade ≤1 or baseline, whichever comes first.

Criteria for re-initiation of study treatment following occurrence of a DLT are as follows:

- ANC must be ≥1.5 x 10^9/L (1500/μL);
- Platelets must be ≥75 x 10^9/L (75,000/μL);
- All clinically significant non-hematologic toxicities for which a causal association to study treatment cannot be ruled out must be Grade ≤1 (except alopecia) or returned to baseline.

If the patient does not meet these criteria, dosing will be delayed and the patient should be re-evaluated within 48 to 72 hours. If the next cycle is delayed by more than 21 days for toxicity, the patient should be removed from study treatment. In these situations, if the patient is experiencing clinical benefit and has a favorable risk/benefit profile, study treatment with IMO-2125 may be continued if agreed upon by the Sponsor and the Investigator.

Duration of study: The study treatment period is 29 weeks in the absence of intolerable toxicity or unequivocal disease progression. Continued treatment with pembrolizumab following the completion of IMO-2125 study treatment is at the discretion of the Investigator for patients in the IMO-2125 + pembrolizumab treatment arm.

The study ends approximately 1 year after the last patient in Phase 2 has commenced study treatment. Patients who complete or discontinue study treatment prior to progression will be followed for clinical and radiological evidence of progression, PRO assessments, and immunogenicity assessments at least every 3 months until documentation of RECIST v1.1 progressive disease (PD), start of a subsequent anti-cancer treatment regimen, withdrawal of consent, death, or Sponsor notification that follow-up is no longer required, whichever comes first. Best response to first subsequent therapy, AEs which are Grade ≥3, and concomitant medications used to treat these AEs, will also be captured during the follow-up phase of the study.

After documentation of PD or use of a subsequent anti-cancer treatment regimen, all patients will be contacted by telephone every 3 months for survival follow-up until the site is notified by the Sponsor that survival follow-up is no longer required.

Assessments

Safety: Safety assessments will include a comprehensive evaluation of AEs and/or toxicity based on:

- Results of monitoring vital signs (blood pressure, heart rate, respiratory rate, and body temperature);
- Results of clinical chemistry, hematology/coagulation, complement testing, thyroid function testing, and urinalysis tests;
- ECG results;
- Changes in physical examination;
- Need for concomitant medications;
- ECOG performance status.

Hematology assessment will include a complete blood count (CBC) with a differential and a coagulation profile will include prothrombin time (PT) and activated partial thromboplastin time (aPTT). The clinical chemistry panel will include the liver function tests (AST, ALT, and serum bilirubin), blood urea nitrogen, complement (total hemolytic complement activity 50 [CH50], and complement components C3 and C4), and serum creatinine. The urinalysis will include urinary protein.

Pharmacokinetics: The plasma PK of single-dose IMO-2125 and the PK of repeat-dose IMO-2125 administered by intratumoral injection in combination with ipilimumab or pembrolizumab will be evaluated at each of the dose levels. The following parameters will be determined for IMO-2125 plasma PK, if appropriate:

- Maximum plasma concentration (C_{max});
- Time of C_{max} (t_{max});
- Area under the curve from 0 to last measurable plasma concentration (AUC_{0-t}).

Serum concentrations of ipilimumab and pembrolizumab will be monitored on Weeks 2, 5, 8, 11, 17, and 23. For patients who continue pembrolizumab treatment, pembrolizumab pre-dose PK samples should be collected before dosing at all visits. A post-dose pembrolizumab PK sample should be collected 30 minutes after the initiation of pembrolizumab infusion at Week 23 (if administered).

Efficacy: Efficacy will be evaluated by clinical examination and imaging studies. Treatment decisions should be based on patient benefit as assessed by irRC in Phase 1 and by irRECIST in Phase 2 rather than RECIST v1.1.

Exploratory: Exploratory variables will be assessed at pre-treatment and post-treatment and may include, but are not limited to:

- PRO: Periodic assessments will be made using the EORTC-QTQ-C30
- Biomarkers (CD8+ T cells, natural killer cells, pDC/myeloid DC, memory T cells in tumor tissue, T cells, and cytokine levels in blood)
- Any potential association between these biomarkers and antitumor activity

- Gene profiling (with ribonucleic acid [RNA] and deoxyribonucleic [DNA] extraction)
- Immunogenicity (antibodies to IMO-2125, ipilimumab, and pembrolizumab)

For Phase 1, biopsies of the injected tumor will be performed at the Screening Visit (within 21 days prior to first treatment); within 24 to 48 hours after IMO-2125 injection on Week 1 (Cycle 1); Week 2 (Cycle 1; optional); during Week 8 (Cycle 3); and optionally at Week 13 (Cycle 4) and at the time of disease progression or during Week 23, whichever is later. Tumor biopsies of the designated non-injected lesion will be performed at Screening, prior to the first dose of ipilimumab or pembrolizumab (optional), and during Week 8. For Phase 2, tumor biopsies are optional at all specified visits. Surgical methods (e.g., punch or core) are preferred over Fine Needle Aspiration where feasible.

Biopsies should be done prior to study treatment administration. For those patients who have liver or other visceral metastases injected with IMO-2125, repeat biopsy of liver or other visceral tumor lesions may not always be possible. Therefore, repeat biopsies will be performed only when feasible in these patients.

The Week 8 (Cycle 3) and Week 13 (Cycle 4) biopsies may be performed within a ±3 day window. If tumor response is observed early during initial treatment, the Week 8 biopsies may be performed at an earlier time point so as to ensure meaningful biomarker information is obtained prior to complete resolution of tumor.

Statistical methods: Continuous variables will be summarized using descriptive statistics such as mean, standard deviation, median, and range. Categorical variables will be summarized by count and proportion, and if specified, with 95% confidence intervals for the proportion. Missing data will not be imputed except as described in the Statistical Analysis Plan.

Data will be analyzed at the end of dose-finding for each treatment. Phase 2 data will be analyzed at the end of Phase 2 (approximately 1 year after the last patient in Phase 2 has commenced study treatment).

Efficacy populations will include:

- Primary Ipilimumab + IMO-2125 Efficacy Evaluable (PIIEE) Population: all patients who are ipilimumab-naïve on study entry (including those who received ipilimumab only in the adjuvant setting); and who are treated at the RP2D for the IMO-2125 + ipilimumab combination, regardless of which phase of the study they receive it; and who received at least one dose of each study drug.
- Secondary Ipilimumab + IMO-2125 Efficacy Evaluable (SIIEE) Population: all patients who are not ipilimumab-naïve on study entry; and who are treated at the RP2D for the IMO-2125 + ipilimumab combination, regardless of which phase of the study they receive it; and who received at least one dose of each study drug.
- Primary Pembrolizumab + IMO-2125 Efficacy Evaluable (PPIEE) Population: all patients who are treated at the RP2D for the IMO-2125 + pembrolizumab combination, regardless of which phase of the study they receive it; and who received at least one dose of each study drug.
- Safety Population: all patients who received at least one dose of IMO-2125.
- DLT Evaluable Population: all patients in the Safety Population who continue

participation in the study for the entire DLT evaluation period, or who discontinue prematurely due to a DLT.

- PK Population: All subjects in the Safety Population who have ≥1 post-dose sample analyzed for study drug.

Analysis of Efficacy

The primary efficacy endpoint, ORR assessed by the Investigator using RECIST v1.1, will be analyzed for the first 21 efficacy-evaluable patients in the PIIEE Population using a one-sided, one sample exact binomial test with $\alpha = 0.025$ in each test. The proportion of patients achieving an overall response will be tested against the null rates of 0.11 and 0.05 for ipilimumab and pembrolizumab, respectively. ORR by RECIST v1.1 will also be summarized descriptively for all subjects in the PIIEE.

The ORR and DCR using irRECIST criteria will be summarized descriptively in the PIIEE, SIIEE, and PPIEE Populations by dose with the n, percentage, and exact 95% confidence intervals. DCR will also be summarized by RECIST v1.1.

The OS and PFS proportions will be estimated at 6 and 12 months; OS and PFS will also be analyzed overall. For time-to-event endpoints (OS, PFS, and DoR), the Kaplan-Meier method will be used to estimate the probability of event-free survival. Patients who have not experienced the event at the data cut-off date for study closure will be censored. Patients who are lost to follow up will be censored at the last valid disease assessment for PFS and date of last contact for OS. Kaplan-Meier plots will be produced for OS and PFS by treatment arm.

Analysis of Exploratory Endpoints

Patterns of missing data will be described for PRO. Mean change from Baseline in the global health status score over time will be summarized and presented graphically. A mixed model for repeated measures may be used to assess the statistical significance of changes from Baseline. Exploratory endpoint analyses will be fully described in the statistical analysis plan.

Determination of Sample Size

The primary objective of Phase 2 is to assess the preliminary clinical activity, defined as the investigator-assessed ORR, of IMO-2125 in combination with ipilimumab or of IMO-2125 in combination with pembrolizumab in patients with progression on or following PD-(L)1 inhibitor therapy for metastatic melanoma. Given that two primary hypotheses are being tested (regarding the ORR of IMO-2125 and ipilimumab and the ORR of IMO-2125 and pembrolizumab), a Bonferroni correction has been applied to the alpha to control the Type I error rate for the trial.

Assuming the ORR for patients who receive ipilimumab alone is at most 11% (the historical response rate in patients who are PD-1 inhibitor naïve), and a target ORR of 35% for patients who receive IMO-2125 + ipilimumab combination treatment, a sample size of 21 patients would achieve 77% power to detect a 24% difference in response rates using a one-sided significance level of 2.5%.

The IMO-2125 + ipilimumab treatment arm will use a two-stage design with a targeted Type I error rate of 0.025 to test the null response rate of 0.11 against the alternative of at least 35%. With this method, 10 patients will be treated and monitored for a RECIST v1.1 response in the first stage. For this arm, if 2 or more patients have a RECIST v1.1 response in Stage 1, then the

treatment arm will continue to Stage 2, in which 11 more patients will be treated. If at least 6 of the 21 total patients have a RECIST v1.1 response, then the null hypothesis H_o will be rejected in favor of the alternative H_a. In this treatment arm, this design has statistical power of 77%, an expected sample size of 13.33 under the null hypothesis, and a probability of stopping at the end of the first stage of 69.7% if the response proportion is ≤0.11.

Assuming a RECIST v1.1 ORR for patients who receive pembrolizumab alone following failure of a PD-1 inhibitor is at most 5%, and a target ORR of 35% for patients who receive IMO-2125 + pembrolizumab combination treatment, a sample size of 21 efficacy-evaluable patients would achieve 96% power to detect a 30% difference in response rates using a one-sided significance level of 2.5%.

The IMO-2125 + pembrolizumab treatment arm will use a two-stage design with a targeted Type I error rate of 0.025 to test the null response rate against the alternative of at least 35%. If at least 1 patient has a RECIST v1.1 response in Stage 1, then the treatment arm will continue to Stage 2 and treat 11 additional patients. If at least 4 of the 21 total patients have a RECIST v1.1 response, then the null hypothesis H_o will be rejected in favor of the alternative H_a. In this treatment arm, this design has statistical power of 96%, an expected sample size of 14.41, and a probability of stopping at the end of the first stage of 60% if the response proportion is ≤0.05.

Analysis of PK

For each cohort, the plasma IMO-2125 concentration data will be analyzed by non-compartmental PK analysis. Descriptive statistics will be provided for concentration data and all PK assessment values by study drug (IMO-2125, ipilimumab, and pembrolizumab), dose, and time, as appropriate.

Dose proportionality using the power model will be evaluated in an exploratory manner, if the data permit. If insufficient data are available to assess dose proportionality using the power model, dose normalized data will be presented for a graphical assessment.

The potential effects of IMO-2125 on the PK of ipilimumab and pembrolizumab will be evaluated.

Date of Synopsis: 27 March 2018

Table 1: Phase 1: Schedule of Evaluations

Week [4]	Screen [5]	Treatment Period (Cycle [1])													Follow-up	
		1			2	3	4			5		6		7	Safety [2]	Ongoing [3] (every 3 months)
		1	2	3	5	8	11	13	14	17	20	23	26	29/ EOT	32	
Informed consent	X															
Inclusion/Exclusion	X															
Demogr/med hx [6]	X															
Adverse events	Continuous															X [7]
Concomitant Meds		Continuous														X [8]
ECOG	X	X			X	X	X			X		X		X	X	
CBC with diff	X	X	X	X	X	X	X			X		X		X	X	
Coagulation [9]	X	X [10]			X	X	X			X		X		X	X	
Chemistry profile	X	X [10]	X	X	X	X	X			X		X		X	X	
Thyroid functions	X		X		X	X	X			X		X		X	X	
CH50/C3/C4	X				X	X	X			X		X		X	X	
Urinalysis	X					X				X					X	
Vital signs [11]	X	X	X	X	X	X	X			X		X		X	X	
ECG	X		X [12]				X[12]								X	
Directed physical [13]	X	X			X	X	X			X		X		X	X	
Pregnancy test	X														X	
Tumor biopsies/biomarkers [14, 19]	X	X [15]	X [16]			X		X [16]				X [16]				
Blood biomarkers [19]		X [17]	X [17]		X[18]	X[18]								X [18]		
Radiology	X					X [20]				X [20]				X [20]		X [21]
Response [22]						X [20]				X [20]				X [20]		X [21]
PRO [23]		X				X				X				X		X [21]
IMO-2125 dosing		X	X	X	X	X	X			X		X		X		
Ipilimumab dosing			X		X	X	X									
Pembrolizumab dosing			X		X	X	X		X [24]	X [24]	X [24]	X [24]	X [24]	X [24]	X [24]	X [24]
PK testing [25]		X	X	X	X	X	X		X [26]	X [26]	X [26]	X [26]	X [26]	X [26]	X[26]	
Immunogenicity [27]		X			X		X			X		X		X	X	X[28]

Abbreviations: AE=adverse event; aPTT=activated partial thromboplastin time; C3=complement component 3; C4=complement component 4; CBC=complete blood count; CH50=total hemolytic complement activity 50; CR=complete response; Demogr=Demographic; diff=differential; ECG=electrocardiogram; ECOG=Eastern Cooperative Oncology Group; EOT= End of Treatment; hx=history; INR=international normalized ratio; irRC=immune-related response criteria; med=medical; PK=pharmacokinetic; PR=partial response; PRO=patient reported outcomes; PT=prothrombin time; RECIST=Response Evaluation Criteria in Solid Tumors

[1] Please note, the number of weeks per cycle varies. Cycle 1 is 4 weeks in length to account for an IMO-2125 priming dose. Cycles 2, 3, and 4 are 3 weeks in length, and Cycles 5, 6, and 7 are included as maintenance dosing and are 6 weeks in length.

[2] The Safety Follow-up Visit should be 21 days following the last dose of IMO-2125 (± 5 days).

[3] Includes ongoing follow-up every 3 months until documented disease progression, next melanoma treatment, withdrawal of consent, death, or Sponsor notification that follow-up is no longer required.

[4] All assessments and IMO-2125 dosing will occur within a ±2-day window. Ipilimumab and pembrolizumab will be dosed per their respective labels.

[5] All Screening tests and assessments must be performed within 21 days of the start of Week 1 of Cycle 1, unless otherwise noted. All patients who sign an informed consent and are screened and qualify for the study will be considered enrolled.

[6] Including melanoma history and prior melanoma treatment history.

[7] Grade ≤2 AEs do not need to be reported.

[8] Only concomitant medications for the treatment of Grade ≥3 AEs will be captured.

[9] PT, aPTT, INR.

[10] Chemistry profile and coagulation tests do not have to be conducted if Screening tests were conducted within 7 days of the Cycle 1 Week 1 Visit.

[11] Blood pressure, heart rate, respiratory rate, and temperature.

[12] Week 2 ECG pre-dose and at 2 hours post-IMO-2125 administration. Week 11 ECG at 2 hours post-IMO-2125 administration.

[13] Including assessment of melanoma lesions.

[14] Biopsy of the tumor to be injected with IMO-2125 and biopsy of a tumor that will not be injected. See Section 13.2 and the Laboratory Manual for details on the collection of biopsies and analyses of biomarkers.

[15] Biopsy of the injected tumor should occur within 24 to 48 hours after injection (no more than 48 hours). The blood biomarker samples will be collected on Day 1 before IMO-2125 administration then 4 hours (serum for cytokines), and within 24 to 48 hours after the injection, and also pre-dose at the Cycle 1 Week 2 Visit (serum for cytokines).

[16] Optional biopsy.

[17] The blood biomarker samples will be collected on Day 1 before IMO-2125 administration, then 4 hours (serum for cytokines), and within 24 to 48 hours after the injection, and also pre-dose at the Cycle 1 Week 2 Visit (serum for cytokines)

[18] To be collected pre-ipilimumab dosing and post-dosing.

[19] Biopsies and blood biomarker samples will not be performed ex-US.

[20] Radiologic assessment and Investigator assessment of response at Week 8, Week 17, and Week 29 may be conducted within a ±7-day window.

[21] At least every 3 months until progression, start of next melanoma treatment, withdrawal of consent, death, or Sponsor notification that follow up is no longer required.

[22] In Phase 1, response assessed using irRC and RECIST v1.1. Best response to first subsequent treatment should also be captured. Confirmatory scans for CR, PR, and progressive disease should be performed ≥4 weeks after the date the response was first documented.

[23] The PRO assessments should be completed before study drug administration and AE assessments.

[24] For patients assigned to the IMO-2125 + pembrolizumab treatment arm, continued pembrolizumab dosing per the approved product label is permitted at the discretion of the Investigator.

[25] PK: blood sampling for analysis of plasma concentrations of IMO-2125 and serum concentrations of ipilimumab, and pembrolizumab (See Table 3 for specific collection times).
[26] For patients who continue pembrolizumab treatment, pembrolizumab pre-dose PK samples should be collected before dosing at all visits. A post-dose pembrolizumab PK sample should be collected 30 minutes after initiation of pembrolizumab infusion at Week 23 and Week 32. Pharmacokinetic samples at Week 32 are optional.
[27] Immunogenicity: blood sampling for analysis of antibodies to IMO-2125, ipilimumab, and pembrolizumab will be performed prior to any dosing at that visit.
[28] For patients in Ongoing Follow-up (i.e., those discontinued from study treatment before progression or new anticancer treatment), the immunogenicity samples are required at the scheduled visits. For patients in survival follow-up (i.e., after progressive disease or start of new anti-cancer treatment), immunogenicity assessments are optional (e.g., if a patient comes to the investigator site for a Survival Follow-up Visit rather than the usual telephone contact).

Table 2: Phase 2: Schedule of Evaluations

Week [4]	Screen [5]	Treatment Period (Cycle [1])												Follow-up	
		1			2	3	4			5		6		7	Safety [2]	Ongoing [3] (every 3 months)
		1	2	3	5	8	11	13	14	17	20	23	26	29/ EOT	32	
Informed consent	X															
Inclusion/Exclusion	X															
Demogr/med hx [6]	X															
Adverse events	Continuous															X [7]
Concomitant Meds		Continuous														X [8]
ECOG	X	X			X	X	X			X		X		X	X	
CBC with diff	X	X	X	X	X	X	X			X		X		X	X	
Coagulation [9]	X	X [10]			X	X	X			X		X		X	X	
Chemistry profile	X	X [10]	X	X	X	X	X			X		X		X	X	
Thyroid functions	X		X		X	X	X			X		X		X	X	
CH50/C3/C4	X				X	X	X			X		X		X	X	
Urinalysis	X					X				X					X	
Vital signs [11]	X	X	X	X	X	X	X			X		X		X	X	
ECG	X		X [12]				X[12]								X	
Directed physical [13]	X	X			X	X	X			X		X		X	X	
Pregnancy test	X														X	
Tumor biopsies/biomarkers [14, 17]	X	X [15]	X			X		X				X				
Blood biomarkers [17]		X [16]	X [16]			X[16]										
Radiology	X					X [18]				X [18]				X [18]		X [19]
Response [20]						X [18]				X [18]				X [18]		X [19]
PRO [21]		X				X				X				X		X [19]
IMO-2125 dosing		X	X	X	X	X	X			X		X		X		
Ipilimumab dosing			X		X	X	X									
Pembrolizumab dosing			X		X	X	X		X [22]	X [22]	X [22]	X [22]	X [22]	X [22]	X [22]	X [22]
PK testing [23]		X	X	X	X	X	X		X [24]	X [24]	X [24]	X [24]	X [24]	X [24]	X [24]	
Immunogenicity [25]		X			X		X			X		X		X	X	X[26]

Abbreviations: AE=adverse event; aPTT=activated partial thromboplastin time; C3=complement component 3; C4=complement component 4; CBC=complete blood count; CH50=total hemolytic complement activity 50; CR=complete response; Demogr=Demographic; diff=differential; ECG=electrocardiogram; ECOG=Eastern Cooperative Oncology Group; EOT= End of Treatment; hx=history; INR=international normalized ratio; irRECIST=immune-related Response Criteria in Solid Tumors; med=medical; PK=pharmacokinetic; PR=partial response; PRO=patient reported outcomes; PT=prothrombin time; RECIST=Response Evaluation Criteria in Solid Tumors; RP2D=recommended Phase 2 dose

[1] Please note, the number of weeks per cycle varies. Cycle 1 is 4 weeks in length to account for an IMO-2125 priming dose. Cycles 2, 3, and 4 are 3 weeks in length, and Cycles 5, 6, and 7 are included as maintenance dosing and are 6 weeks in length.

[2] The Safety Follow-up Visit should be 21 days following the last dose of IMO-2125 (± 5 days).

[3] Includes ongoing follow-up every 3 months until documented disease progression, next melanoma treatment, withdrawal of consent, death, or Sponsor notification that follow-up is no longer required.

[4] All assessments and IMO-2125 dosing will occur within a ±2-day window. Ipilimumab and pembrolizumab will be dosed per their respective labels.

[5] All Screening tests and assessments must be performed within 21 days of the start of Week 1 of Cycle 1, unless otherwise noted. All patients who sign an informed consent and are screened and qualify for the study will be considered enrolled.

[6] Including melanoma history and prior melanoma treatment history.

[7] Grade ≤2 AEs do not need to be reported.

[8] Only concomitant medications for the treatment of Grade ≥3 AEs will be captured.

[9] PT, aPTT, INR.

[10] Chemistry profile and coagulation tests do not have to be conducted if Screening tests were conducted within 7 days of the Cycle 1 Week 1 Visit.

[11] Blood pressure, heart rate, respiratory rate, and temperature.

[12] Week 2 ECG pre-dose and at 2 hours post-IMO-2125 administration. Week 11 ECG at 2 hours post-IMO-2125 administration.

[13] Including assessment of melanoma lesions.

[14] In Phase 2, all tumor biopsies are optional. See Section 13.2 and the Laboratory Manual for details on the collection of biopsies and analyses of biomarkers.

[15] Biopsy of the injected tumor should occur within 24 to 48 hours after injection (no more than 48 hours). The blood biomarker samples will be collected on Day 1 before IMO-2125 administration then 4 hours (serum for cytokines), and within 24 to 48 hours after the injection, and also pre-dose at the Cycle 1 Week 2 Visit (serum for cytokines).

[16] In Phase 2, blood biomarker samples will be collected from at least 20 patients treated at the IMO-2125 RP2D after which the Sponsor will determine if additional samples are needed. The blood biomarker samples will be collected on Day 1 before IMO-2125 administration, then 4 hours (serum for cytokines), and within 24 to 48 hours after the injection, and also pre-dose at the Cycle 1 Week 2 Visit (serum for cytokines) and Cycle 3 Week 8 Visit.

[17] Biopsies and blood biomarker samples will not be performed ex-US.

[18] Radiologic assessment and Investigator assessment of response at Week 8, Week 17, and Week 29 may be conducted within a ±7-day window.

[19] At least every 3 months until progression, start of next melanoma treatment, withdrawal of consent, death, or Sponsor notification that follow up is no longer required.

[20] In Phase 2, response assessed using irRECIST and RECIST v1.1. Best response to first subsequent treatment should also be captured. Confirmatory scans for CR, PR, and progressive disease should be performed ≥4 weeks after the date the response was first documented.

[21] The PRO assessments should be completed before study drug administration and AE assessments.

[22] For patients assigned to the IMO-2125 + pembrolizumab treatment arm, continued pembrolizumab dosing per the approved product label is permitted at the discretion of the Investigator.

[23] PK: blood sampling for analysis of plasma concentrations of IMO-2125 and serum concentrations of ipilimumab, and pembrolizumab (See Table 3 for specific collection times). For each combination in Phase 2, the collection of plasma concentration samples will be done on at least 20 patients treated at the IMO-2125 RP2D after which the Sponsor will determine if additional samples are needed.

[24] For patients who continue pembrolizumab treatment, pembrolizumab pre-dose PK samples should be collected before dosing at all visits. A post-dose pembrolizumab PK sample should be collected 30 minutes after initiation of pembrolizumab infusion at Week 23 and Week 32. Pharmacokinetic samples at Week 32 are optional.

[25] Immunogenicity: blood sampling for analysis of antibodies to IMO-2125, ipilimumab, and pembrolizumab will be performed prior to any dosing at that visit.

[26] For patients in Ongoing Follow-up (i.e., those discontinued from study treatment before progression or new anticancer treatment), the immunogenicity samples are required at the scheduled visits. For patients in survival follow-up (i.e., after progressive disease or start of new anti-cancer treatment), immunogenicity assessments are optional (e.g., if a patient comes to the investigator site for a Survival Follow-up Visit rather than the usual telephone contact).

Table 3: Schedule of PK Blood Sampling for IMO-2125, Ipilimumab, and Pembrolizumab

	Cycle 1			Cycle 2	Cycle 3	Cycle 4		Cycle 5		Cycle 6		Cycle 7	Safety Follow-up[1]
	Week 1	Week 2	Week 3	Week 5	Week 8	Week 11	Week 14	Week 17	Week 20	Week 23	Week 26	Week 29 /EOT	Week 32
IMO-2125													
Pre-dose	X	X	X	X	X	X						X	
Post-dose													X[2]
30 m (±5 m)	X					X						X	
1 h (±10 m)	X					X						X	
1.5 h (±10 m)	X					X						X	
3 h (±15 m)	X					X						X	
Ipilimumab													
Pre-dose		X		X	X	X		X [3]		X [3]			
Post-dose													X[2]
90 m after start of infusion (±5 m)		X				X							
Pembrolizumab													
Pre-dose		X		X	X	X	X	X	X	X	X	X	X[2]
Post-dose													
30 m after start of infusion (±5 m)		X				X				X			X[2]

Abbreviations: EOT=End of Treatment; h=hour; m=minute; PK=pharmacokinetic

[1] Collection of PK samples at the Safety Follow-up Visit is optional.

[2] IMO-2125 (plasma samples) and ipilimumab (serum) PK samples may be collected at any time during the Safety Follow-up Visit. Optional pre- and post-dose pembrolizumab serum PK samples are collected for those patients continuing pembrolizumab treatment at this visit. If pembrolizumab treatment was stopped, a sample may be collected at any time during the visit.

[3] Pre-IMO-2125 dose.

2. TABLE OF CONTENTS, LIST OF TABLES, AND LIST OF FIGURES

TABLE OF CONTENTS

LIST OF TABLES

3. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
βhCG	Beta human chorionic gonadotropin
δ	Dose-limiting toxicity rate
AE	Adverse event
ALT	Alanine aminotransferase
ANC	Absolute neutrophil count
aPTT	Activated partial thromboplastin time
AST	Aspartate aminotransferase
AUC_{0-t}	Area under the curve from 0 to last measurable plasma concentration
$AUC_{0-\infty}$	Area under curve from 0 to infinity
C3/C4	Complement component 3/4
CBC	Complete blood count
CFR	Code of Federal Regulations
CH50	Total hemolytic complement activity 50
CpG	Unmethylated CG dinucleotides (cytosine-phosphate-guanine)
CL/F	Clearance
C_{max}	Maximum plasma concentration
CPI	Checkpoint inhibitor
CR	Complete response
CRC	Cohort Review Committee
CRO	Contract Research Organization
CS	Clinically significant
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTLA-4	Cytotoxic T lymphocyte antigen-4
DCR	Disease control rate
DLT	Dose-limiting toxicity
DNA	Deoxyribonucleic acid
DoR	Duration of response
DRR	Durable response rate
EC	Ethics Committee
ECG	Electrocardiogram

Abbreviation	Definition
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
EDC	Electronic Data Capture
EE	Efficacy Evaluable
EORTC	European Organisation for Research and Treatment of Cancer
FDA	Food and Drug Administration
FNA	Fine Needle Aspiration
GCP	Good Clinical Practice
HCV	Hepatitis C virus
HIPAA	Health Insurance Portability and Accountability Act
HIV	Human immunodeficiency virus
ICF	Informed consent form
ICH	International Council for Harmonisation
IFN	Interferon
IL	Interleukin
IMO	Immune Modulatory Oligonucleotide
IP-10	Interferon-inducible protein-10
irAE	Immune-related adverse event
IRB	Institutional Review Board
irPD	irRECIST progressive disease
irRC	Immune-related response criteria
irRECIST	Immune-related Response Evaluation Criteria in Solid Tumors
ISR	Injection site reaction
IUD	intra-uterine device
i.v.	Intravenous(ly)
LFT	Liver function test
mAb	Monoclonal antibody
MCP	Monocyte chemoattractant protein
MRT	Mean residence time
MTD	Maximum tolerated dose
NCI	National Cancer Institute
NFκB	Nuclear factor kappa-light-chain-enhancer of activated B cells
NK	Natural killer

Abbreviation	Definition
ORR	Objective response rate
OS	Overall survival
PAMP	Pathogen-associated molecular pattern
Pap	Papanicolaou
PBMC	Peripheral blood mononuclear cell
PD	Progressive disease
PD-1	Programmed cell death-1
pDC	Plasmacytoid dendritic cell
PFS	Progression-free survival
PHI	Protected health information
PI	Principal Investigator
PIIEE	Primary Ipilimumab + IMO-2125 Efficacy Evaluable
PK	Pharmacokinetic
PPIEE	Primary Pembrolizumab + IMO-2125 Efficacy Evaluable
PR	Partial response
Pr	Probability
PRO	Patient reported outcomes
PT	Prothrombin time
QLQ-C30	Quality of Life Questionnaire-CORE 30
QoL	Quality of life
RANTES	Regulated on activation, normal T cell expressed and secreted
RBC	Red blood cell
RECIST	Response Evaluation Criteria in Solid Tumors
RNA	Ribonucleic acid
RP2D	Recommended Phase 2 dose
SAE	Serious adverse event
s.c.	Subcutaneous(ly)
SD	Stable disease
SFU	Safety Follow-up
SIIEE	Secondary Ipilimumab + IMO-2125 Efficacy Evaluable
SUSAR	Suspected Unexpected Serious Adverse Reaction
$t_{1/2}$	Terminal exponential half-life
Th	T helper

Abbreviation	Definition
TIL	Tumor-infiltrating lymphocyte
TLR	Toll-like receptor
TNF-α	Tumor necrosis factor-alpha
t_{max}	Time of C_{max}
ULN	Upper limit of normal
USPI	United States product insert
Vd/F	Volume of distribution
WBC	White blood cell
WOCBP	Women of childbearing potential

4. BACKGROUND INFORMATION AND RATIONALE

4.1. Metastatic Melanoma: The Disease Under Study

Melanoma is a malignant tumor of melanocytes which are found predominantly in skin, but also in the mucous membranes and eye. Melanoma causes the majority of skin cancer-related deaths. In 2014, 76,100 people in the US were newly diagnosed with either invasive or in situ melanoma and 9,710 cases were fatal. While the incidence of many types of cancer has remained stable or declined, the incidence rates are increasing for melanoma and the probability of developing melanoma increases with age (Siegel 2015).

Although melanoma is a rare form of skin cancer, it comprises over 75% of skin cancer deaths. Patients with early (stage 1) lesions have 3-year survival rates (>90%); however, patients with late-stage melanoma often have poor prognoses and survival rates (≤10%) with a median survival of <8 months from time of diagnosis (Lachiewicz 2008).

Melanoma treatment is dependent upon the stage of the cancer at the time of detection and the properties of the tumor. Tumors in early stages can be removed surgically. However, if a biopsy reveals that the cancer has metastasized and spread to lymph nodes, treatments are more likely to include radiation and chemotherapy regimens. While the goal of chemotherapy treatments is to induce apoptosis, or cell death, of the cancer cells, healthy noncancerous cells are often affected and are responsible for many of the adverse effects of systemic non-specific therapies. A new approach to cancer therapy is immunotherapy; stimulation of the patient's own immune mechanisms that are responsible for naturally eliminating cancer cells.

4.2. Current Standard of Care Therapy

Melanoma that has metastasized is typically treated with systemic therapy; surgery and radiation can be used in a palliative manner to treat symptoms of local tumor growth. Cytotoxic chemotherapies (both alone and in combinations) have been used for more than 30 years and include alkylating agents (dacarbazine, temozolomide, and nitrosoureas), the platinum analogs, and the microtubular toxins (vinca alkaloids and toxanes) (Bhatia 2009).

In 1998, the Food and Drug Administration (FDA) approved the use of recombinant interleukin (IL)-2 to treat advanced melanoma (Atkins, 1999; Atkins, 2000) and interferon (IFN)-α has also been used as treatment either after surgery or in combination with other melanoma therapies (Kirkwood, 2000). More recently, checkpoint inhibitors (CPIs) have emerged as a new immunology-based frontier to effect antitumor activity. Ipilimumab is a monoclonal antibody (mAb) targeted to cytotoxic T lymphocyte antigen-4 (CTLA-4). CTLA-4, present on CD4+ and CD8+ T lymphocytes is involved in maintaining a specific population of regulatory T cells and is a negative regulator of T cell activation (Brunet 1987; Levings 2001). By blocking the inhibitory action of CTLA-4, ipilimumab enhances immune function and has been found to augment T cell proliferation and activation (Walunas 1994). Pembrolizumab and nivolumab are mAbs targeted to programmed cell death-1 (PD-1) (Shin and Ribas 2015). The combination of ipilimumab with anti-PD-1 antibodies for the treatment of metastatic melanoma has demonstrated impressive antitumor activity, including 11.5 months median progression-free survival (PFS; Larkin 2015) and 61% objective response rate (ORR; Postow 2015), but with increased toxicity over

single-agent therapy. An unmet need remains in this patient population for novel CPI combination therapy approaches with improved safety profiles and an increased response rate (Zamarin and Postow 2015).

Intratumoral administration of IMO-2125 is a logical complement to CPIs. Intratumoral IMO-2125 has been shown in nonclinical models to improve systemic antitumor immunity through stimulation of local antigen presentation, generation of cytotoxic T lymphocytes, and increasing the number and extent of tumor-infiltrating T cells, which is highly correlated with the effectiveness of CPI therapy (Tumeh 2014).

4.3. Toll-like Receptors and Their Agonists

The human innate immune system recognizes biochemical patterns that may be associated with pathogens (pathogen-associated molecular patterns, or PAMPs). Immune system cells contain toll-like receptors (TLRs) that recognize PAMPs. Ten functional TLRs have been identified in humans. Some TLRs are expressed on the cell surface and recognize PAMPs such as lipopeptides, lipopolysaccharides, and flagellin. Other TLRs are expressed intracellularly on endosomal membranes and recognize single- and double-stranded ribonucleic acid (RNA; TLRs 3, 7, and 8) or deoxyribonucleic acid (DNA) containing unmethylated cytosine-guanine (CpG) dinucleotides (TLR9), which are patterns associated with viruses or bacteria. The cellular distribution of TLRs also varies. TLR9 in humans is expressed only in plasmacytoid dendritic cells (pDCs) and B cells, both of which are components of the peripheral blood mononuclear cells (PBMCs) (Takeda and Akira 2005; Wickelgren 2006). Activation of some TLRs causes signaling cascades that can promote cytokine production through the nuclear factor kappa-light-chain-enhancer of activated B cells (NFκB) or an IFN regulator factor mechanism (Abreu 2010).

TLR9 agonists induce pDCs to produce type I IFN and other cytokines and chemokines, which in turn activate other immune cells including T cells, monocytes, natural killer (NK) cells, and macrophages (Liu, 2005). Agonists of TLR9 also induce activation, differentiation, and proliferation of B cells (Bernasconi 2002). Together, the innate and adaptive immune responses generated through TLR9 produce a profile of potentially antitumor cytokines and chemokines, antigen-specific cytotoxic T lymphocytes, and enhanced antigen presentation capabilities (Liu 2005).

4.3.1. Toll-like Receptor Agonists in the Treatment of Solid Tumors

Human TLR7 and TLR9 are expressed primarily on pDCs (Takeda and Akira 2005; Wickelgren 2006), which play a fundamental role in the regulation of the immune response during tumor development. Plasmacytoid DCs are present in high numbers within cutaneous melanoma and tumor-draining lymph nodes; however, the infiltration of these cells is correlated with a poor clinical outcome. Within the melanoma tumor environment, pDCs were found to promote a T helper (Th) 2-type response with a regulatory immune profile, promoting tumor progression (Aspord 2013). In contrast, pDC activation via a TLR9 agonist facilitates Th1-type adaptive immune responses, including the generation of antigen-specific antibodies, cytotoxic T lymphocytes, and memory T cells, all of which can lead to T cell-mediated tumor destruction.

4.4. IMO-2125

4.4.1. Mechanism of Action

Immune Modulatory Oligonucleotide-2125 (IMO-2125), a novel phosphorothioate oligodeoxynucleotide, is composed of 2 strands of modified DNA joined at their 3' ends. IMO-2125 was created by Idera Pharmaceuticals, Inc. through a structure activity approach to the design of TLR-targeted drug candidates based on modifications of classical CpG DNA (Yu, 2002; Kandimalla, 2003; Kandimalla, 2005). IMO-2125 is designed to act as an agonist of TLR9.

IMO-2125, acting as an agonist of TLR9, induces a broad spectrum of innate and adaptive immune responses, including antigen-specific cytotoxic T lymphocyte responses. IMO-2125 stimulates pDCs and B cells through TLR9 to initiate a rapid innate immune response characterized by secretion of cytokines and chemokines including IL-1β, IL-6, IL-12, IFN-γ, interferon gamma-induced protein (IP)-10, tumor necrosis factor (TNF)-α, monocyte chemoattractant protein-1 (MCP-1), and, particular to pDC cells, high amounts of IFN-α. A secondary phase of the innate immune response is activation of NK cells, monocytes, and neutrophils and margination of lymphocytes out of systemic circulation. These hematological effects are evident consistently at 24 hours post-dose. T cells are induced by the cytokine/chemokine response into a Th1-type cellular response that includes production of cytotoxic T lymphocytes and antigen-specific memory T cells.

4.4.2. Nonclinical Pharmacodynamics

When IMO-2125 was subcutaneously (s.c.) administered into cynomolgus monkeys, plasma concentrations of IFN-α began to increase early, peaking at approximately 8 hours after treatment and remaining detectable for at least 96 hours at a dosage of 4 mg/kg (Trombino 2007a). Other signs of immune stimulation following in vivo administration of IMO-2125 included increased plasma concentrations of IL-12 and IP-10; changes in trafficking of white blood cells (WBCs), particularly a transient decrease peripheral blood lymphocytes at 24 hours post-dose; and increased expression of the activation marker CD69 on T cells, B cells, and NK cells (Trombino 2007b).

Peripheral blood mononuclear cells, including pDCs and B cells, were isolated from healthy volunteers and stimulated in vitro with IMO-2125 for 6 to 48 hours (Bhagat 2007a, Bhagat 2007b, Bhagat 2007c, Bhagat 2007d, Bhagat 2007e). IFN-α and IP-10 were induced in a time- and concentration-dependent manner. IMO-2125 also induced multiple other cytokines and chemokines, including IL-1β, IL-12, MCP-1, and regulated on activation, normal T cell expressed and secreted (RANTES). Further indications of in vitro immune stimulation in these cultures were the induction of B cell proliferation and increased expression of CD86 and CD69 activation markers on B cells and pDCs (Bhagat 2007f, Bhagat 2007g; Bhagat 2007h).

4.4.2.1. Studies in Models of Disease

The nonclinical rationale for use of IMO-2125 in immune oncology comes from mechanism of action studies in vitro and in vivo and from antitumor activity in mouse xenograft models. Clinical proof of concept is derived from studies in patients with chronic hepatitis C virus (HCV) infection.

- Cytokine induction profile in in vitro studies using human PBMCs and pDCs show IMO-2125 induces a wide range of cytokines and chemokines, including IFN-α, IP-10, MCP-1, MIP-1, MIP-1α, MIP-1β, and RANTES, which have been implicated in the intratumoral mechanism of action;
- Induction of IFN-α and IP-10 in cynomolgus monkeys, with activation of T cells, B cells, and NK cells;
- Tumor growth inhibition in murine xenograft models and induction of splenic CD8+ lymphocytes in combination with an anti-CTLA-4 mAb;
- Induction of IFN-α and IP-10 in clinical studies.

In summary, IMO-2125 has shown potent activity as a TLR9 agonist, particularly with regard to pDC production of IFN-α. Intratumoral administration in mouse xenograft models shows promising antitumor activity, especially in combination with an anti-CTLA-4 antibody representative of CPIs. IMO-2125 has been well tolerated in clinical studies with 4 weeks of once or twice weekly s.c. administration. The goal of the clinical development program for IMO-2125 in immune oncology is to demonstrate its safety and activity in combination with CPIs. This is the first study to evaluate IMO-2125 in combination with a marketed anti-CTLA-4 mAb and anti-PD-1 mAb in recurrent or metastatic melanoma.

4.5. Previous Human Experience

IMO-2125 strongly induces production of endogenous IFN-α and has been studied previously as a potential treatment for patients with chronic HCV infection with the FDA Division of Antiviral Products. Two studies have been conducted with systemic administration of IMO-2125; both studies were conducted in patients with HCV infection. IMO-2125 was administered s.c. at dosages up to 0.48 mg/kg/week in 96 patients. Full details are provided in the Investigator's Brochure. The most common adverse events (AEs) were mild to moderate flu-like symptoms and injection site reactions (ISRs).

4.6. Rationale for Study Design and Selection of Dose

This study will be a 2-part study with two treatment arms. The primary objective of Phase 1 is to characterize the safety and determine a recommended Phase 2 dose (RP2D) of IMO-2125 when administered in combination with ipilimumab or when administered in combination with pembrolizumab in patients with metastatic melanoma. The maximum tolerated dose (MTD)/RP2D for IMO-2125 may differ between the combination of IMO-2125 and ipilimumab and the combination of IMO-2125 and pembrolizumab. The primary objective of Phase 2 is to assess preliminary clinical activity of each combination at the respective RP2D(s) in patients with metastatic melanoma that is not responsive to PD-1 inhibitor therapies, using Response Evaluation Criteria in Solid Tumors v1.1 (RECIST; Eisenhauer, 2009).

4.6.1. Rationale for this Phase 1/2 Study

IMO-2125, a synthetic phosphorothioate oligonucleotide that acts as a direct agonist of TLR9, stimulates both the innate and adaptive immune systems, and induces the expression of an array of endogenous cytokines and chemokines, including IL-1β, IL-6, IL-12, IFN-α, IFN-γ, IP-10, TNF-α, and MCP-1. In preclinical studies IMO-2125 has shown dose-dependent antitumor activity associated with changes in the tumor microenvironment, increased T-cell infiltration, and induction of durable, tumor-specific memory. In combination with anti-CTLA-4 or anti-PD-1, IMO-2125 has shown greater antitumor activity than with either agent alone. Therefore, the combination of IMO-2125 with either ipilimumab or pembrolizumab may offer a novel therapy to benefit patients with metastatic melanoma.

4.6.1.1. Rationale for Intratumoral Injection of IMO-2125

Systemically administered TLR9 agonists have shown limited activity as cancer therapeutics alone or in combinations with other agents (Smith, 2014; Chan, 2015). Poor clinical responses after intravenous (i.v.) administration may be due, in part, to the fact that activated T cells failed to migrate to the tumor (Lou, 2011). Early studies by Nierkens (2009), showed that agonists of TLR9 were most effective when administered in close proximity to tumor antigens, and that i.v. and s.c. routes of TLR9 agonist administration were less effective than peri-tumoral injections (den Brok, 2004; Baines and Celis 2003; Heckelsmiller, 2002).

In preclinical models, intratumoral IMO-2125 administration leads to a dose-dependent decrease in treated and distant tumor volume, increase in infiltrating CD8+ T cells, and specific cytotoxic T cell responses against tumor antigens which are associated with durable tumor specific immune memory. Intratumoral IMO-2125 administration modulates the tumor microenvironment by increasing infiltration of tumor-infiltrating lymphocytes (TILs) and by changing checkpoint gene expression. The combination of intratumoral IMO-2125 and an anti-CTLA-4 mAb resulted in improved inhibition of tumor growth, regression of systemic lung metastases and infiltration of TILs versus monotherapy with either agent. The combination of intratumoral IMO-2125 with an anti-PD-1 antibody also showed more potent antitumor activity than either agent alone (Wang CRI-CIMT-EATI-AACR Meeting, 2015; Wang, AACR-NCI-EORTC International Conference on Molecular Targets and Cancer Therapeutics, 2015).

4.6.2. Rationale for Population

Despite recent advances in the treatment of melanoma, only a small minority of patients experience dramatic clinical benefit from any of the available immunotherapies as single agents. The combination of ipilimumab with nivolumab is associated with higher response rates, but at the expense of significant additive toxicity, and median survival is still less than a year (Larkin, 2015). Thus, new treatment approaches that build on the now-established proof of concept for immunotherapy are sorely needed. Patients who relapse after treatment with a PD-1 inhibitor have a particular unmet need since no therapy has been shown to be effective in this setting.

4.6.3. Rationale for Design

The Phase 1/2 design allows for optimal dose selection for IMO-2125 in combination with ipilimumab or in combination with pembrolizumab, followed by expansion at the RP2D(s) to evaluate preliminary efficacy and to generate additional long-term safety follow up data.

4.6.4. IMO-2125 Starting Dose Rationale

In Phase 1, the starting dose level of IMO-2125 will be 4 mg, which was calculated based on the doses of IMO-2125 that have been administered s.c. to 96 patients with chronic HCV infection. These patients received dosages ranging from 0.04 to 0.48 mg/kg. Based on this prior human safety experience, a dosage of 0.08 mg/kg was selected as the starting dose and then set as a fixed dose by assuming a conservative patient weight of 60 kg for a calculated starting dose level of 4.8 mg. A lower dose level was selected as the fixed starting dose level (4 mg) as an added safety margin.

IMO-2125 will be administered as a once-weekly intratumoral injection for the first 3 weeks of Cycle 1, followed by intratumoral injections on Weeks 5, 8, 11, 17, 23, and 29 (Day 1 of Cycles 2 through 7). Ipilimumab will be administered as a 90-minute i.v. infusion at 3 mg/kg once every 3 weeks for four cycles, consistent with the approved product label. Pembrolizumab will be administered as a 30-minute i.v. infusion at 200 mg once every 3 weeks for four cycles per the approved product label, after which continued administration is at the discretion of the Investigator for patients in the IMO-2125 + pembrolizumab treatment arm. Patients who initiated treatment at the 2 mg/kg dose may continue treatment using either the 200 mg dose or the 2 mg/kg dose. If institutional practice requires certain patients to be treated using weight-based pembrolizumab dosing, those patients may be treated with the 2 mg/kg dose.

Pembrolizumab safety compares favorably to ipilimumab (Robert, 2015), thus dosing of IMO-2125 in combination with pembrolizumab can be initiated at any dose level previously established as showing acceptable safety for the ipilimumab combination. IMO-2125 dose level escalation or de-escalation for each combination will be done independently of the other combinations, as appropriate, when the respective targets are functionally distinct (Parry, 2005).

5. STUDY OBJECTIVES

5.1. Primary Objective

The primary objective of Phase 1 is to characterize the safety and determine an RP2D of IMO-2125 when administered in combination with ipilimumab or when administered in combination with pembrolizumab in patients with metastatic melanoma. The MTD and RP2D for IMO-2125 may differ between the combination of IMO-2125 and ipilimumab and the combination of IMO-2125 and pembrolizumab.

The primary objective of Phase 2 is to assess the preliminary clinical activity of IMO-2125 in combination with ipilimumab or in combination with pembrolizumab at the respective RP2D(s) in patients with metastatic melanoma that is not responsive to PD-1 inhibitor therapy, using RECIST v1.1 (Eisenhauer, 2009).

5.2. Secondary Objectives

The secondary objectives of Phase 1 are to determine the plasma pharmacokinetics (PK) of single-dose IMO-2125 and repeat-dose IMO-2125 administered by intratumoral injection in combination with ipilimumab or pembrolizumab. An additional secondary objective of Phase 1 is to describe any preliminary antitumor activity.

The secondary objectives of Phase 2 are to further assess the safety and tolerability of IMO-2125 in combination with ipilimumab or in combination with pembrolizumab in patients with metastatic melanoma and to assess treatment response using immune-related Response Evaluation Criteria in Solid Tumors (irRECIST) and RECIST v1.1, overall survival (OS), OS at 6 and 12 months, PFS, PFS at 6 and 12 months, durable response rate (DRR), duration of response (DoR), and disease control rate (DCR).

5.3. Exploratory Objectives

The exploratory objectives of Phase 1 and 2 are to assess patient reported outcomes (PRO), pre- and post-treatment blood biomarkers, pre- and post-treatment tumor biopsies for immunological assessment, and explore any potential association between these biomarker measures and antitumor activity. In addition, anti-IMO-2125, anti-ipilimumab, and anti-pembrolizumab antibody formation will be assessed.

6. STUDY ENDPOINTS

6.1. Primary Endpoints

The primary endpoint of Phase 1 is to characterize the safety of IMO-2125 when administered in combination with ipilimumab or when administered in combination with pembrolizumab.

The primary endpoint in Phase 2 is clinical activity, defined as objective response as assessed by the Investigator using RECIST v1.1.

6.2. Secondary Endpoints

The secondary endpoints in Phase 1 are:

- PK assessments for IMO-2125;
- ORR assessed using irRC and RECIST v1.1

The secondary endpoints in Phase 2 include:

- Safety and tolerability (type and frequency of AEs, clinical laboratory values, electrocardiograms [ECGs], and vital sign measurements) for each combination;
- Duration of response using RECIST v1.1;
- ORR and duration of response using irRECIST;
- PFS, defined as time from the initiation of treatment to disease progression by irRECIST and RECIST v1.1, or death from any cause;
- PFS at 6 and 12 months;
- OS, defined as time from initiation of treatment to death from any cause;
- OS at 6 and 12 months;
- Durable response rate by irRECIST and RECIST v1.1, defined as the rate of complete response (CR) plus partial response (PR) lasting at least 180 days continuously and beginning within the first 12 months of study;
- Disease control rate by irRECIST and RECIST v1.1, defined as the rate of CR, PR, or stable disease (SD).

6.3. Exploratory Endpoints

The pre- and post-treatment exploratory endpoints of Phase 1 and 2 include, but are not limited to, PRO using the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-CORE 30 (EORTC QLQ-C30), blood biomarkers (e.g., IFN-γ and other plasma cytokines) and tumor markers to assess any potential association between immune response to IMO-2125 at the Week 8 tumor biopsy with tumor response in both injected and uninjected tumor lesions at Week 13 or at Week 23 (depending on the protocol version under which the patients were enrolled).

7. PATIENTS TO BE RECRUITED

7.1. Patient Recruitment

Enrollment during the Phase 1 dose-escalation portion and the Phase 2 portion of the study is open to adult patients with advanced/metastatic melanoma.

Patient selection and recruitment will be organized and overseen by the Investigator at the site following approval of the study protocol by the Institutional Review Board (IRB) or Ethics Committee (EC). All patients who sign an informed consent, are screened, and either qualify or do not qualify for the study will be documented in the screening and enrollment log. Appropriate documentation will be made indicating the willingness of the patient to participate and consent to the conduct of the study before initiating any study-related procedures.

7.2. Inclusion Criteria

To be eligible for this study, all patients must meet all of the following inclusion criteria. These criteria apply to both the Phase 1 dose-escalation portion and the Phase 2 portion of this study.

1. Patients must have histologically confirmed metastatic melanoma with measurable, stage III (lymph node or in transit lesions) or stage IVA, IVB, or IVC disease.
2. Patients must have symptomatic or radiographic progression during or after treatment with a PD-(L)1 inhibitor administered either as monotherapy or in combination.
    a. The interval between last PD-(L)1 directed treatment and start of study treatment should be at least 21 days.
    b. Prior BRAF or MEK inhibitor treatment is not required. However, for patients with known BRAF status:
        i. Those with BRAF wild type may have had a maximum of two previous systemic regimens for the treatment of melanoma.
        ii. Those with a BRAF mutation may have had a maximum of three previous systemic regimens for the treatment of melanoma.
    c. Prior ipilimumab is permitted.
    d. Previous treatment with either a PD-1 inhibitor (for patients enrolling on the IMO-2125 + pembrolizumab combination) or CTLA-4 inhibitor (for patients enrolling on the IMO-2125 + ipilimumab combination) should not have been accompanied by dose-limiting toxicity (DLT) for which permanent discontinuation is recommended (per USPI).
        i. Patients with a history of Grade ≥2 gastrointestinal symptoms (e.g., diarrhea, colitis) during prior checkpoint inhibitor treatment should be discussed with the Idera Medical Monitor during the Screening Period before starting study treatment.
3. Phase 1 patients must have at least two measurable tumor lesions ≥1.0 cm that are accessible to biopsy. Phase 2 patients must have at least one measurable lesion (per RECIST v1.1) which may be the same site that is used for the intratumoral injections.
4. Patients must be ≥18 years of age.

5. Patients must have Eastern Cooperative Oncology Group (ECOG) Performance Status ≤2 (Oken, 1982) (Section 21.1).
6. Patients must meet the following laboratory criteria:
   a. Absolute neutrophil count (ANC) ≥1.5 x 10^9/L (1500/mm^3)
   b. Platelet count ≥75 x 10^9/L (75,000/mm^3)
   c. Hemoglobin ≥8.0 g/dL (4.96 mmol/L)
   d. Serum creatinine ≤1.5 x upper limit of normal (ULN) or calculated creatinine clearance ≥60 mL/minute
   e. Aspartate aminotransferase (AST) ≤2.5 x ULN; alanine aminotransferase (ALT) ≤2.5 x ULN; AST/ALT <5 x ULN if liver involvement
   f. Serum bilirubin ≤1.5 x ULN, except in patients with Gilbert's Syndrome who must have a total bilirubin <3 mg/dL
7. Women of childbearing potential (WOCBP) and men must agree to use effective contraceptive methods from Screening throughout the study treatment period and until at least 90 days after the last dose of IMO-2125, 3 months after the last dose of ipilimumab, or at least 4 months after the last dose of pembrolizumab.

   Non-childbearing potential is defined as a woman who meets ***either*** of the following criteria: a) postmenopausal state defined as no menses for 12 months without an alternative medical cause, or b) documented hysterectomy, bilateral tubal ligation, or bilateral oophorectomy.

   Effective contraception methods are defined as ***one*** of the following:

   a. True abstinence, defined as refraining from heterosexual intercourse, when this is in line with the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods), declaration of abstinence for the duration of a trial, and withdrawal are not acceptable methods of contraception.
   b. Condoms and spermicide
   c. Diaphragm and spermicide
   d. Oral or implanted hormonal contraceptive (e.g., Implanon™)
   e. An intra-uterine device (IUD)
8. WOCBP must have a negative pregnancy test (serum or urine) prior to the first dose of study treatment.
9. Patients must be willing and able to sign the informed consent and comply with the study protocol.
10. Patients must have an anticipated life expectancy >3 months.

7.3. Exclusion Criteria

Patients meeting any of the following criteria will be excluded from the study:

1. Patients who have received prior therapy with a TLR agonist, excluding topical agents. Patients who have received experimental vaccines or other investigational immune therapies should be discussed with the Medical Monitor to confirm eligibility.
2. Patients who have received systemic treatment with IFN-α within the previous 6 months prior to enrolling into this study.
3. Patients with known hypersensitivity to any oligodeoxynucleotide.
4. Patients with active autoimmune disease requiring disease-modifying therapy.
5. Patients requiring concurrent systemic steroid therapy higher than physiologic dose (7.5 mg/day of prednisone).
6. Patients with any form of active primary or secondary immunodeficiency.
7. Patients with another primary malignancy that has not been in remission for at least 3 years. The following are exempt from the 3 year limit: non-melanoma skin cancer, curatively treated localized prostate cancer with non-detectable prostate-specific antigen, cervical carcinoma in situ on biopsy or a squamous intraepithelial lesion on Papanicolaou (Pap) smear, and thyroid cancer (except anaplastic).
8. Patients with active systemic infections requiring antibiotics or active hepatitis A, B, or C.
9. Patients who are hepatitis B surface antigen positive.
10. Patients with a known diagnosis of human immunodeficiency virus (HIV) infection.
11. WOCBP who are pregnant or breast feeding.
12. Patients who have had prior anaphylactic or other severe infusion reaction associated with human antibody administration.
13. Patients with known central nervous system, meningeal, or epidural disease. Patients with stable brain metastases following definitive local treatment are eligible if steroid requirement is less than 7.5 mg/day of prednisone (or equivalent).
14. Patients with impaired cardiac function or clinically significant cardiac disease such as:
    a. New York Heart Association Class III or IV cardiac disease, including preexisting clinically significant ventricular arrhythmia, congestive heart failure, or cardiomyopathy
    b. Unstable angina pectoris ≤6 months prior to study participation
    c. Acute myocardial infarction ≤6 months prior to study participation
    d. Other clinically significant heart disease (i.e., Grade ≥3 hypertension, history of labile hypertension, or poor compliance with an anti-hypertensive regimen)
15. Ocular melanoma.

8. STUDY DESIGN

8.1. Overview

This is a two arm, open-label Phase 1/2 study to assess the safety, tolerability, PK, immunogenicity, and efficacy of IMO-2125 when administered in combination with ipilimumab or in combination with pembrolizumab. Patients with metastatic melanoma who have experienced symptomatic or confirmed radiographic progression during or after treatment with an anti-PD-(L)1 agent (alone or in combination) will be eligible. Prior BRAF or MEK inhibitor treatment is not required. The study will be conducted in two parts: a dose-escalation portion (Phase 1) to evaluate safety and tolerability of multiple dose levels and a Phase 2 portion to assess preliminary efficacy.

8.1.1. Phase 1

The Phase 1 portion of the study will explore escalating dose levels of IMO-2125 (from 4 to 32 mg with de-escalation to 2 mg allowed for each IMO-2125 combination). For each cohort, IMO-2125 will be administered as a once-weekly intratumoral injection for 3 consecutive weeks in Cycle 1, followed by intratumoral injections on Weeks 5, 8, 11, 17, 23, and 29 (Day 1 of Cycles 2 through 7). Both ipilimumab and pembrolizumab will be administered as per the USPI every 3 weeks beginning Day 1 of Cycle 1 Week 2. Continued pembrolizumab dosing following the study period is permitted at the discretion of the Investigator for patients in the IMO-2125 + pembrolizumab treatment arm. The dosing schedule is summarized in Table 4.

Table 4: Schedule of Dosing for Phase 1 and Phase 2

	Cycle															
	1				**2**			**3**			**4**			**5**	**6**	**7**
Study week	1	2	3	4	5	6	7	8	9	10	11	12	13	17	23	29
IMO-2125 + ipilimumab																
IMO-2125	X	X	X	-	X	-	-	X	-	-	X	-	-	X	X	X
Ipilimumab	-	X	-	-	X	-	-	X	-	-	X	-	-	-	-	-
IMO-2125 + pembrolizumab																
IMO-2125	X	X	X	-	X	-	-	X	-	-	X	-	-	X	X	X
Pembrolizumab	-	X	-	-	X	-	-	X	-	-	X	X[1]				

Note: On weeks when the combinations are administered, administration of ipilimumab or pembrolizumab will be first, followed by IMO-2125. IMO-2125 administration must occur within a ±2 day window of the scheduled dosing day.

[1] For patients in the IMO-2125 + pembrolizumab treatment arm, continued pembrolizumab dosing per the approved product label is permitted at the discretion of the Investigator.

Patients assigned to 11 weeks of IMO-2125 under previous versions of the protocol who have not yet reached the end of the Treatment Period may receive the Week 17, 23, and 29 injections at the discretion of the treating Investigator.

Each cohort will be monitored for the occurrence of DLTs. The DLT evaluation period will be Cycle 1 (Weeks 1 through 4). If a patient discontinues study participation before the DLT evaluation period is finished due to reasons other than experiencing a DLT, that patient must be replaced so that the cohort may be properly evaluated. More information about the review of DLTs and the escalation of dose levels between cohorts is provided in Section 8.1.3, Section 8.1.4, and Section 8.1.5.

There are 3 patients planned per cohort. During Phase 1, the Sponsor will assign patients to a treatment arm (IMO-2125 + ipilimumab or IMO-2125 + pembrolizumab) by cohort. The Sponsor will maintain a prioritization schedule for cohort assignment in a separate document. A Cohort Review Committee (CRC) will be convened prior to each dose level escalation to review the available data and provide recommendations on study conduct. After completing the DLT evaluations for all planned IMO-2125 doses in either combination, supplemental cohorts of up to 5 patients each may be enrolled with either combination at doses up to and including the MTD. CRC review is not required for initiation of these supplemental cohorts but safety review meetings will still take place monthly throughout Phase 1 of the study. After completion of either Phase 1 treatment arm and determination of the RP2D for that arm, the Phase 2 portion for the completed treatment arm may be initiated. It is not necessary for Phase 1 to be completed in both treatment arms before Phase 2 is started. After Phase 2 in either treatment arm is initiated, the Sponsor will assign the treatment arm, cohort, and phase for patients.

Dose-limiting toxicity evaluations and CRC reviews for any additional immunotherapy combination cohorts will be done as described for the ipilimumab and pembrolizumab combinations.

8.1.2. Phase 2

The Phase 2 portion of the study will assess preliminary efficacy, using investigator-assessed RECIST v1.1, of IMO-2125 + ipilimumab, IMO-2125 + pembrolizumab, and any additional combinations that are studied in Phase 1. The dose level of IMO-2125 to be administered for each treatment arm will be the RP2D for the combination, as determined in Phase 1.

Phase 2 will enroll at least 60 patients treated at the IMO-2125 + ipilimumab RP2D. This will include at least 21 patients in the primary IMO-2125 + ipilimumab efficacy-evaluable population (as defined in Section 16.2) and up to 20 patients in the secondary IMO-2125 + ipilimumab efficacy-evaluable population.

In the IMO-2125 + pembrolizumab Phase 2 cohort, enrollment will continue until 21 patients in the IMO-2125 + pembrolizumab efficacy-evaluable population have been treated at the IMO-2125 + pembrolizumab RP2D.

Phase 1 patients treated at the RP2D for either combination will contribute to these totals.

For each treatment arm, a two-stage design will be used and futility analyses performed as described in Section 16.1.

If a patient discontinues treatment before completing at least one efficacy evaluation for reasons other than toxicity, then that patient will be replaced with the replacement assigned to the same treatment arm and dose level as the patient who dropped out early.

Combination therapy in Phase 2 will continue using the same schedule as Phase 1 (Table 4).

8.1.3. Dose Escalation and Stopping Rules

Up to five dose levels for IMO-2125 are initially planned (Table 5).

Table 5: Treatment Doses to be Investigated

Dose Level	IMO-2125	Ipilimumab	Pembrolizumab
-1	2 mg	3 mg/kg	200 mg
+1	4 mg	3 mg/kg	200 mg
+2	8 mg	3 mg/kg	200 mg
+3	16 mg	3 mg/kg	200 mg
+4	32 mg	3 mg/kg	200 mg

In Phase 1, the study will enroll patients in planned cohorts of 3, beginning at Dose Level +1 for the ipilimumab treatment arm and beginning at Dose Level +2 for the pembrolizumab treatment arm once safety of the IMO-2125 + ipilimumab combination has been established for that level. A charter will be used to guide the CRC's decision-making.

Additionally, if, due to observed toxicity, it proves difficult to provide IMO-2125 for 3 consecutive weeks in Cycle 1, the decision may be taken by the CRC to add cohorts where alternative schedules of IMO-2125 administration will be explored.

The MTD will be determined from the assessment of DLTs during the first treatment cycle of each cohort (Section 8.1.5). Using a prior beta(1,1) distribution of the DLT rate δ_i for each dose level i, the MTD is defined as the highest dose level for which the mean of the posterior distribution of toxicity is closest to but less than 25% among all the evaluated doses i for which Pr ($\delta_i > 0.25 \mid$ data) <0.80.

The RP2D(s) will be selected from dose level(s) at or below the MTD. Additional dose levels may be studied if the MTD(s) have not been reached and pharmacodynamic activity is deemed to be inadequate. At the time of completion of the Phase 1 portion of the study, an analysis of the data will be performed.

8.1.3.1. Phase 2 Stopping Rules

Additional patients will be enrolled at the RP2D level(s) established in the Phase 1 portion of the study for a total of approximately 90 to 100 patients enrolled in the study. DLTs will be continuously monitored throughout the study. Assuming a prior beta (0.6, 1.4) distribution for the overall toxicity rate for a treatment, a Phase 2 arm will terminate if the Pr ($\delta_t > 0.25 \mid$ data) >0.80, where δ_t is the DLT rate attributable to the treatment. The decision rule for terminating due to toxicity is presented in Table 6. The method used to produce the decision rule and operating characteristics was designed by Thall (2006).

Table 6: Phase 2 Stopping Boundaries

If there are this many first-cycle DLTs or more	3	4	5	6	7	8	9	10
Stop if this many patients (or fewer) have begun treatment	7	10	13	17	20	24	27	29

8.1.4. Cohort Review Committee

The CRC composition and duties are described in a charter. Once the last patient in a given cohort has completed their first cycle of study treatment, a CRC meeting will be convened to review all safety data and decide whether DLTs were observed. Based on the CRC's adjudication of DLTs observed in a cohort, they will guide decisions on the dose level that the subsequent cohort will be administered.

A review of all relevant available data will occur between the Sponsor and participating Institution(s) at least monthly for the duration of the study.

8.1.5. Definition of Dose-limiting Toxicities

Toxicity will be evaluated according to the National Cancer Institute (NCI) Common Terminology Criteria for AEs (CTCAE) v4.03 toxicity criteria. Dose-limiting toxicities are defined as those events that will require dose modification; therefore, DLT criteria should be referenced throughout the Phase 1 and 2 portions of the study. The DLT evaluation period will be Cycle 1 (Weeks 1 through 4).

For the purposes of dose level escalation and determination of the MTD(s), only DLTs (as defined below) that occur during the first cycle of treatment will be considered in decisions regarding dose level escalation; however, DLTs or other clinically significant toxicities that occur throughout the observation period will be considered when determining the RP2D(s) for use in this trial and in subsequent clinical trials.

During Cycle 1 of the dose escalation portion, if two of the three patients in a cohort experience the same Grade 2, treatment-related AE, then subsequent increases in dose level will proceed in increments less than 100%. If more than one cohort is treated at the same dose level and greater than 67% of patients treated at that dose level experience the same Grade 2 treatment-related AE (Table 7), dose level escalation will proceed in increments less than 100%. In such a case, specific dose level increments will be decided by the CRC.

Protocol-defined hematologic DLTs include:

- CTCAE Grade 4 neutropenia ≥7 days;
- CTCAE Grade 3 or 4 neutropenia with fever ≥38.5°C;
- CTCAE Grade 3 thrombocytopenia with bleeding;
- CTCAE Grade 4 thrombocytopenia ≥7 days.

Protocol-defined non-hematologic DLTs include:

- Grade ≥3 vomiting or nausea ≥14 days despite the use of optimal anti-emetic treatments;
- Grade ≥3 diarrhea ≥14 days despite the use of optimal anti-diarrheal treatments which should include infliximab as per institutional guidelines;
- Serum creatinine >3.0 x ULN;

- AST or ALT >5 x ULN; in patients with liver metastasis who entered the study with Grade 2 elevation of AST or ALT, an AST or ALT increase ≥50% relative to baseline and lasting ≥1 week;
- Bilirubin ≥3.0 x ULN;
- Bilirubin ≥2.0 x ULN with ALT >3 x ULN in patients without liver metastases;
- Other non-hematologic toxicities of Grade ≥3, except for the following:
  - AEs related to underlying disease;
  - CTCAE Grade 3 fatigue <14 days;
  - Alopecia;
  - Isolated, asymptomatic elevations in biochemistry laboratory values lasting ≤14 days. This includes electrolyte abnormalities that respond to medical intervention.

Ipilimumab-related DLTs:

- Grade ≥4 immune-mediated dermatitis (except skin reaction at site of injection);
- Grade ≥3 immune-mediated endocrinopathy (with the exception of Grade 3 autoimmune thyroiditis that resolves to Grade 1 or baseline within 28 days of onset);
- Grade ≥3 immune-mediated enterocolitis;
- Grade ≥3 immune-mediated hepatitis with the exception of Grade 3 immune-mediated hepatitis that resolves to Grade 1 or baseline within 28 days of onset;
- Grade ≥3 immune-mediated neuropathy, pancreatitis, meningitis, nephritis, and pneumonitis that are considered to be possibly, probably, or definitely related to study therapy as determined by the Investigator;
- Any persistent IMO-2125-related toxicity that leads to a delay of scheduled (per standard of care) ipilimumab >14 days.

Pembrolizumab-related DLTs:

- Grade ≥3 pneumonitis or recurrent Grade 2 pneumonitis;
- Grade ≥3 nephritis;
- Grade ≥3 infusion-related reactions;
- Inability to reduce corticosteroid dose to 10 mg or less of prednisone or equivalent per day within 12 weeks;
- Any Grade ≥3 treatment-related AE that recurs.

If at any time during the study, a patient experiences a DLT as outlined above, the toxicity in question must be assessed for attribution based on the known toxicity profiles for ipilimumab, pembrolizumab, and IMO-2125. If assessment can be clearly attributed to one of the drugs in the combination, then dosing should be interrupted and the toxicity should be followed until

resolution, stabilization, or return to baseline. Treatment with the other agent may continue during this time period. If attribution cannot be clearly ascribed to one agent versus the other, then both IMO-2125 and ipilimumab (or pembrolizumab) should be stopped and the toxicity should be followed until resolution, stabilization, or return to baseline. If treatment is to be resumed, then re-initiation criteria must be met. If the DLT was clearly related to IMO-2125 or if attribution cannot be clearly determined, then IMO-2125 must be administered at a lower dose level (a minimum reduction of at least 1 dose level). If the DLT recurs after a dose level reduction, then treatment should be discontinued.

Patients who experience a non-laboratory, IMO-2125-related DLT must be evaluated weekly, at a minimum, until resolution to Grade ≤1 or baseline and then at least monthly until return to baseline or stabilization of the event, whichever comes first. For abnormal laboratory values that qualify as DLTs, patients will be followed twice weekly until values return to Grade ≤1 or baseline, whichever comes first.

Criteria for re-initiation of study treatment following occurrence of a DLT are as follows:

- ANC must be ≥1.5 x 10^9/L (1500/μL);
- Platelets must be ≥75 x 10^9/L (75,000/μL);
- All clinically significant non-hematologic toxicities for which a causal association to study treatment cannot be ruled out must be Grade ≤1 (except alopecia) or returned to baseline.

If the patient does not meet these criteria, dosing will be delayed and the patient should be re-evaluated within 48 to 72 hours. If the next cycle is delayed by more than 21 days for toxicity, the patient should be removed from study treatment. In these situations, if the patient is experiencing clinical benefit and has a favorable risk/benefit profile, study treatment with IMO-2125 may be continued if agreed upon by the Sponsor and the Investigator.

8.1.6. Safety Assessment for Immunologically Related Toxicity

Based on an incidence of Grade 3 or greater immune-mediated AEs associated with use of ipilimumab or pembrolizumab of approximately 12% to 15%, the following safety precautions will be followed. Examples of relevant toxicities include the following: enterocolitis, hepatitis, dermatitis, neuropathy, endocrinopathy, nephritis, pneumonitis, pancreatitis, non-infectious myocarditis, uveitis, and iritis.

During dose level escalation, if any of the following is observed, the CRC will be convened to review all safety findings for all patients treated in that cohort and all previous cohorts, including those events that occurred beyond Cycle 1, to guide next steps.

- If more than one patient experiences a Grade ≥3, immune-related adverse event (irAE) in a cohort of 3 patients;
- If more than two patients experience a Grade ≥3 irAE in cohorts of 6 patients.

During the Phase 2 portion of the trial, if the incidence of Grade ≥3 irAEs observed in Cycle 1 or in subsequent cycles of treatment exceeds 25%, the CRC will be convened to review all safety findings from all patients treated in the study to guide next steps.

8.2. Duration of Study

8.2.1. Treatment Duration

The study treatment period is 29 weeks (as per Table 4) in the absence of intolerable toxicity or unequivocal disease progression. Continued treatment with pembrolizumab following the completion of IMO-2125 study treatment is at the discretion of the Investigator for patients in the IMO-2125 + pembrolizumab treatment arm.

8.2.2. Study Duration

The study ends approximately 1 year after the last patient in Phase 2 has commenced study treatment. Patients who complete or discontinue study treatment prior to progression will be followed for clinical and radiological evidence of progression, PRO assessments, and immunogenicity assessments at least every 3 months until documentation of RECIST v1.1 progressive disease (PD), start of a subsequent anti-cancer treatment regimen, withdrawal of consent, death, or Sponsor notification that follow-up is no longer required, whichever comes first. Best response to first subsequent therapy, AEs which are Grade ≥3, and concomitant medications used to treat these AEs, will also be captured during the follow-up phase of the study (Table 1 and Table 2).

After documentation of PD or use of a subsequent anti-cancer treatment regimen, all patients will be contacted by telephone every 3 months for survival follow-up until the site is notified by the Sponsor that survival follow-up is no longer required.

8.3. Number of Patients

The study will enroll approximately 90 to 100 patients. It is estimated that approximately 30 patients will be treated in the dose-finding portion of Phase 1 and approximately 60 to 70 additional patients will be treated in the Phase 2 portion of the study.

8.4. Benefits and Risk Assessment

Patients with advanced melanoma who relapse after immunotherapy (and a BRAF or MEK inhibitor, if indicated) have an estimated survival that is measured only in months with no approved therapeutic options. Preliminary experience with the IMO-2125 + ipilimumab regimen is encouraging and the combination appears to be tolerable (Uemera, 2017). Based on these data, the benefit:risk is likely to be favorable if the efficacy objectives of the study are achieved.

9. STUDY PROCEDURES BY VISIT

Following is a listing of the procedures to be performed at each study visit. See the Schedules of Evaluations (Table 1 for Phase 1 and Table 2 for Phase 2) to view the study procedures in detail in a tabular format.

9.1. Screening (Up to 21 Days Before Day 1 of Week 1, Cycle 1)

The following information will be captured at the Screening Visit:

- Informed consent
- Inclusion/exclusion criteria
- Demography and medical history, including melanoma history and melanoma treatment history
- Physical examination (should include, but not be limited to, areas related to the inclusion/exclusion criteria in addition to height and body weight) and assessment of melanoma lesions
- ECOG performance status (Oken, 1982) (Section 21.1)
- Target tumor lesions will be identified and assessed per RECIST v1.1 criteria.
- The injected and non-injected tumor lesions for biopsy (biopsies optional in Phase 2) will be identified and recorded on the electronic case report form (eCRF), if performed.
- Tumor biopsies are to be performed by surgical method (e.g., core or punch) or Fine Needle Aspiration (FNA) within 21 days prior to first treatment
- Radiological assessment
- Vital signs
- Electrocardiogram
- Complete blood count (CBC) with differential and chemistry profile (including liver function tests [LFTs])
- Complement (total complement activity 50 [CH50], complement component 3 [C3], and complement component 4 [C4])
- Coagulation tests
- Thyroid function profile
- Serum or urine pregnancy test for WOCBP
- Urinalysis with microscopic exam
- AEs

9.2. Cycle 1 Dosing Days (Weeks 1, 2, and 3)

Adverse event and concomitant medication monitoring will be performed on an ongoing basis.

9.2.1. Pre-dose

Before dosing, the following will be performed:

- Physical examination (any areas related to the inclusion/exclusion criteria and body weight) and assessment of melanoma lesions (Week 1 only)
- Vital signs
- ECOG Performance Status (Week 1 only)
- CBC with differential and chemistry profile (including LFTs)
- Coagulation tests (Week 1 only)
- Thyroid function profile (Week 2 only)
- ECG (Week 2 only)
- AEs
- Concomitant medication monitoring
- PK assessments (see Table 3)
- Immunogenicity assessments (Week 1 only)
- In Phase 2, all tumor biopsies are optional. See Section 13.2 and the Laboratory Manual for details on the collection of biopsies and analyses of biomarkers.
- Blood biomarker samples
  - Week 1: Blood for PBMC and serum for cytokines
  - Week 2: Serum for cytokines
- PRO using the EORTC QLQ-C30 (Week 1 only)

9.2.2. Study Drug Administration

- IMO-2125 by intratumoral injection (Day 1 of Week 1, Week 2, and Week 3)
- Ipilimumab or pembrolizumab i.v. infusion (Day 1 of Week 2 only)

9.2.3. Post intratumoral IMO-2125 Injection

- AEs (including DLTs)
- **Week 1 only**: blood biomarker samples collected 4 hours (serum for cytokines) and 24 to 48 hours post-dose (blood for PBMC and serum for cytokines).
- In Phase 2, all tumor biopsies are optional. See Section 13.2 and the Laboratory Manual for details on the collection of biopsies and analyses of biomarkers.

- PK assessments (Weeks 1 and 2 only; see Table 3)
- ECG (Week 2 only; 2 hours post-dose IMO-2125 administration)

9.3. Cycle 2, Cycle 3, Cycle 4, Cycle 5, Cycle 6, and Cycle 7 Dosing Days (Weeks 5, 8, 11, 17, 23, and 29)

9.3.1. Pre-dose

Before dosing, the following will be performed:

- Physical examination (any areas related to the inclusion/exclusion criteria and body weight) and assessment of melanoma lesions
- Vital signs
- ECOG Performance Status
- CBC with differential and chemistry profile (including LFTs)
- Complement (CH50, C3, C4)
- Coagulation tests
- Thyroid function profile
- Urinalysis with microscopic exam (Weeks 8 and 17 only)
- AEs
- Concomitant medication monitoring
- Radiological assessment (Weeks 8, 17, and 29/EOT only)
- Investigator assessment of response (Weeks 8, 17, and 29/EOT only)
- PK assessments (see Table 3)
- Immunogenicity assessments (Weeks 5, 11, 17, 23, and 29/EOT only)
- Blood biomarker assessments (Weeks 5, 8, and 29/EOT only during Phase 1 and Week 8 only during Phase 2)
- The longest diameter of the injected tumor will also be assessed, when possible.
- In Phase 2, all tumor biopsies are optional. See Section 13.2 and the Laboratory Manual for details on the collection of biopsies and analyses of biomarkers.
- PRO using the EORTC QLQ-C30 (Weeks 8, 17, and 29/EOT only)

9.3.2. Study Drug Administration

- IMO-2125 by intratumoral injection
- Ipilimumab or pembrolizumab i.v. infusion

9.3.3. Post-dose

- AEs
- PK assessments (Week 11 only; see Table 3)
- Blood biomarker assessment (Weeks 5, 8, and 29/EOT only during Phase 1)
- ECG (Week 11 only; 2 hours post-dose IMO-2125 administration)

In addition, radiological assessment (computed tomography [CT]) and Investigator assessment of response will be conducted at Week 8 only (±7 days).

9.4. Cycle 4 (Week 13)

- Tumor biopsies by surgical method (e.g., core or punch) or FNA at Week 13 (Cycle 4) are optional for both Phase 1 and Phase 2, and may occur within a ±3 day window

9.5. Safety Follow-up Visit (21 Days after Last Dose of IMO-2125)

The following information will be captured at the Safety Follow-up (SFU) Visit (21 days ± 5 days following the last dose of IMO-2125):

- Physical examination (any areas related to the inclusion/exclusion criteria and body weight) and assessment of melanoma lesions
- Vital signs
- ECOG Performance Status
- CBC with differential and chemistry profile (including LFTs)
- Complement (CH50, C3, C4)
- Coagulation tests
- Thyroid function profile
- Serum or urine pregnancy test for WOCBP
- Urinalysis with microscopic exam
- ECG
- AEs
- Concomitant medication monitoring
- PK assessments (see Table 3)
- Immunogenicity assessments

9.6. Early Withdrawal

Any patient may withdraw from the study at any time for any reason, without prejudice for his or her continued care. Also, an Investigator may withdraw a patient from the study in cases of noncompliance or if, for any reason, he or she feels it is in the patient's best interest.

If a patient withdraws early, SFU Visit procedures should be performed if possible. Reasons for withdrawal must be recorded.

9.7. Unscheduled Visits

Unscheduled visits and assessments may be conducted at Investigator's discretion in response to new clinical observations or AEs. If performed, unscheduled disease assessments will be recorded at an unscheduled visit. Appropriate data from unscheduled visits should be recorded in the eCRF.

10. STUDY TREATMENTS

10.1. IMO-2125

IMO-2125, a novel phosphorothioate oligodeoxynucleotide, is composed of two strands of modified DNA joined at the 3' ends. IMO-2125 is a hygroscopic white to off-white amorphous solid obtained by lyophilization; it is highly soluble in aqueous media.

IMO-2125 will be administered by intratumoral injection for all doses (between 2 and 32 mg; refer to Section 8.1).

IMO-2125 drug product is supplied as lyophilized powder for reconstitution or as an aqueous sterile solution. For the lyophilized product, each 5-mL glass vial contains IMO-2125 sodium salt equivalent to 25 mg/vial of IMO-2125 free acid. IMO-2125 drug product contains no excipients or preservatives. For the aqueous sterile solution, each vial contains IMO-2125 sodium salt equivalent to 8 mg/mL of IMO-2125 free acid compounded with 0.9% sodium chloride.

10.2. Ipilimumab

Ipilimumab will be provided by the site as the commercially available product.

10.3. Pembrolizumab

Pembrolizumab will be provided by the site as the commercially available product.

10.4. Drug Handling and Administration

10.4.1. Drug Delivery to Site

After the research site has submitted all approved regulatory and study start-up documents, Idera Pharmaceuticals, Inc. will initiate a requisition for IMO-2125 to be delivered to the site via its distribution facility. All IMO-2125 shipments are sent at 2°C to 8°C. Upon receipt, the pharmacist or appropriate technician/designee must inspect the contents, verify temperature conditions, and confirm receipt of goods. Ipilimumab and pembrolizumab will be provided by the site using commercial supplies.

Drug inventory will be maintained by the site. The site must inform Idera Pharmaceuticals, Inc., in writing, by facsimile, or e-mail of additional study drug needs at least 2 weeks before the required receipt date.

10.4.2. Drug Storage

10.4.2.1. IMO-2125 Storage

Vials of IMO-2125 drug product are to be stored at 2°C to 8°C and storage temperature must be continuously monitored. Instructions for reconstitution will be included in the Pharmacy Manual.

IMO-2125 must be stored in a securely locked enclosure. Access is strictly limited to the pharmacist before preparation.

10.4.2.2. Ipilimumab Storage

Vials of ipilimumab are to be stored at 2°C to 8°C and protected from light (refer to the current Package Insert for more details).

10.4.2.3. Pembrolizumab Storage

Vials of pembrolizumab are to be stored at 2°C to 8°C and protected from light (refer to the current Package Insert for more details).

10.4.3. Administration

10.4.3.1. IMO-2125

IMO-2125 will be administered to each patient at one of five dose levels: 2, 4, 8, 16, or 32 mg. IMO-2125 will be administered as a series of intratumoral injections administered as per Table 4. Patients will remain at the study site for observation for a minimum of 30 minutes following each administration of IMO-2125. A single tumor should be selected for injection throughout the study and designated as the "injected tumor" on the appropriate CRF.

The injected tumor will be selected from (in order of priority) pathologic draining lymph nodes, superficial or s.c. metastases, or deep (visceral) metastases, the latter requiring interventional radiology support. A separate (i.e., "noninjected") tumor lesion should be identified as the distant lesion to be biopsied (optional in Phase 2) and recorded on the CRF. Note that tumor biopsies should be done prior to study treatment administration. If a full dose can no longer be practically administered into the designated tumor for injection, another tumor may be selected. In the event that complete tumor regression occurs in all accessible lesions prior to completion of therapy, any remaining IMO-2125 doses should be administered into the tumor bed, except in the case of visceral lesions where remaining doses should be given s.c. to minimize procedural risks.

The assigned dose of IMO-2125 will be administered into the "injected tumor" by qualified medical personnel using an appropriate method for needle localization. It is recommended that the tumors be injected with 25-gauge needle; however, the choice of needle will be at the Investigator's discretion. IMO-2125 should be thoroughly distributed within the injected tumor while avoiding necrotic areas, with a fanning method (spread the injection across several angles throughout the lesions, to maximize the IMO-2125 in the injected lesion).

The total injected dose should remain constant; however, injection volume may need to be adjusted if the "injected tumor" decreases in size (see the Pharmacy Manual for more details). In the event a full dose can no longer be practically administered into the "injected tumor," another lesion may be selected.

10.4.3.2. Ipilimumab

Ipilimumab will be administered (per the current Package Insert) i.v. over 90 minutes at 3 mg/kg on Day 1 of every 3-week cycle, for a total of 4 doses, except in Cycle 1, where ipilimumab will be administered on Day 8. IMO-2125 administration should follow ipilimumab administration. Due to logistical reasons, it may not be feasible to always administer IMO-2125 and ipilimumab on the same day. In this situation, IMO-2125 must be administered within the ±2 day study visit window.

10.4.3.3. Dose Interruption for Ipilimumab-Related Toxicities

A scheduled dose of ipilimumab will be withheld for any moderate immune-mediated adverse reactions or for symptomatic endocrinopathy. For patients with complete or partial resolution of AEs (Grade 0-1), and who are receiving less than 7.5 mg prednisone or equivalent per day, ipilimumab may be resumed at a dosage of 3 mg/kg every 3 weeks until administration of all 4 planned doses or 16 weeks from first dose, whichever occurs earlier.

Ipilimumab is to be permanently discontinued for any of the following:

- Persistent moderate adverse reactions or inability to reduce corticosteroid dose to 7.5 mg prednisone or equivalent per day.
- Failure to complete full treatment course within 16 weeks from administration of first dose.
- Severe or life-threatening adverse reactions, including any of the following:
  - Colitis with abdominal pain, fever, ileus, or peritoneal signs; increase in stool frequency (7 or more over baseline), stool incontinence, need for i.v. hydration for more than 24 hours, gastrointestinal hemorrhage, and gastrointestinal perforation
  - AST or ALT >5x the ULN or total bilirubin >3x the ULN
  - Stevens-Johnson syndrome, toxic epidermal necrolysis, or rash complicated by full thickness dermal ulceration, or necrotic, bullous, or hemorrhagic manifestations
  - Severe motor or sensory neuropathy, Guillain-Barré syndrome, or myasthenia gravis
  - Severe immune-mediated reactions involving any organ system (e.g., nephritis, pneumonitis, pancreatitis, non-infectious myocarditis)
  - Immune-mediated ocular disease that is unresponsive to topical immunosuppressive therapy

If a patient experiences moderate enterocolitis, the Investigator should administer anti-diarrheal treatment, and if persistent for more than 1 week should initiate systemic corticosteroids at a dose of 0.5 mg/kg/day prednisone or equivalent and infliximab according to institutional guidelines. Testing for latent tuberculosis (purified protein derivative skin test) is recommended.

Mild to moderate dermatitis, such as localized rash and pruritis, should be treated symptomatically with administration of topical or systemic corticosteroids if there is no improvement of symptoms within 1 week.

The Investigator should administer corticosteroid eye drops to patients who develop uveitis, iritis, or episcleritis. Ipilimumab should be permanently discontinued for immune-mediated ocular disease that is unresponsive to local immunosuppressive therapy.

If patients need to discontinue ipilimumab due to any severe immune-related toxicities listed above, the Investigator may administer systemic corticosteroids at a dose of 1 to 2 mg/kg/day of prednisone or equivalent. Upon improvement to Grade 1 or less, the Investigator should initiate

corticosteroid taper and continue to taper over at least 1 month. Standard institutional practices may also be implemented to treat these patients.

10.4.3.4. Pembrolizumab

Pembrolizumab will be administered (per the current Package Insert) i.v. over 30 minutes at 200 mg on Day 1 of every 3-week cycle, for a total of 4 doses, except in Cycle 1, where pembrolizumab will be administered on Day 8. For patients assigned to the IMO-2125 + pembrolizumab arm, at the discretion of the Investigator, after completing IMO-2125 study treatment, dosing of pembrolizumab may continue every 3 weeks per the approved label. IMO-2125 administration should follow pembrolizumab administration when co-administered during Cycles 1 to 7. Due to logistical reasons, it may not be feasible to always administer IMO-2125 and pembrolizumab on the same day. In this situation, IMO-2125 must be administered within the ±2 day study visit window.

Patients who initiated treatment at the 2 mg/kg dose may continue treatment using either the 200 mg dose or the 2 mg/kg dose. If institutional practice requires certain patients to be treated using weight-based pembrolizumab dosing, those patients may be treated with the 2 mg/kg dose.

10.4.3.5. Dose Interruption for Pembrolizumab-Related Toxicities

Withhold pembrolizumab for any of the following:

- Grade 2 pneumonitis
- Grade 2 or 3 colitis
- Grade 3 or 4 endocrinopathies
- Grade 2 nephritis
- AST or ALT >3 and up to 5 x ULN or total bilirubin >1.5 and up to 3 x ULN
- Any other severe or Grade 3 treatment-related adverse reaction

Resume pembrolizumab in patients whose adverse reactions recover to Grade 0-1.

Permanently discontinue pembrolizumab for any of the following:

- Any life-threatening adverse reaction (excluding endocrinopathies controlled with hormone replacement therapy)
- Grade 3 or 4 pneumonitis or recurrent pneumonitis of Grade 2 severity
- Grade 3 or 4 nephritis
- AST or ALT >5 x ULN or total bilirubin >3 x ULN; for patients with liver metastasis who begin treatment with Grade 2 AST or ALT, if AST or ALT increases by ≥50% relative to baseline and lasts for at least 1 week
- Grade 3 or 4 infusion-related reactions
- Inability to reduce corticosteroid dose to 10 mg or less of prednisone or equivalent per day within 12 weeks

- Persistent Grade 2 or 3 adverse reactions (excluding endocrinopathies controlled with hormone replacement therapy) that do not recover to Grade 0-1 within 12 weeks after last dose of pembrolizumab
- Any severe or Grade 3 treatment-related adverse reaction that recurs

10.4.3.6. Supportive Care Guidelines for Hypophysitis

Refer to the prescribing information for ipilimumab or pembrolizumab for additional information.

Patients should be monitored for signs and symptoms of hypophysitis such as adrenal insufficiency, hyperthyroidism, or hypothyroidism.

Patients being treated with ipilimumab should have treatment withheld if they develop symptomatic hypophysitis. Treatment with corticosteroids at a dose of 1 to 2 mg/kg/day of prednisone or equivalent should be initiated along with appropriate hormone replacement therapy. Consider a referral to an endocrinologist. Ipilimumab treatment may be resumed after resolution to Grade ≤1 and decrease of the corticosteroid dose to <7.5 mg/day prednisone or equivalent. Ipilimumab should be permanently discontinued for symptomatic reactions lasting ≥6 weeks or inability to reduce the corticosteroid dose to <7.5 mg/day prednisone or equivalent.

Patients being treated with pembrolizumab should have treatment withheld for hypophysitis Grade ≥2. Initiate treatment with corticosteroids and hormone replacement as clinically indicated. Consider a referral to an endocrinologist. Pembrolizumab treatment may be resumed after resolution to Grade ≤1. Pembrolizumab should be permanently discontinued for life-threatening hypophysitis not controlled with hormone replacement therapy, inability to decrease corticosteroid dose to <10 mg/day prednisone or equivalent within 12 weeks, persistent Grade 2 or 3 hypophysitis not controlled with hormone replacement therapy that does not resolve within 12 weeks, or recurrence of Grade 3 or higher hypophysitis.

10.5. Labeling

The product label contains the elements required by national and local authorities for investigational products. IMO-2125 will be shipped directly to the Investigator site.

10.6. Drug Accountability

Idera Pharmaceuticals, Inc. or designated Contract Research Organization (CRO) will provide drug accountability logs, a pharmacy binder, and other study drug preparation worksheets, as necessary. Each vial of IMO-2125 is labeled with a single-panel label. The accountability logs and worksheets are considered source documentation for each dose preparation. Instructions on how these forms should be used and filed will be reiterated at the site initiation visit.

10.6.1. IMO-2125 Dose Reduction

If at any time during the study, a patient experiences a DLT as outlined in Section 8.1.5, the toxicity must be assessed according to the guidelines described in that section to determine continued dosing (refer to Section 8.1.5).

The site must obtain the agreement of the clinical Medical Monitor for dosage reductions. If a patient is considered to have received an inadequate exposure to study drug relative to his or her planned dose level for non-study drug related reasons, he or she will be considered for replacement in the study, after discussion between Investigators, the site, and Idera Pharmaceuticals, Inc. If inadequate exposure to study drug is due to toxicity, this will be taken into account in the evaluation of DLT for that dose level (see Section 8.1.3).

10.6.2. Discontinuation of Study Drug

The study drug will be discontinued in any patient who is unable to tolerate it as evidenced by severe or persistent intolerable AEs despite dose modification.

10.7. Concomitant and Prohibited Medications

10.7.1. Concomitant Medications

With the exception of the prohibited drugs listed in Section 10.7.2, concomitant prescription drugs and over-the-counter drugs are permitted. These should be recorded on the eCRF starting with medications taken 30 days before the patient signs the informed consent form (ICF).

10.7.2. Prohibited Medications

The following drugs are prohibited while the patient is in this study:

- Anti-cancer therapies other than those specified in the protocol
- Drugs that either stimulate or suppress the immune system:
  - Systemic steroid therapy higher than physiologic dose (>7.5 mg/day of prednisone or equivalent)

    Note: For patients with pre-existing endocrine insufficiency, stress doses of replacement steroid treatment may be given on the day of and the day after study treatment administration (i.e., dosing with IMO-2125, ipilimumab, or pembrolizumab). Additional need for steroid replacement should be discussed with the Medical Monitor.
  - Topical and inhaled steroids may be acceptable after consultation with the Medical Monitor
  - Live vaccines (attenuated vaccines are permitted)
- Experimental vaccines
- Investigational/experimental medicines

11. ADVERSE EVENT REPORTING

11.1. Adverse Events

Adverse events should be assessed continuously throughout the study and recorded on the eCRF. Reporting during the follow-up phase of the study should be limited to Grade ≥3 AEs, associated concomitant medications, and serious adverse events (SAEs; see Table 1 and Table 2).

11.1.1. Definition of Adverse Events

11.1.1.1. Adverse Event

An AE is any untoward medical occurrence temporally associated with the use of a medical product in a patient, ***whether or not*** the event is considered causally related to the medical product.[1] An AE can be a new occurrence or an existing process that increases significantly in intensity or frequency.

11.1.1.2. Serious Adverse Event

An AE is **serious** when the patient outcome is one or more of the following:

- Death.
- Life-threatening, meaning that the patient was at immediate risk of death from the event at the time that the event occurred. It does not include an event which hypothetically might have caused death if it occurred in a more severe form.
- Hospitalization, initial or prolonged, meaning that a hospital admission and/or prolongation of a hospital stay was required for the treatment of the AE, or occurred as a consequence of the event. It does not include a pre-planned elective hospital admission for treatment or diagnostic procedures, or, in general, a hospital admission of less than 24 hours duration.
- Disability or incapacity that is persistent or significant.
- Congenital anomaly or birth defect.
- Important medical event that, although not immediately life-threatening, requires intervention in order to prevent one of the other serious outcomes listed above. Examples of such events are allergic bronchospasm requiring intensive treatment in an emergency room or at home; blood dyscrasias or convulsions that do not result in hospitalization; or the development of drug dependency or drug abuse.

[1] A medical product may be a drug or a device being used either prior to or after regulatory approval. The medical product in this protocol will hereafter be referred to as study drug (synonym: investigational agent).

11.1.1.3. Suspected Unexpected Serious Adverse Reaction (SUSAR)

A SUSAR is defined as an SAE that meets ***both*** the following criteria with respect to study drug:

- *Suspected* — is assessed as related or possibly related to study drug (see Section 11.1.3.3);
- *Unexpected* — compared to the study drug-related AEs described in the Investigator's Brochure, the event meets ***any*** of the following criteria:
  - The event was not previously described;
  - The event is now characterized as more severe (see Section 11.1.3.2);
  - The event is now characterized more specifically (e.g., an event of "interstitial nephritis" in a patient receiving an agent previously described as associated with "acute renal failure").

In clinical trials involving ill patients, events considered related to the natural history of the disease under study or to lack of efficacy (that is, the event is considered more likely related to those factors than to other factors, including study drug) are not considered "unexpected." Lack of efficacy is recorded as specified elsewhere in the Protocol.

11.1.2. Recording Adverse Events

Procedures for the collection and recording of AEs are as follows:

- From obtaining informed consent through the SFU Visit, there will be active surveillance to identify all AEs. Events will be recorded in the AE portion of the electronic data capture (EDC), with particular attention to whether the onset of the event was before or after the administration of the first dose of study drug. All recorded events will be included in applicable line listings, but only events with onset after administration of the first dose will be included in summaries of treatment-emergent AEs.
- After the end of study, surveillance will be passive (only events brought to the Investigator's attention will be considered) and only events assessed as SUSARs will be recorded (see Section 11.1.1.3).
- In accordance with the FDA guidance document – Safety Reporting Requirements for Investigational New Drugs (INDs) and Bioavailability/Bioequivalence (BA/BE) Studies – disease progression does not require reporting as an AE or SAE. However, signs and symptoms related to disease may be reported at the discretion of the Investigator.

11.1.3. Characterizing Adverse Events

For each AE recorded the following characteristics will be noted.

11.1.3.1. Description of Event

The diagnosis or description will be as specific and complete as possible (i.e., "lower extremity edema," rather than just "edema"). Whenever possible, signs and symptoms due to a common

etiology will be reported as an integrated diagnosis; for example, cough, runny nose, sneezing, sore throat and head congestion would be reported as "upper respiratory infection."

11.1.3.2. Date and Time of Onset

The date and time at which the event was first apparent will be recorded, if known. The time of onset of symptoms may be appreciably earlier than the date and time the Investigator becomes aware of the event. Some events may be apparent to the patient and Investigator independently, and information from each may contribute to the final report. For example, a patient may report the onset of a rash two days prior to being seen by a physician who makes a diagnosis of herpes zoster based on appearance and laboratory confirmation. In that case, there is a single AE, with the date of onset based on the date of the initial observation by the patient and a specific description (herpes zoster) based on the clinical exam and tests.

11.1.3.3. Relationship to Study Drug

This determination is based on the Investigator's clinical judgment regarding the likelihood that the study drug caused the AE and may include consideration of some or all of the following factors:

- Alternative possible causes of the AE, including the patient's underlying disease or co-morbid conditions, other drugs, other host and environmental factors.
- Temporal sequence between the exposure to study drug and the AE.
- Whether the clinical or laboratory manifestations of the AE are consistent with known actions or toxicity of the study drug.
- Whether the AE resolved or improved with decreasing the dose level or stopping the study drug (i.e., dechallenge); or recurred or worsened with re-exposure to the drug (i.e., rechallenge).

The relationship between the study drug and the AE will be described using one of the following categories:

- ***Related*** — the study drug is more likely the cause of the AE than other factors.
- ***Possibly related*** — there is a *reasonable* possibility that the study drug is the cause of the AE, including that the study drug and another factor(s) are equally likely as causes of the AE.
- ***Unlikely related*** — another factor is considered more likely the cause of the AE than the study drug.
- ***Not related*** — another factor is considered to be the cause of the AE.

Related and possibly related AEs may result during the use of the study drug as planned (per protocol), or from abuse, withdrawal or over-dosage of the agent.

11.1.3.1. Immune-related Adverse Events

The following list of AEs, which have been associated with the use of immunotherapy agents, will be considered to be immune-related and should be considered as such unless another etiology can be clearly established:

- Adrenal insufficiency
- Hypophysitis
- Hypopituitarism
- Other endocrinopathies
- Colitis
- Enterocolitis
- Dermatitis CTCAE Grade ≥3
- Autoimmune dermatitis CTCAE Grade ≥3
- Guillain Barre syndrome
- Hepatitis
- Myasthenia gravis
- Pneumonitis
- Stevens Johnson Syndrome
- Toxic epidermal necrolysis
- Uveitis
- Iritis
- Any AEs that the Investigator considers to be of autoimmune or immune-related origin (those AE terms designated as such in the eCRF).

Immune-related AEs will be summarized in the clinical study report.

11.1.3.2. Severity

The severity of clinical AEs (i.e., symptoms reported by the patient and/or signs observed by the Investigator) will be assessed using the guidelines summarized in Table 7 based on CTCAE v4.03 criteria.

Table 7: Estimating Severity Grade

Grade 1/Mild	Asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated
Grade 2/Moderate	Minimal, local, or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living[1]
Grade 3/Severe	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care activities of daily living[2]
Grade 4/Life-threatening	Life-threatening consequences; urgent intervention indicated
Grade 5/Death	Death related to adverse event

1. Instrumental activities of daily living refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.
2. Self-care activities of daily living refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

11.1.3.3. Grading of Laboratory Safety Tests for Reporting and Analysis

Treatment-emergent abnormal laboratory results will be handled as follows:

- Graded using NCI-CTCAE Version 4.03 criteria
- Assessed as potential DLT events based on pre-specified criteria (see Section 8.1.5)
- Reported as AEs when assessed as clinically significant ("CS") using the procedures and criteria detailed in Section 11.1.2.

11.1.3.4. Management of Study Drug upon Occurrence of an Adverse Event

For each AE the Investigator will indicate which one of the following actions regarding the administration of study drug was taken because of that AE:

- ***Discontinued*** — study drug was stopped permanently due to the AE.
- ***Dosing Interrupted*** — study drug regimen was modified by being temporarily halted, i.e., 1 or more doses were not administered, but drug was not stopped permanently.
- ***Dose Decreased*** — study drug regimen was modified by subtraction, i.e., by decreasing the frequency, strength or amount.
- ***None*** — no change in the administration of study mediation.

For patients whose treatment is paused and then resumed at a lower dose level due to events such as DLTs (see Section 8.1.5), the management of study drug will be recorded as "Dose Decreased."

11.1.3.5. Actions Taken for Management of Adverse Event

Adverse events will be followed and managed by the Investigator, including obtaining any supplemental studies needed to define the nature and/or cause of the event (e.g., laboratory tests, diagnostic procedures, consultation with other health care professionals).

For each AE the Investigator will categorize as follows the actions taken to manage the AE:

- ***Concomitant medication*** — one or more medications (prescription or over-the-counter) were started or increased in dose; non-medication actions may *also* have been ordered.
- ***Other action*** — *only* non-medication action(s) were ordered as management of the AE (e.g., bed placed in Trendelenburg position, warm compresses applied to access site).
- ***No action*** — no actions were ordered for management of the AE.

11.1.3.6. Follow-up and Outcome of Adverse Events

If possible, AEs will be followed until resolved (synonyms: recovered, recuperated, ended) either with or without sequelae, including for patients who prematurely discontinue study participation. For AEs that are assessed as not drug-related and are not resolved at the end-of-study visit, follow-up may be limited with the approval of the Medical Monitor.

The outcome of each event will be described using the following categories:

- ***Resolved without sequelae*** — the event resolved and patient returned to baseline.
- ***Resolved with sequelae*** — the event resolved but the patient is left with residual problems (e.g., functional deficits, pain).
- ***Resolving*** — at the last observation, the event was improving.
- ***Not Resolved*** — at the last observation, the event was unchanged.
- ***Death (Fatal)*** — to be used for the *one* AE which, in the judgment of the Investigator, was the *primary* cause of death.
- ***Unknown*** — there were no observations after the onset (initial observation or report) of the event.

Note: Resolving and Not Resolved may also be used for AEs that were unresolved at the time a patient died, but were *not* assessed as the primary cause of death.

11.1.3.7. Date and Time of Outcome

For each class of outcome as defined above, Table 8 indicates the date and time to be recorded. As discussed in detail for date/time of onset (see Section 11.1.3.2), determining the date/time an event resolved (ended) should reflect the type of event and the source of the information.

Table 8: Date and Time of Outcome for Adverse Event by Outcome Class

Outcome assigned to Adverse Event	Date and Time to be Recorded
Resolved (with or without sequelae)	Date and time event observed or reported as resolved
Death	Date and time of death
Resolving or Not Resolved	Date and time of last observation
Unknown	None (see definition above)

11.1.4. Reporting Adverse Events

11.1.4.1. Where to Report Serious Adverse Events

Serious AE reporting will be performed by the site using the EDC system; detailed training will be provided during site initiation. Reports and supporting materials relating to SAEs will be scanned and uploaded into the EDC system. Contact information for the Medical Monitor and the Pharmacovigilance services is provided in the Emergency Contact Information section of this protocol.

In the event an SAE cannot be submitted via EDC, contact information is provided in the Emergency Contact Information section of this protocol for alternative submission methods.

11.1.4.2. Procedures for Reporting Serious Adverse Events to the Sponsor

The ***initial notification*** of each SAE will be entered into the EDC system ***within 24 hours*** of the time the Investigator (or the Investigator's designee) becomes aware that the event has occurred. The following items will be entered into the appropriate EDC section (any items not available should be explicitly noted):

- Protocol number, study site, patient number.
- Investigator's name and contact information (phone, email).
- Description of the event (i.e., date and time of onset, initial assessment, treatments and course).
- Current status of the patient and the event.
- Criteria by which the event was assessed as serious.
- Date of the first injection of study drug.
- Date of the last injection of study drug prior to the event.
- Assessment of relationship of study drug to the event.
- Whether the study drug was discontinued or adjusted as a result of the event.

The following ***additional*** information will be entered within 2 days for death and life-threatening events and within 4 days for all other SAEs:

- Narrative summary of the event — to include specific information that will assist in understanding the event, e.g., relevant medical history, co-morbid conditions, physical exam, diagnostics, assessment, treatments (including concomitant medications), response to treatment, course, and outcome (if known);
- Copies of relevant medical reports — including diagnostic procedures (e.g., laboratory, ECG, x-ray), surgical procedures, and consultations.

Additional documentation may be submitted as part of a follow-up report.

11.1.4.3. Other Reportable Events

Certain events that occur in the absence of an AE should be reported to the Sponsor. These include the following:

- Pregnancy exposure (patient becomes pregnant while taking study drug). Should a female patient or partner of a male patient become pregnant during the study, the patient will inform the Investigator. The patient will be asked to follow up with the study site to report the eventual outcome of the pregnancy. The information will be tracked by the Sponsor.
- Lactation exposure (patient was taking study drug while nursing an infant).
- Accidental exposure (someone other than the patient was exposed to study drug).
- Overdose (patient received more than the prescribed dose of study drug within a given timeframe).

- Other medication errors that potentially place patients at greater risk of harm than was previously known or recognized (e.g., study drug was administered via incorrect route).

11.1.4.4. Requirements for Expedited and Periodic Reporting of Adverse Events

Suspected unexpected serious adverse reactions are required to be reported rapidly to regulatory authorities and to IRBs/ECs (typically within 7 days for fatal or life-threatening SUSARs; within 15 days for all other SUSARs). The Sponsor and the Investigator will work together to meet these reporting requirements.

12. SAFETY ASSESSMENTS

12.1. Vital Signs

Vital sign measurements will be taken at intervals as specified in the Schedules of Evaluations (Table 1 and Table 2) and Section 9. Where feasible, vital signs should be measured before having blood drawn for laboratory evaluations. Blood pressure measurements should be taken with the patient in a sitting position, preferably for approximately 5 minutes.

12.2. Laboratory Assessments

Instructions for conducting laboratory assessments and processing samples will be provided in a study manual to the study staff before study initiation. Laboratory tests will be performed at intervals as specified in the Schedules of Evaluations (Table 1 and Table 2) and Section 9. Blood and urine samples will be analyzed for the analytes presented in Table 9.

Table 9: Laboratory Measurements

Hematology	Chemistry	Urinalysis (Dipstick)	Other
Basophils	Albumin	Glucose	**Thyroid Profile**
Eosinophils	Alkaline phosphatase	pH	TSH
Lymphocytes	ALT	Leukocytes	Free thyroxine (free T4)
Atypical lymphocytes	AST	Nitrite	Total or free triiodothyronine (total or free T3)
Monocytes	Total bilirubin	Urobilinogen	
Neutrophils	BUN	Protein	**Coagulation**
Hematocrit	Creatinine	Occult blood	PT
Hemoglobin	Calcium	Specific gravity	aPTT
MCH	CO_2	Ketones	INR
MCHC	Sodium, chloride, and potassium	Bilirubin	
MCV	Cholesterol		**Complement**
Platelet count	GGT	**Microscopy**	CH50
RBC count	Glucose	Bacteria	C3
WBC count	Lactate dehydrogenase	Crystals	C4
	Phosphate	Casts (cellular, granular, and hyaline)	
	Total protein	RBC	
	Triglycerides	WBC	
	Uric acid	Epithelial cells	
	βhCG for WOCBP		

βhCG=beta human chorionic gonadotropin; ALT=alanine aminotransferase; aPTT= activated partial thromboplastin time; AST=aspartate aminotransferase; BUN=blood urea nitrogen; C3=complement component 3; C4=complement component 4; CH50=total complement activity 50; GGT=gamma glutamyltransferase; INR=international normalized ratio; MCH=mean corpuscular hemoglobin; MCHC=mean corpuscular hemoglobin concentration; MCV=mean corpuscular volume; PT=prothrombin time; RBC=red blood cell; TSH=thyroid-stimulating hormone; WBC=white blood cell; WOCBP=women of childbearing potential

12.3. Other Safety Assessments

12.3.1. Physical Examination

A medical history will be taken at the Screening Visit. A physical examination (including special attention to each of the inclusion and exclusion criteria in the protocol) and assessments of melanoma lesions will be performed as outlined in the Schedules of Evaluations (Table 1 and Table 2).

Patient height will be recorded at the Screening Visit only.

12.3.2. Electrocardiogram Monitoring

A resting 12-lead ECG will be performed at intervals as specified in the Schedules of Evaluations (Table 1 and Table 2) and Section 9.

12.3.3. ECOG Performance Status

The patient's ECOG performance status will be evaluated per guidance in Section 21.1 as outlined in the Schedules of Evaluations (Table 1 and Table 2).

13. PHARMACOKINETICS AND IMMUNE RESPONSE

The timing of sample collection is provided in the Schedules of Evaluations (Table 1 and Table 2) and the Schedule of PK Blood Sampling (Table 3). Detailed instructions and materials for all blood sampling will be provided in a separate study manual and kits.

13.1. Pharmacokinetic Assessments

The plasma PK of single-dose IMO-2125 and the PK of repeat-dose IMO-2125 administered by intratumoral injection in combination with ipilimumab or pembrolizumab will be evaluated at each of the dose levels. The following parameters will be determined for IMO-2125 plasma PK, if appropriate:

- Maximum plasma concentration (C_{max})
- Time of C_{max} (t_{max})
- Area under the curve from 0 to last measurable plasma concentration (AUC_{0-t})

Serum concentrations of ipilimumab and pembrolizumab will be monitored on Weeks 2, 5, 8, 11, 17, and 23. For patients who continue pembrolizumab treatment, pembrolizumab pre-dose PK samples should be collected before dosing at all visits. A post-dose pembrolizumab PK sample should be collected 30 minutes after initiation of pembrolizumab infusion at Week 23.

For each combination in Phase 2, the collection of plasma concentration samples will be done on at least 20 patients treated at the IMO-2125 RP2D after which the Sponsor will determine if additional samples are needed. The Sponsor will then inform the Investigators whether or not to continue collecting plasma concentration samples.

The relationship between PK assessments, safety, efficacy, and pharmacodynamics variables will be explored whenever possible.

13.2. Pharmacodynamic Markers of Immune Response

For Phase 1, biopsies of the injected tumor will be performed at the Screening Visit (within 21 days prior to first treatment); within 24 to 48 hours after IMO-2125 injection on Week 1 (Cycle 1); Week 2 (Cycle 1; optional); during Week 8 (Cycle 3); and optionally at Week 13 (Cycle 4) and at the time of disease progression or during Week 23, whichever is later. Tumor biopsies of the designated non-injected lesion will be performed at Screening, prior to the first dose of ipilimumab or pembrolizumab (optional), and during Week 8. For Phase 2, tumor biopsies are optional at all specified visits. Surgical methods (e.g., punch or core) are preferred over FNA where feasible.

For those patients who have liver or other visceral metastases injected with IMO-2125, repeat biopsy of liver or other visceral tumor lesions may not always be possible. Therefore, repeat biopsies will be performed only when feasible in these patients. Note that tumor biopsies should be done prior to study treatment administration.

The Week 8 (Cycle 3) and Week 13 (Cycle 4) biopsies may be performed within a ±3 day window. If tumor response is observed early during initial treatment, the Week 8 biopsies may

be performed at an earlier time point so as to ensure meaningful biomarker information is obtained prior to complete resolution of tumor.

Exploratory variables will be assessed at pre-treatment and post-treatment and may include, but are not limited to:

- Biomarkers (CD8+ T cells, NK cells, pDC/myeloid DC, memory T cells in tumor tissue, T cells, and cytokine levels in blood)
- Any potential association between these biomarkers and antitumor activity
- Gene profiling (with RNA and DNA extraction)
- Immunogenicity (antibodies to IMO-2125, ipilimumab, or pembrolizumab)

13.2.1. Immunogenicity Analyses

Exploratory analyses will include assessing the occurrence of antibodies to the administered oligonucleotide (anti-IMO-2125 antibodies), as well as antibodies to the administered ipilimumab or pembrolizumab (refer to Table 1 and Table 2).

13.2.2. Immunologic Evaluations

Immunologic evaluations will include, but not be limited to:

- Immunophenotyping with flow cytometry (on biopsies from patients enrolled in the Phase 1 portion);
- The assessment of TCR Vß CDR3 clonal diversity will be done using ImmunoSeq™ (Adaptive Biotechnologies, Seattle, WA);
- NanoString gene expression analyses.

14. ASSESSMENT OF EFFICACY

14.1. Tumor Response

Tumor response will be assessed using immune-related response criteria (irRC) and RECIST v1.1 in Phase 1 and using irRECIST and RECIST v1.1 in Phase 2 (Section 21.2, Section 21.4, and Section 21.3, respectively). Efficacy evaluation should include clinical examination and CT or magnetic resonance imaging scanning of known sites of disease. Ultrasound studies performed for needle biopsy localization or IMO-2125 dosing should not be used to assess tumor status (in accordance with RECIST v1.1). The same method(s) of assessment should be used throughout the study for consistency wherever feasible. Response should be assessed at Weeks 8, 17, and 29 and at least every 3 months thereafter until progression or start of a new anti-cancer therapy (see Section 8.2.2). Response assessments of CR, PR, and progressive disease must be confirmed by imaging ≥4 weeks after the initial documentation of response.

15. ASSESSMENT OF PATIENT REPORTED OUTCOMES

15.1. EORTC QLQ-C30

The EORTC QLQ-C30 is an integrated system for assessing the health-related quality of life (QoL) of cancer patients participating in international clinical trials. The EORTC has adopted a modular approach to QoL assessment, consisting of a core questionnaire to be administered, if necessary with a module specific to tumor site, treatment modality, or a QoL dimension (Aaronson, 1993).

The EORTC QLQ-C30 is the product of more than a decade of collaborative research. It is a questionnaire for patient self-completion, composed of multi-item and single-item measures. These include 5 functional scales (physical, role, emotional, social, and cognitive), 3 symptom scales (fatigue, nausea and vomiting, and pain) and a global health status/QoL scale, and 6 single items (dyspnea, insomnia, appetite loss, constipation, diarrhea, and financial difficulties) (Aaronson, 1993).

All of the scales and single-item measures range in score from 0 to 100. A high scale score represents a higher response level. Thus, a high score for a functional scale represents a high/healthy level of functioning, a high score for the global health status/QoL represents a high QoL, but a high score for a symptom scale/item represents a high level of symptomatology/problems.

The EORTC QLQ-C30 will be administered to all subjects according to the Schedule of Evaluations (Table 1 and Table 2). To minimize bias in the PRO data, the PRO assessments should be completed before study drug administration and AE assessments.

16. STATISTICAL ANALYSIS METHODS

Please refer to Section 8.1.3 for the rules around dose level escalation and stopping.

16.1. Determination of Sample Size

The primary objective of Phase 2 is to assess the preliminary clinical activity, defined as the investigator-assessed ORR, of IMO-2125 in combination with ipilimumab or of IMO-2125 in combination with pembrolizumab in patients with progression on or following PD-(L)1 inhibitor therapy for metastatic melanoma. Given that two primary hypotheses are being tested (regarding the ORR of IMO-2125 and ipilimumab and the ORR of IMO-2125 and pembrolizumab), a Bonferroni correction has been applied to the alpha to control the Type I error rate for the trial.

Assuming the ORR for patients who receive ipilimumab alone is at most 11% (the historical response rate in patients who are PD-1 inhibitor naïve), and a target ORR of 35% for patients who receive the IMO-2125 + ipilimumab combination treatment, a sample size of 21 patients would achieve 77% power to detect a 24% difference in response rates using a one-sided significance level of 2.5%.

The IMO-2125 + ipilimumab treatment arm will use a two-stage design with a targeted Type I error rate of 0.025 to test the null response rate of 0.11 against the alternative of at least 35%. With this method, 10 patients will be treated and monitored for a RECIST v1.1 response in the first stage. For this arm, if 2 or more patients have a RECIST v1.1 response in Stage 1, then the treatment arm will continue to Stage 2, in which 11 more patients will be treated. If at least 6 of 21 patients have a RECIST v1.1 response, then the null hypothesis H_o will be rejected in favor of the alternative H_a. In this treatment arm, this design has statistical power of 77%, an expected sample size of 13.33 under the null hypothesis, and a probability of stopping at the end of the first stage of 69.7% if the response proportion is ≤0.11.

At least 60 patients may be enrolled in this arm, including the 21 ipilimumab-naïve patients who will be used to test the null hypothesis. These 60 patients will include those with primary exposure to ipilimumab. The purpose of treating ~40 patients in addition to those needed for the hypothesis test is to improve the precision of the ORR estimate in the primary efficacy population and to allow preliminary assessment of safety and preliminary efficacy in the population with prior exposure to ipilimumab. The 95% exact confidence intervals for a range of sample sizes for an ORR of at least 0.35 is in Table 10.

Table 10: ORR and Confidence Intervals with an ORR of At Least 0.35 for Possible Sample Sizes

n=21	n=30	n=35	n=40	n=45
0.381 (0.1811, 0.6156)	0.367 (0.1993 , 0.5614)	0.371 (0.2147, 0.5508	0.375 (0.2273 , 0.5420)	0.356 (0.2187, 0.5122)

Assuming a RECIST v1.1 ORR for patients who receive pembrolizumab alone following failure of a PD-1 inhibitor is at most 5%, and a target ORR for patients who receive the IMO-2125 + pembrolizumab combination treatment of 35%, a sample size of

21 efficacy-evaluable patients would achieve 96% power to detect a 30% difference in response rates using a one-sided significance level of 2.5%.

The IMO-2125 + pembrolizumab treatment arm will use a two-stage design with a targeted Type I error rate of 0.025 to test the null response rate against the alternative of at least 35%. If at least 1 patient has a RECIST v1.1 response in Stage 1, then the treatment arm will continue to Stage 2 and treat 11 additional patients. If at least 4 of the 21 total patients have a RECIST v1.1 response, then the null hypothesis H_o will be rejected in favor of the alternative H_a. In this treatment arm, this design has statistical power of 96%, an expected sample size of 14.41, and a probability of stopping at the end of the first stage of 60% if the response proportion is ≤0.05.

16.2. Analysis Populations

- Primary Ipilimumab + IMO-2125 Efficacy Evaluable (PIIEE) Population: all patients who are ipilimumab-naïve on study entry (including those who received ipilimumab only in the adjuvant setting) and who are treated at the RP2D for the IMO-2125 + ipilimumab combination, regardless of which phase of the study they receive it; and who received at least one dose of each study drug.
- Secondary Ipilimumab + IMO-2125 Efficacy Evaluable (SIIEE) Population: all patients who are not ipilimumab-naïve on study entry and who are treated at the RP2D for the IMO-2125 + ipilimumab combination, regardless of which phase of the study they receive it; and who received at least one dose of each study drug.
- Primary Pembrolizumab + IMO-2125 Efficacy Evaluable (PPIEE) Population: all patients who are treated at the RP2D for the IMO-2125 + pembrolizumab combination, regardless of which phase of the study they receive it; and who received at least one dose of each study drug.
- Safety Population: all patients who received at least one dose of IMO-2125.
- DLT Evaluable Population: all patients in the Safety Population who continue participation in the study for the entire DLT evaluation period, or who discontinue prematurely due to a DLT.
- PK Population: All subjects in the Safety Population who have ≥1 post-dose sample analyzed for study drug.

16.3. General Considerations

Continuous variables will be summarized using descriptive statistics such as mean, standard deviation, median, and range. Categorical variables will be summarized by count and proportion, and if specified, with 95% confidence intervals for the proportion. Missing data will not be imputed except as described in the Statistical Analysis Plan.

Data will be analyzed at the end of dose-finding for each treatment. Phase 2 data will be analyzed at the end of Phase 2 (approximately 1 year after the last patient in Phase 2 has commenced study treatment).

16.4. Analysis of Safety

Analysis of DLTs will be performed on the DLT Evaluable Population. All other safety analyses will be performed on the Safety Population.

Dose-limiting toxicities will be summarized by dose level with the n and percentage.

Vital signs, laboratory values, and ECG values will be summarized descriptively; no formal statistical hypotheses will be tested.

For laboratory values that are continuous, shift tables from baseline to worst value on study will be produced. Laboratory values that are out of the normal range as graded by CTCAE criteria will be flagged in listings, and any values that are judged by the Investigator as clinically significant will also be flagged as such.

Adverse events will be tabulated by MedDRA System Organ Class and Preferred Term. Adverse event tables will be produced by treatment group. Adverse event summaries will be as follows: overall, by severity, and related AEs. Listings of any deaths, SAEs, and AEs leading to discontinuation of treatment will be produced.

Any abnormal findings from physical examinations will be reported as AEs. As such, physical examination results will not be summarized.

Concomitant medications will be coded by World Health Organization drug class and Anatomical Therapeutic Chemical text and tabulated as such. The ECOG performance status will be tabulated by dose group and visit.

16.5. Analysis of Pharmacokinetics

For each cohort, the plasma IMO-2125 concentration data will be analyzed by non-compartmental PK analysis. Descriptive statistics will be provided for concentration data and all PK assessment values by study drug (IMO-2125, ipilimumab, and pembrolizumab), dose, and time, as appropriate.

Dose proportionality using the power model will be evaluated in an exploratory manner, if the data permit. If insufficient data are available to assess dose proportionality using the power model, dose normalized data will be presented for a graphical assessment.

The potential effects of IMO-2125 on the PK of ipilimumab and pembrolizumab will be evaluated.

16.6. Analysis of Efficacy

The primary analysis of efficacy in the Phase 2 IMO-2125 + ipilimumab arm, including the hypothesis test of the ORR, will be performed on the first 21 patients in the PIIEE Population as defined in Section 16.2. An analysis on those in the SIIEE Population will also be performed; efficacy analysis in the combined PIIEE and SIIEE Populations may also be summarized. The primary analysis of efficacy in the Phase 2 IMO-2125 + pembrolizumab arm will be performed on the PPIEE Population as defined in Section 16.2.

Patients will be categorized into subgroups based on whether they had previously been treated with talimogene or another oncolytic viral vector prior to enrollment in this study.

16.6.1. Analysis of Primary Treatment Effect Parameter

The primary efficacy endpoint, ORR assessed by the Investigator using RECIST v1.1, will be analyzed for the first 21 efficacy-evaluable patients in the PIIEE Population using a one-sided, one sample exact binomial test with $\alpha = 0.025$ in each test. The proportion of patients achieving an overall response will be tested against the null rates of 0.11 and 0.05 for ipilimumab and pembrolizumab, respectively (Hodi, 2010). ORR by RECIST v1.1 will also be summarized descriptively for all subjects in the PIIEE.

16.6.2. Analysis of Secondary Treatment Effect Parameters

The ORR and DCR using irRECIST criteria will be summarized descriptively in the PIIEE, SIIEE, and PPIEE Populations by dose with the n, percentage, and exact 95% confidence intervals. DCR will also be summarized by RECIST v1.1.

The OS and PFS proportions will be estimated at 6 and 12 months; OS and PFS will also be analyzed overall. For time-to-event endpoints (OS, PFS, and DoR), the Kaplan-Meier method will be used to estimate the probability of event-free survival. Patients who have not experienced the event at the data cut-off date for study closure will be censored. Patients who are lost to follow up will be censored at the last valid disease assessment for PFS and date of last contact for OS. Kaplan-Meier plots will be produced for OS and PFS by treatment arm.

16.7. Exploratory Analyses

Patterns of missing data will be described for PRO. Mean change from Baseline in the global health status score over time will be summarized and presented graphically. A mixed model for repeated measures may be used to assess the statistical significance of changes from Baseline. Exploratory endpoint analyses will be fully described in the statistical analysis plan.

17. DATA COLLECTION

17.1. Required Data

The full study dataset will be collected for patients who enter the treatment phase of the study, unless the patient withdraws consent. If a patient discontinues the study (for any reason, drug-related or other), every effort will be made to complete the SFU Visit within 21 days of the last dose (±5 days).

All required data for this study will be collected by EDC and all data collected in this study will be listed in the clinical study report.

17.2. Data Collection and Tracking

Qualified study staff at each site will perform primary data collection from source-document reviews. The designated CRO will perform clinical monitoring, including review of eCRFs with verification to the source documentation.

Safety laboratory and ECG data from the Screening Visit through the SFU Visit will be collected at the participating site. A Central Lab may be used to track and analyze the complement, PK and immunogenicity testing.

Site staff will enter data into a 21 CFR Part 11 compliant eCRF. The frequency and procedures for the handling of data within the clinical database will be documented in detail in the Data Management Plan.

18. STUDY RESPONSIBILITIES

18.1. Investigator Responsibilities

The Investigator should not deviate from the protocol. In medical emergencies, the Investigator may use his/her medical judgment and may remove a study participant from immediate hazard before notifying Idera Pharmaceuticals, Inc. (or its representative) and the IRB/EC in writing regarding the type of emergency and the course of action taken.

18.2. Study Data Reporting and Processing

The eCRF will be reviewed by the Principal Investigator (PI) at the site. The PI will electronically sign the eCRF to verify that he or she has reviewed the recorded data. This review and sign-off may be delegated to a qualified physician appointed as a sub-investigator by the PI. The transfer of duties to a sub-investigator will be recorded on the delegation list (kept on file at the site) and all sub-investigators are to be listed on appropriate regulatory forms (e.g., FDA Form 1572). The Investigator must ensure that all site staff involved in the conduct of the study are trained on and familiar with the protocol and all study-specific procedures and that they have appropriate knowledge of the study agents.

18.3. Training

The training of appropriate clinical site personnel will be the responsibility of the designated CRO. The PI is responsible for ensuring that his or her staff conducts the study according to the protocol. To ensure proper administration of study agents, uniform data collection, and protocol compliance, the designated CRO will present a formal training session to study site personnel, to include instructions for study procedures, the investigational plan, instructions on in-hospital data collection, methods for soliciting data from alternative sources, schedules for follow up with the study site coordinators, and regulatory requirements. Detailed feedback regarding completion of forms will be provided by the designated CRO in the course of regular site monitoring.

18.4. Monitoring the Investigational Site

Monitoring of the study (which may be delegated by the Sponsor to a CRO) will be performed according to the Study Monitoring Plan.

18.5. Study Documentation

Study documentation includes all eCRFs, source documents, monitoring logs, appointment schedules, Sponsor-Investigator correspondence, and regulatory documents (e.g., signed protocol and amendments, IRB/EC correspondence and approval, approved and signed patient consent forms, Statement of Investigator form, and clinical supplies receipts and distribution records).

The Investigator will prepare and maintain complete and accurate study documentation in compliance with Good Clinical Practice (GCP) standards and applicable regional, federal, state, and local laws, rules, and regulations; and, for each patient participating in the study, will promptly complete all eCRFs and such other reports as required by this protocol following

completion or termination of the clinical study or as otherwise required pursuant to any agreement with Idera Pharmaceuticals, Inc.

By signing the protocol, the Investigator acknowledges that, within legal and regulatory restrictions and institutional and ethical considerations, study documentation will be promptly and fully disclosed to the designated CRO and Idera Pharmaceuticals, Inc. by the Investigator upon request and also will be made available at the Investigator's site upon request for inspection, copying, review, and audit at reasonable times by representatives of Idera Pharmaceuticals, Inc. or responsible government agencies as required by law. The Investigator agrees to promptly take any reasonable steps that are requested by Idera Pharmaceuticals, Inc. or the designated CRO as a result of an audit to cure deficiencies in the study documentation and eCRFs.

18.6. Source Documentation

Source documents include all recordings of observations or notations of clinical activities and all reports and records necessary for the evaluation and reconstruction of the clinical study. Accordingly, source documents include, but are not limited to, laboratory reports, ECG tracings, x-rays, radiologist reports, patient diaries, biopsy reports, ultrasound photographs, patient progress notes, hospital charts, pharmacy records (including drug preparation worksheets), and any other similar reports or records of any procedure performed in accordance with the protocol.

Whenever possible, the original recording of an observation should be retained as the source document; however, a photocopy is acceptable provided that it is a clear, legible, and exact duplication of the original document.

Regulations require that Investigators maintain information in the study patient's medical records that corroborates data collected on the eCRF. In order to comply with these regulatory requirements, the following information will be maintained and made available as required by the study monitors, auditors, and/or regulatory inspectors:

1. Medical history/physical condition of the study patient before involvement in the study sufficient to verify protocol entry criteria
2. Medical record documenting that informed consent was obtained for the patient's participation in the study
3. Dated and signed notes for each patient visit, including results of examinations
4. Notations on abnormal lab results and their resolution
5. Dated printouts or reports of special assessments (e.g., ECG reports)
6. Description of AEs and follow up of the AEs (minimally, event description, severity, onset date, duration, relation to study device, outcome, and treatment for AE)
7. Notes regarding concomitant medications taken during the study (including start and stop dates)
8. Patient's condition upon completion of or withdrawal from the study

18.7. Protocol Deviations

A protocol deviation is defined as an event where the Investigator or site personnel did not conduct the study according to the investigational study protocol or the Investigator Agreement.

18.8. Study Supply Accountability

The Investigator will maintain complete and accurate records of the receipt and disposition of all investigational agents. When the enrollment is complete, the Investigator will be notified by Idera Pharmaceuticals, Inc. and, in a timely manner, will destroy the study drug in a documented fashion, as directed by Idera Pharmaceuticals, Inc.

18.9. Data Transmittal and Record Retention

Required data will be entered in the appropriate eCRF at the time of or as soon as possible after the patient visit or the availability of test results. All completed eCRFs will be reviewed by a representative of the designated CRO at regular intervals according to the Study Monitoring Plan as the study proceeds.

The Investigator will maintain the records of study drug disposition, final eCRFs, worksheets, and all other study-specific documentation, e.g., study file notebooks or source documentation, until notified by Idera Pharmaceuticals, Inc. that records may be destroyed. Idera Pharmaceutical, Inc. retains the right to evaluate imaging studies used to make efficacy assessments, including central imaging facility review.

The Investigator(s) must maintain all Essential Documents (as listed in the International Council for Harmonisation [ICH] Guideline for GCP) until notified by Idera Pharmaceuticals, Inc. or its designees, and in accordance with all local laws regarding retention of records.

The Investigator must obtain written permission from Idera Pharmaceuticals, Inc. or its designees before disposing of any records. To avoid error, the Investigator will contact Idera Pharmaceuticals, Inc. before the destruction of any records pertaining to the study. The Investigator will promptly notify Idera Pharmaceuticals, Inc. or its designees in the event of accidental loss or destruction of any study records. In addition, Idera Pharmaceuticals, Inc. will be contacted if the Investigator plans to leave the institution so that arrangements can be made for the transfer of records.

18.10. Study Closeout

Upon completion of the study (defined as all patients have completed all follow-up visits, all eCRFs are complete, and all queries have been resolved), the designated CRO will notify the site of closeout, and a study closeout visit will be performed. All unused study materials will be collected and returned to Idera Pharmaceuticals, Inc. or the designated CRO. The study monitor will ensure that the Investigator's regulatory files are up to date and complete, and that any outstanding issues from previous visits have been resolved. Other issues to be reviewed at the closeout visit include: discussing retention of study files, possibility of site audits, publication policy, and notifying the IRB/EC of study closure.

18.11. Audit/Inspections

Quality assurance personnel from Idera Pharmaceuticals, Inc., or its partners, may conduct audits at the study site. Audits will include, but not be limited to: audit trail of data handling and processes, standard operating procedures, drug supply, presence of required documents, the informed consent process, and comparison of the eCRF with source documents. The Investigator agrees to accommodate and participate in audits conducted at a reasonable time in a reasonable manner, as needed.

Regulatory authorities worldwide may conduct inspections of the Investigator during or after the study. The Investigator should contact Idera Pharmaceuticals, Inc. immediately if this occurs and must fully cooperate with Regulatory Authorities inspections conducted at a reasonable time in a reasonable manner.

Idera Pharmaceuticals, Inc. retains the right to conduct independent review of radiologic scans for up to 3 years following completion of the study.

19. ETHICAL CONSIDERATIONS

By signing this protocol, the Investigator agrees to conduct the study in compliance with the protocol, the International Council for Harmonisation (ICH) GCP guidelines, the Declaration of Helsinki, and all applicable federal, state, and local laws, rules, and regulations relating to the conduct of the clinical study.

19.1. Role of Sponsor

As the study Sponsor, Idera Pharmaceuticals, Inc. has overall responsibility for the conduct of the study, including assurance that the study meets the regulatory requirements. In this study, Idera Pharmaceuticals, Inc. will have certain direct responsibilities and will delegate other responsibilities to the designated CRO. The CRO will ensure adherence to the Sponsor's general responsibilities and other responsibilities as agreed between the designated CRO and Idera Pharmaceuticals, Inc., e.g., selection of Investigators, monitoring, and protocol amendments.

19.2. Informed Consent

The Investigator has both ethical and legal responsibility to ensure that each patient being considered for inclusion in this study is given a full explanation of the study. Written informed consent will be obtained from all patients (or their guardians or legal representatives) before any study-related procedures (including any pre-treatment procedures, such as pre-procedure sedation) are performed or given.

Written informed consent will be documented on an ICF approved by the same IRB/EC responsible for approval of this protocol. The ICF will conform to ICH GCP guidelines and to the institutional requirements for informed consent and applicable regulations. The Investigator agrees to obtain approval from Idera Pharmaceuticals, Inc. of any ICF intended for use in the study, prior to submission for IRB/EC approval.

The consent form will be reviewed with the prospective study patient or his or her legal representative, and the Investigator or qualified designee will be available to answer questions regarding procedures, risks, and alternatives.

Once the appropriate essential information has been provided to the patient and fully explained by the Investigator or qualified designee, and it is felt that the patient understands the implications of participating, the patient and the Investigator or designee will sign and date the IRB/EC-approved written ICF. The patient will receive a copy of the signed ICF. The original signed and dated ICF will be kept in the site's regulatory file. Documentation of the patient's informed consent for and participation in this study will be noted in the patient's medical record.

If the patient is illiterate, an impartial witness is required to be present during the entire informed consent reading and discussion. Afterward, the patient should be asked to sign and date the ICF, if capable. The impartial witness should also sign and date the ICF along with the individual who read and discussed the informed consent (i.e., study staff personnel).

The patient or his or her legally acceptable representative will be informed in a timely manner if new information becomes available that may be relevant to the patient's willingness to continue

participation in the trial. The communication of this information to the patient will be documented.

19.3. Confidentiality of Patients

Patient confidentiality will be maintained throughout the clinical study in a way that ensures the information can always be tracked back to the source data. For this purpose, a unique patient identification code (ID number and patient name code) will be used that allows identification of all data reported for each patient.

Patient information collected in this study will comply with the standards for protection of privacy of individually identifiable health information as promulgated in the Health Insurance Portability and Accountability Act (HIPAA) and as mandated in 45 CFR 160 and 164. All records will be kept confidential and the patient's name will not be released at any time. Patient records will not be released to anyone other than Idera Pharmaceuticals, Inc. or its designees, and responsible regulatory authorities, when requested. In all cases, caution will be exercised to assure the data are treated confidentially and that the patient's privacy is guaranteed.

19.4. Authorization for Use and Disclosure of Protected Health Information

An authorization for use and disclosure of protected health information (PHI) under the HIPAA Privacy Rule (45 CFR 164.102 et seq) will be obtained from every study patient before, or at the time of, enrollment. It will be presented to, and signed by, the patient at the same time as the ICF. The Investigator is responsible for obtaining patients' (or their legal representatives') authorizations and signatures and for explaining the elements of the HIPAA authorization form if necessary.

The HIPAA authorization may be either a separate form or included in the study ICF, dependent upon local requirements. If a separate HIPAA document is signed, the Investigator will append one signed original of each executed HIPAA authorization to the study patient's signed ICF and file it in the site's regulatory file. If a second copy of the signed ICF is filed in the patient's medical records, an additional copy of the signed HIPAA authorization form will be appended. Patients will be given the other signed duplicate for their personal records.

The HIPAA authorization form will contain all elements required under the HIPAA Privacy Rule. By law, site IRB/EC approval of the Sponsor-provided authorization form for use in this study is not required, and no such approval will be sought or requested. However, Idera Pharmaceuticals, Inc., upon request, will provide advance copies of its HIPAA authorization form to the Investigator or the site's privacy board or privacy official and will work with the site to eliminate any concerns.

The Investigator or the site will promptly inform Idera Pharmaceuticals, Inc. of any restrictions on the use or disclosure of PHI of any patient to which the site or the Investigator have agreed under the Privacy Rule. The Investigator or the site will also promptly inform Idera Pharmaceuticals, Inc. of any written revocation of any patient's HIPAA authorization.

19.5. Human Patient Protections

19.5.1. Research Patient Selection and Justification of Exclusions

There will be no exclusion from participation in the study on the basis of ethnicity or race. Patients younger than 18 years of age will be excluded from the study, as the target population is adults. Women of childbearing potential will have serum- and urine-human chorionic gonadotropin testing before enrollment in order to avoid potential fetal exposure. Cognitively impaired individuals, prisoners, or other institutionalized persons will be allowed to participate only after documented consultation with the IRB/EC.

Patients who are identified will be referred to the Investigator or authorized designee for screening. Patients will then undergo the screening process, during which they will have multiple opportunities to ask questions. The PI or authorized designee will provide a detailed discussion of the protocol and answer any remaining questions. The patient will be given time to consider study participation. No coercion or undue influence on this decision will be used. Only those patients who give written, informed consent, meet prescreening requirements, and successfully complete screening testing before the date of planned study drug administration will be considered for participation in the study. Specific consent is required for serum samples to be stored for future studies in coagulation and inflammation. Participation in the study is not contingent upon a patient's agreement to provide additional serum samples.

Blood specimens will be coded to ensure patient confidentiality.

19.5.2. Risks/Discomforts of Study Participation

IMO-2125 is designed to stimulate the immune system and some low-grade and transient signs and/or symptoms may occur:

- Low-grade elevation in body temperature
- Mild headache
- Chills
- Diaphoresis
- Myalgia
- Fatigue

In addition, patients may experience some or none of the following manifestations of local site injection reactions:

- Erythema (characteristically maximal by second day)
- Induration (sometimes persisting for up to 1 week)
- Pain (usually mild and requiring no treatment)
- Tenderness to the touch

Patients will undergo the study procedures detailed in Section 9, some of which can be expected to cause mild discomfort.

19.6. Institutional and Ethics Review

This protocol and a patient ICF, participant information sheet, and any proposed advertising material, must be reviewed and approved by an IRB/EC, applicable regulatory authorities, and host institution(s) for written approval (where applicable) before enrollment of patients and release of investigational product. Documentation of IRB/EC approval and the approved consent form must be received by Idera Pharmaceuticals, Inc. or its designees prior to obtaining the patient's informed consent. Amendments to the original approved documents, where applicable, will also be submitted to and approved by the above parties. Investigators will comply with the appropriate IRB/EC reporting requirements.

19.7. Financial Disclosure

In compliance with 21 CFR 54.4, any listed or identified Investigator or sub-investigator (including the spouse and any dependent children of said individuals) directly involved in the treatment or evaluation of research patients will disclose required information for the time period during which the Investigator is participating in the study and for 1 year following completion of the study.

20. LIST OF REFERENCES

Aaronson NK, Ahmedzai S, Bergman B, Bullinger M, Cull A, Duez NJ, et al. The European Organisation for Research and Treatment of Cancer QLQ-C30: A quality-of-life instrument for use in international clinical trials in oncology. J Natl Cancer Inst. 1993;85:365-376.

Abreu MT. Toll-like receptor signaling in the intestinal epithelium: how bacterial recognition shapes intestinal function. Nat Rev Immnol. 2010;10:131-144.

Aspord C, Leccia MT, Charles J, Plumas J. Plasmacytoid dendritic cells support melanoma progression by promoting Th2 and regulatory immunity through OX40L and ICOSL. Cancer Immunol Res. 2013;1:402-415.

Atkins MB, Kunkel L, Sznol M, Rosenberg SA. High-dose recombinant interleukin-2 therapy in patients with metastatic melanoma: long-term survival update. Cancer J Sci. 2000;Am 6 (Suppl 1): S11-4.

Atkins MB, Lotze MT, Dutcher JP, Fisher RI, Weiss G, Margolin K, et al. High-dose recombinant interleukin 2 therapy for patients with metastatic melanoma: analysis of 270 patients treated between 1985 and 1993. J Clin Oncol. 1999;17: 2105-2116.

Baines J, Celis E. Immune-mediated tumor regression induced by CpG-containing oligodeoxynucleotides. Clin Cancer Res. 2003;9:2693-2700.

Bernasconi N, Traggiai E, Lanzavecchia A. Maintenance of serological memory by polyclonal activation of human memory B cells. Science. 2002;298:2199-2202.

Bhagat, L. Time dependent cytokine secretion by human PBMCs in vitro in response to IMO-2125 treatment. Idera Study. 2007a;Number PH2125-012.

Bhagat, L. Time dependent cytokine secretion by human PBMCs in vitro in response to IMO-2125 treatment. Idera Study. 2007b;Number PH2125-012A.

Bhagat L. Time dependent cytokine secretion by human pDCs in vitro in response to IMO-2125 treatment. Idera Study. 2007c;Number PH2125-015A.

Bhagat L. To test the concentration dependent effect of IMO-2125 on IFN-a secretion by human plasmacytoid dendritic cells in vitro. Idera Study. 2007d;Number PH2125-016.

Bhagat L. To test the concentration dependent effect of IMO-2125 on IFN-a secretion by human PBMCs in vitro. Idera Study. 2007e;Number PH2125-019.

Bhagat, L. To test the concentration dependent effect of IMO-2125 in human B-cell proliferation assays. Idera Study. 2007f;Number PH2125-026.

Bhagat, L. Activation of human B-cells by IMO-2125: A flow cytometry study. Idera Study. 2007g;Number PH2125-027.

Bhagat, L. Activation of human pDCs by IMO-2125: A flow cytometry study. Idera Study. 2007h;Number PH2125-028.

Bhatia S, Tykodi SS, Thompson JA. Treatment of metastatic melanoma: an overview. Oncology. 2009;23:488-496.

Bohnsack O, Ludajic K, Hoos A. Adaptation of the immune-related response criteria: irRECIST. Ann Onc. 2014;25(Suppl-4):iv361-iv372.

Brunet JF, Denizot F, Luciani MF, Roux-Dosseto M, Suzan M, Mattei MG, et al. A new member of the immunoglobulin superfamily--CTLA-4. Nature. 1987;328(6127):267-270.

Chan E, Kwak EL, Hwang J, Heiskala M, de La Bourdonnaye G, Mita M. Open-label phase 1b study of FOLFIRI plus cetuximab plus IMO-2055 in patients with colorectal cancer who have progressed following chemotherapy for advanced or metastatic disease. Cancer Chemother Pharmacol. 2015 Jan 28. [Epub ahead of print].

Common Terminology Criteria for Adverse Events (CTCAE). Version 4.03, 14 June 2010. U.S. Department of Health and Human Services, National Institutes of Health, National Cancer Institute. NIH Publication No. 09-5410.

den Brok MH, Sutmuller RP, van der Voort R, Bennink EJ, Figdor CG, Ruers TJ, et al. In situ tumor ablation creates an antigen source for the generation of antitumor immunity. Cancer Res. 2004;64:4024-4029.

Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, et al. New response evaluation criteria in solid tumours: Revised RECIST guideline (version 1.1). Eur J Cancer. 2009;45:228-247.

Heckelsmiller K, Rall K, Beck S, Schlamp A, Seiderer J, Jahrsdörfer B, et al. Peritumoral CpG DNA elicits a coordinated response of CD8 T cells and innate effectors to cure established tumors in a murine colon carcinoma model. J Immunol. 2002;169:3892-3899.

Hodi FS, O'Day SJ, McDermott DF, Weber RW, Sosman JA, Haanen JB, et al. Improved survival with ipilimumab in patients with metastatic melanoma. N Engl J Med. 2010;363:711-723.

Kandimalla ER, Bhagat L, Wang D, Yu D, Zhu FG, Tang J, et al. Divergent synthetic nucleotide motif recognition pattern: design and development of potent immunomodulatory oligodeoxyribonucleotide agents with distinct cytokine induction profiles. Nucleic Acids Res. 2003;31(9):2393-2400.

Kandimalla ER, Bhagat L, Li Y, Yu D, Wang D, Cong YP, et al. Immunomodulatory oligonucleotides containing a cytosine-phosphate-2'-deoxy-7-deazaguanosine motif as potent toll-like receptor 9 agonists. Proc Natl Acad Sci USA. 2005;102(19):6925-6930.

Kirkwood JM, Ibrahim JG, Sondak VK, Richards J, Flaherty LE, Ernstoff MS, et al. High- and low-dose interferon alfa-2b in high-risk melanoma: first analysis of intergroup trial E1690/S9111/C9190. J Clin Oncol. 2000;18:2444-2458.

Lachiewicz AM, Berwick M, Wiggins CL, Thomas NE. Epidemiologic support for melanoma heterogeneity using the surveillance, epidemiology, and end results program. J Invest Dermatol. 2008;128:1340-1342.

Larkin J, Hodi FS, Wolchok JD. Combined Nivolumab and Ipilimumab or Monotherapy in Untreated Melanoma. N Engl J Med. 2015;373(13):1270-1.

Levings MK, Sangregorio R, Roncarolo MG. Human cd25(+)cd4(+) t regulatory cells suppress naive and memory T cell proliferation and can be expanded in vitro without loss of function. J Exp Med. 2001;193:1295-1302.

Liu YJ. IPC: professional type 1 interferon-producing cells and plasmacytoid dendritic cell precursors. Annu Rev Immunol. 2005;23:275-306.

Lou Y, Liu C, Lizée G, Peng W, Xu C, Ye Y, et al. Antitumor activity mediated by CpG: the route of administration is critical. J Immunother. 2011;34:279-288.

Nierkens S, den Brok MH, Roelofsen T, Wagenaars JA, Figdor CG, Ruers TJ, et al. Route of administration of the TLR9 agonist CpG critically determines the efficacy of cancer immunotherapy in mice. PLoS One. 2009;4:e8368.

Nishino M, Giobbie-Hurder A, Gargano M, et al. Developing a common language for tumor response to immunotherapy: immune-related response criteria using unidimensional measurements. Clin Cancer Res. 2013;19(14):3936-43.

Oken MM, Creech RH, Tormey DC, Horton J, Davis TE, McFadden ET, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol. 1982;5:649-655.

Parry RV, Chemnitz JM, Frauwirth KA, Lanfranco AR, Braunstein I, Kobayashi SV, et al. CTLA-4 and PD-1 receptors inhibit T-cell activation by distinct mechanisms. Mol Cell Biol. 2005;25(21):9543-9553.

Postow MA, Chesney J, Pavlick AC, Robert C, Grossman K, McDermott D, et al. Nicolumab and ipilimumab versus ipilimumab in untreated melanoma. N Engl J Med. 2015;372(21):2006-17.

Robert C, Schachter J, Long GV, Arance A, Grob JJ, Mortier L, et al. Pembrolizumab versus Ipilimumab in Advanced Melanoma. N Engl J Med. 2015;372(26):2521-2532.

Shin DS, Ribas A. The evolution of checkpoint blockade as a cancer therapy: what's here, what's next? Curr Opin Immunol. 2015;33:23-35.

Siegel RL, Miller KD, Jemal A. Cancer Statistics, 2015. CA Cancer J Clin. 2015;65(1):5-29.

Smith DA, Conkling P, Richards DA, Nemunaitis JJ, Boyd TE, Mita AC, et al. Antitumor activity and safety of combination therapy with the Toll-like receptor 9 agonist IMO-2055, erlotinib, and bevacizumab in advanced or metastatic non-small cell lung cancer patients who have progressed following chemotherapy. Cancer Immunol Immunother. 2014;63(8):787-796.

Takeda K, Akira S. Toll-like receptors in innate immunity. Int Immunol. 2005;Jan;17(1):1-14.

Thall PF, Cook JD, Estey E. Adaptive dose selection using efficacy-toxicity trade-offs: illustrations and practical considerations. J Biopharm Stat. 2006;16(5):623-638.

Trombino AF. A report of cytometry and hematology analyses from samples collected in immunopharmacological screening of oligonucleotide test articles in cynomolgus monkeys. Idera Study. 2007a;Number PH2125-006.

Trombino AF. Report of cytokine, flow cytometry and hematology analyses from samples collected in immunopharmacological screening of oligonucleotide test articles in cynomolgus monkeys: IMO-2125, experiments 1, 2 and 3. Idera Study. 2007b;Number PH9999-007.

Tumeh PC, Harview CL, Yearley JH, Shintaku IP, Taylor EJ, Robert L, et al. PD-1 blockade induces responses by inhibiting adaptive immune resistance. Nature. 2014; 515(7528):568-571.

Walunas TL, Lenschow DJ, Bakker CY, Linsley PS, Freeman GJ, Green JM, et al. CTLA-4 can function as a negative regulator of T cell activation. Immunity. 1994;1:405-413.

Wickelgren I. Targeting the tolls. Science. 2006;312:184-187.

Wolchok JD, Hoos A, O'Day S, Weber JS, Hamid O, Lebbé C, et al. Guidelines for the evaluation of immune therapy activity in solid tumors: immune-related response criteria. Clin Cancer Res. 2009;15:7412-7420.

Yu D, Zhu FG, Bhagat L, Wang H, Kandimalla ER, Zhang R, et al. Potent CpG oligonucleotides containing phosphodiester linkages: in vitro and in vivo immunostimulatory properties. Biochem Biophys Res Commun. 2002;297(1):83-90.

Zamarin D, Postow MA. Immune checkpoint modulation: Rational design of combination strategies. Pharmacol Ther. 2015;S0163-7258. [Epub ahead of print].

21. APPENDICES

21.1. Eastern Cooperative Oncology Group

ECOG Performance Status:

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

21.2. Immune-Related Response Criteria (irRC)

During Phase 1, subject management and response assessments will be performed according to irRC (Wolchok, 2009).

Appendix Table 1: Overall Response using irRC:

Response assessment	Description
irCR	Complete disappearance of all lesions (whether measurable or not, and no new lesions) Confirmation by a repeat, consecutive assessment ≥4 weeks after first documentation
irPR	Decrease in tumor burden ≥50% relative to baseline Confirmed by a consecutive assessment ≥4 weeks after first documentation
irSD	Not meeting criteria for irCR or irPR, in absence of irPD. A change in tumor burden of neither 50% decrease from baseline nor 25% increase from nadir can be determined.
irPD	Increase in tumor burden ≥25% relative to nadir (minimum recorded tumor burden) Confirmation by a repeat, consecutive assessment ≥4 weeks after the first documentation

Abbreviations: CR=complete response; irRC=Immune-related Response Criteria; PD=progressive disease; PR=partial response; SD=stable disease

Appendix Table 2: Derivation of irRC overall responses

Measurable response	Non-measurable response		Overall irRC response
Target and new, measurable lesions **% change in tumor burden**	**Non-target lesions**	**New non-measurable lesions**	
↓ 100[1]	Absent	Absent	irCR[3]
↓ 100[1]	Stable	Any	irPR[3]
↓ 100[1]	Unequivocal progression	Any	irPR[3]
↓ ≥50[1]	Absent or Stable	Any	irPR[3]
↓ ≥50[1]	Unequivocal progression	Any	irPR[3]
↓ ≥50 to ↑<25[1]	Absent or Stable	Any	irSD
↓ ≥50 to ↑<25[1]	Unequivocal progression	Any	irSD
↑ ≥25[2]	Any	Any	irPD[3]

[1] Decrease relative to baseline
[2] Increase relative to nadir
[3] Confirmed by consecutive scan ≥4 weeks after first documentation

21.3. irRECIST (Immune-Related Response Evaluation Criteria in Solid Tumors)

In Phase 2 of the study, patient management and response assessments will be performed according to irRECIST (Nishino, 2013; Bohnsack, 2014). For irRECIST, a unidimensional measurement is assessed for the longest diameter of each lesion.

Target lesion: ≥10 mm in longest diameter (target nodal lesion ≥15 mm in shortest diameter), representative of the organs involved, and lend themselves to reproducible repeated measurements. Baseline target lesions are limited to a total of 5 with no more than 2 in any single organ. Previously irradiated lesions should not be selected as target lesions unless they have shown unequivocal progression after the radiation.

Non-target lesion: all other lesions, including small lesions (<10 mm in longest diameter or nodal lesions ≥10 mm and <15 mm in shortest diameter) and all truly non-measurable lesions.

Tumor burden: the sum of the longest diameters of all baseline target lesions (use shortest diameter for target nodal lesions) and all measurable new lesions.

Appendix Table 1: Overall Response using irRECIST

Response assessment	Description
irCR	• Complete disappearance of all lesions (and no new measurable or non-measurable lesions). • Pathological lymph nodes (target or non-target) must have diameter <10 mm in short axis. • Requires confirmation by consecutive assessment ≥4 weeks after first documentation.
irPR	• ≥30% decrease in tumor burden from baseline. • No unequivocal progression of baseline non-target lesions. • No unequivocal progression of new, non-measurable lesions. • Requires confirmation by consecutive assessment ≥4 weeks after first documentation.
irSD	• Not meeting criteria for irCR or irPR, in absence of irPD.
irPD	• ≥20% increase in tumor burden from nadir (the minimum recorded tumor burden). • The presence of new, measurable lesions does not define progression. New measurable lesions are added to the assessment of tumor burden. • A substantial, unequivocal worsening of baseline non-target lesions is indicative of irPD. • A substantial, unequivocal worsening of new, non-measurable lesions is indicative of irPD. • Requires confirmation by consecutive assessment ≥4 weeks after the first documentation.

irCR=immune-related complete response; irPD=immune-related progressive disease; irPR=immune-related partial response; irRECIST=Immune-related Response Evaluation Criteria in Solid Tumors; irSD=immune-related stable disease

21.4. RECIST v1.1 Criteria

Adapted from E.A. Eisenhauer, et al: New response evaluation criteria in solid tumors: Revised RECIST guideline (version 1.1). European Journal of Cancer 45 (2009) 228–247.[52]

A. Categorizing Lesions at Baseline

1. Measurable Lesions

Lesions that can be accurately measured in at least one dimension.

- Lesions with longest diameter twice the slice thickness and at least 10 mm or greater when assessed by CT or MRI (slice thickness 5-8 mm).
- Lesions with longest diameter at least 20 mm when assessed by Chest X-ray.
- Superficial lesions with longest diameter 10 mm or greater when assessed by caliper.
- Malignant lymph nodes with the short axis 15 mm or greater when assessed by CT.

NOTE: The shortest axis is used as the diameter for malignant lymph nodes, longest axis for all other measurable lesions.

2. Non-measurable Disease

- Non-measurable disease includes lesions too small to be considered measurable (including nodes with short axis between 10 and 14.9 mm) and truly non-measurable disease such as pleural or pericardial effusions, ascites, inflammatory breast disease, leptomeningeal disease, lymphangitic involvement of skin or lung, clinical lesions that cannot be accurately measured with calipers, abdominal masses identified by physical exam that are not measurable by reproducible imaging techniques.
- Bone disease: Bone disease is non-measurable with the exception of soft tissue components that can be evaluated by CT or MRI and meet the definition of measurability at baseline.
- Previous local treatment: A previously irradiated lesion (or lesion patientive to other local treatment) is non-measurable unless it has progressed since completion of treatment.

3. Normal Sites

- Cystic lesions: Simple cysts should not be considered as malignant lesions and should not be recorded either as target or non-target disease. Cystic lesions thought to represent cystic metastases can be measurable lesions, if they meet the specific

definition above. If non-cystic lesions are also present, these are preferred as target lesions.

- Normal nodes: Nodes with short axis <10 mm are considered normal and should not be recorded or followed either as measurable or non-measurable disease.

4. Recording Tumor Assessments

All sites of disease must be assessed at baseline. Baseline assessments should be done as close as possible prior to study start. For an adequate baseline assessment, all required scans must be done within 28 days prior to treatment and all disease must be documented appropriately. If baseline assessment is inadequate, subsequent statuses generally should be indeterminate.

Note: For the patient population being evaluated in this protocol, the baseline assessment may be completed within 6 weeks prior to randomization.

5. Target Lesions

All measurable lesions up to a maximum of 2 lesions per organ, 5 lesions in total, representative of all involved organs, should be identified as target lesions at baseline. Target lesions should be selected on the basis of size (longest lesions) and suitability for accurate repeated measurements. Record the longest diameter for each lesion, except in the case of pathological lymph nodes for which the short axis should be recorded. The sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions at baseline will be the basis for comparison to assessments performed on study.

- If two target lesions coalesce the measurement of the coalesced mass is used. If a large target lesion splits, the sum of the parts is used.

- Measurements for target lesions that become small should continue to be recorded. If a target lesion becomes too small to measure, 0 mm should be recorded if the lesion is considered to have disappeared; otherwise a default value of 5 mm should be recorded.

NOTE: When nodal lesions decrease to <10 mm (normal), the actual measurement should still be recorded.

6. Non-target Disease

All non-measurable disease is non-target. All measurable lesions not identified as target lesions are also included as non-target disease. Measurements are not required but rather assessments will be expressed as ABSENT, INDETERMINATE, PRESENT/NOT INCREASED, INCREASED. Multiple non-target lesions in one organ may be recorded as a single item on the case report form (eg, 'multiple enlarged pelvic lymph nodes' or 'multiple liver metastases').

B. Objective Response Status at Each Evaluation

Disease sites must be assessed using the same technique as baseline, including consistent administration of contrast and timing of scanning. If a change needs to be made the case must be discussed with the radiologist to determine if substitution is possible. If not, subsequent objective statuses are indeterminate.

1. Target Disease

- Complete Response (CR): Complete disappearance of all target lesions with the exception of nodal disease. All target nodes must decrease to normal size (short axis <10 mm). All target lesions must be assessed.

- Partial Response (PR): Greater than or equal to 30% decrease under baseline of the sum of diameters of all target measurable lesions. The short diameter is used in the sum for target nodes, while the longest diameter is used in the sum for all other target lesions. All target lesions must be assessed.

- Stable: Does not qualify for CR, PR or Progression. All target lesions must be assessed. Stable can follow PR only in the rare case that the sum increases by less than 20% from the nadir, but enough that a previously documented 30% decrease no longer holds.

- Objective Progression (PD): 20% increase in the sum of diameters of target measurable lesions above the smallest sum observed (over baseline if no decrease in the sum is observed during therapy), with a minimum absolute increase of 5 mm.

- Indeterminate. Progression has not been documented, and

  - one or more target measurable lesions have not been assessed;

  - or assessment methods used were inconsistent with those used at baseline;

  - or one or more target lesions cannot be measured accurately (eg, poorly visible unless due to being too small to measure);

  - or one or more target lesions were excised or irradiated and have not reappeared or increased.

2. Non-target Disease

- CR: Disappearance of all non-target lesions and normalization of tumor marker levels. All lymph nodes must be 'normal' in size (<10 mm short axis).

- Non-CR/Non-PD: Persistence of any non-target lesions and/or tumor marker level above the normal limits.

- PD: Unequivocal progression of pre-existing lesions. Generally the overall tumor burden must increase sufficiently to merit discontinuation of therapy. In the presence of SD or PR in target disease, progression due to unequivocal increase in non-target disease should be rare.

- Indeterminate: Progression has not been determined and one or more non-target sites were not assessed or assessment methods were inconsistent with those used at baseline.

3. New Lesions

The appearance of any new unequivocal malignant lesion indicates PD. If a new lesion is equivocal, for example due to its small size, continued assessment will clarify the etiology. If repeat assessments confirm the lesion, then progression should be recorded on the date of the initial assessment. A lesion identified in an area not previously scanned will be considered a new lesion.

4. Supplemental Investigations

- If CR determination depends on a residual lesion that decreased in size but did not disappear completely, it is recommended the residual lesion be investigated with biopsy or fine needle aspirate. If no disease is identified, objective status is CR.
- If progression determination depends on a lesion with an increase possibly due to necrosis, the lesion may be investigated with biopsy or fine needle aspirate to clarify status.

5. Attentive Progression

Patients requiring discontinuation of treatment without objective evidence of disease progression should not be reported as PD on tumor assessment CRFs. This should be indicated on the end of treatment CRF as off treatment due to Global Deterioration of Health Status. Every effort should be made to document objective progression even after discontinuation of treatment.

Appendix Table 2: Objective Response Status at Each Evaluation

Target Lesions	Non-target Disease	New Lesions	Objective status
CR	CR	No	CR
CR	Non-CR/Non-PD	No	PR
CR	Indeterminate or Missing	No	PR
PR	Non-CR/Non-PD, Indeterminate, or Missing	No	PR
SD	Non-CR/Non-PD, Indeterminate, or Missing	No	Stable
Indeterminate or Missing	Non-PD	No	Indeterminate
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

If the protocol allows enrollment of patients with only non-target disease, the following table will be used:

Appendix Table 3: Objective Response Status at Each Evaluation for Patients with Non-Target Disease Only

Non-target Disease	New Lesions	Objective status
CR	No	CR
Non-CR/Non-PD	No	Non-CR/Non-PD
Indeterminate	No	Indeterminate
Unequivocal progression	Yes or No	PD
Any	Yes	PD