PROTOCOL 2125-MEL-301

Study Title	A Randomized Phase 3 Comparison of IMO-2125 with Ipilimumab versus Ipilimumab Alone in Subjects with Anti-PD-1 Refractory Melanoma
Investigational Drug:	IMO-2125 (tilsotolimod)
IND Number:	125515
EUDRACT Number:	2017-002454-36
Sponsor:	Idera Pharmaceuticals, Inc. 505 Eagleview Boulevard Suite 212 Exton, PA, 19341, USA
Protocol Number:	2125-MEL-301
Protocol Version:	4.0
Date:	4 June 2020

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 subjects with informed consent forms, as required by government and International Council for Harmonisation regulations. I further agree to conduct the study and report to Idera Pharmaceuticals, Inc. any adverse experiences in accordance with the terms of this protocol and Good Clinical Practices (GCP).

_____

Principal Investigator Name (print)

_____ _____

Signature Date

Protocol Approval Page

Study Title	A Randomized Phase 3 Comparison of IMO-2125 with Ipilimumab versus Ipilimumab Alone in Subjects with Anti-PD-1 Refractory Melanoma
Protocol Number:	2125-MEL-301
Protocol Version:	4.0
Date:	4 June 2020

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

DocuSigned by:
Shah Rahimian
B2107EC6595F4DB...

June 5, 2020 | 1:38 PM EDT

Shah Rahimian, MD
Vice President, Medical Lead (Oncology)
Idera Sponsor Representative

Date

Version History

Ver. No.	Approval Date	Comment
1.0	05 July 2017	Draft
1.1	10 July 2017	Draft 2
1.2	31 July 2017	Initial submission (submitted to one ex-US Health Authority (Australia TGA)
2.0	05 Feb 2018	Revises inclusion criteria for prior BRAF inhibitor treatment and adjuvant anti-PD-1
		Adds a stratification factor for BRAF mutation status and prior treatment
		Updates the analysis methodology
		Adds secondary endpoint for time to response
		Revises the disease assessment schedule during the first year
		Adds PRO assessment at Week 7 (Arm A) and Week 8 (Arm B)
		Clarifies dosing and assessment procedures
		Updated RECIST v1/1 appendix
3.0	10 July 2019	Updated Medical Monitor Information
		Investigator Statement Updated
		Study Period Updated from 36 to 56 months
		Addition of PD-1 inhibitor as a clarification to nivolumab or pembrolizumab
		Sample Size increase from approximately 308 to approximately 454
		Clarification that IDMC will be performing safety and benefit:risk assessments throughout the study
		Clarification to Exclusion #7 language
		Removal of subcutaneous injections where complete tumor regression occurs in visceral lesions
		Clarification that a range from 1-4mL of IMO-2125 can be injected into the tumor or tumor bed
		IMO-2125 dose modification instruction table updated
		Modified irRECIST updated to irRECIST
		Update to clinically relevant target effect size and clinical assumptions for OS
		Addition of serum samples for anti-drug antibodies for ipilimumab
		Clarification of timing for Active Follow-up
		Clarification on ECG Monitoring for Arm B
		Clarification on AE Reporting 90-day post-last study treatment dose and thereafter
		Administrative changes

Version History

Ver. No.	Approval Date	Comment
4.0	4 June 2020	Clarified process for reporting serious adverse events (SAEs)
		Updated Medical Monitor information
		Clarified disease staging is per AJCC 7 criteria
		Removed irRECIST assessment from secondary endpoints
		Added duration of response as a secondary endpoint
		Modified planned statistical analyses to re-allocate alpha between the primary endpoint family of objective response rate (ORR) followed by overall survival (OS), to include hierarchical testing for ORR followed by OS using the fallback method, to remove interim analysis for OS, and to allow for analysis of final OS at approximately 36 months if the required number of events have not yet been reached
		Clarified requirements related to corticosteroid use
		Modified procedures for assessment of subjects with changes in complement levels
		Included several additional adverse events that should be reported as immune-related in the absence of another etiology

EMERGENCY CONTACT INFORMATION

Reporting of Serious Adverse Events (SAEs)

Any SAE must be reported **within 24 hours via SAE form.** See Section 10.1 (Adverse Events) for definition and reporting procedure for SAEs.

SAEs must be captured on the paper SAE form and reported **by email within 24 hours** to:

Role in Study	Name, Title, Address	Telephone / fax / email
Sponsor Medical Monitor	Shah Rahimian, MD Medical Lead (Oncology) 505 Eagleview Blvd., Suite 212 Exton, PA 19341	Tel: +1 484-348-1642 Mobile: +1 814-691-7377 Email: srahimian@iderapharma.com
24-Hour SAE Reporting	TMC PharmaLodge Farm Barn Elvetham Park Estate Fleet Road, Hartley Wintney Hants, RG27 8AS, UK	Email: Idera@TMCPharma.com Fax: Australia: (02) 8569 0673 Canada: +1 800 364 8501 Czech Republic, France, Germany, Italy, Netherlands, Spain, Sweden, United Kingdom: +44 (0)1189 195 200 Israel: +972 (0) 3761 8089 United States of America: (617) 663 6222

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2. SYNOPSIS

Name of Sponsor/Company: Idera Pharmaceuticals, Inc.

Name of Investigational Product: IMO-2125

Title of Study: A Randomized Phase 3 Comparison of IMO-2125 with Ipilimumab versus Ipilimumab Alone in Subjects with Anti-PD-1 Refractory Melanoma

Study period: The planned end of study will be approximately 56 months (the projected time for the required number of deaths to support the analysis of OS to occur) after the first subject is randomized.	**Phase of development:** Phase 3

Rationale: IMO-2125 is a synthetic phosphorothioate oligonucleotide that acts as a direct agonist of Toll-like receptor (TLR) 9 to stimulate the innate and adaptive immune systems. Activation of TLR9 by IMO-2125 induces high levels of interferon (IFN)-α from plasmacytoid dendritic cells (pDCs) along with an array of endogenous cytokines and chemokines. Intratumoral IMO-2125 monotherapy has been shown to produce abscopal effects in mice, including anti-tumor activity associated with an increase in infiltrating CD8+ T cells, and durable and specific cytotoxic T cell responses against tumor antigens. The combination of intratumoral IMO-2125 with an anti-cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) monoclonal antibody (mAb) results in improved tumor control compared to either agent alone.

An ongoing Phase 1/2 clinical study of intratumoral IMO-2125 in combination with ipilimumab (NCT02644967) shows the combination to be well-tolerated over the entire range of IMO2125 doses tested, with biopsy evidence for dendritic cell activation followed by infiltration of tumor-specific immune cells. Moreover, clinical responses (including durable complete response [CR]) have been seen in subjects previously refractory to programmed cell death-1 (PD-1) inhibitors. Since no therapy has been shown to prolong survival following failure of first-line immunotherapy, this Phase 3 study is being performed to provide definitive evidence for superiority of the IMO2125/ipilimumab combination over currently available therapy.

Objectives:

Primary: Compare the efficacy (measured by objective response rate [ORR] and overall survival [OS]) of intratumoral IMO-2125 in combination with ipilimumab versus ipilimumab alone.

Secondary: Assess other measures of clinical benefit, safety, pharmacokinetics (PK), and patient-reported outcomes (PROs).

Exploratory: Investigate potential biomarkers and the incidence of anti-IMO-2125 and anti-ipilimumab antibodies.

Study design:

Randomized Phase 3 global, multi-center, open-label comparison of ipilimumab with and without intratumoral IMO-2125 in subjects with advanced melanoma who had confirmed disease progression while on a PD-1 inhibitor, e.g., nivolumab or pembrolizumab. Subjects will be randomized 1:1 to treatment arms. The primary endpoint family of the study includes ORR and OS.

Number of subjects (planned): 454

Periodic data reviews will be performed by an Independent Data Monitoring Committee (IDMC) as described in the IDMC Charter. The first IDMC meeting will occur after approximately 20 subjects on each arm have been treated with two doses of ipilimumab. This initial meeting will review safety only.

Inclusion criteria

1. Subjects must be willing and able to sign the informed consent and comply with the study protocol.
2. Must be ≥18 years of age.
3. Histologically confirmed metastatic melanoma with measurable (by Response Evaluation Criteria in Solid Tumors [RECIST] v1.1), Stage III (lymph node or in transit lesions) or Stage IVA, IVB, or IVC disease that is accessible for injection. Stage should be determined using the American Joint Committee on Cancer (AJCC) Cancer Staging Manual, Seventh Edition.
4. Confirmed progression during or after treatment with a PD-1 inhibitor (cannot be part of a bi-specific antibody), e.g., nivolumab or pembrolizumab. Confirmed progression is defined as:
   - Radiological progression (confirmed at least 4 weeks after the initial scan showing progressive disease); or
   - For progression based solely on worsening of non-target or new, non-measurable disease, confirmation by an additional scan at least 4 weeks after the initial scan *unless* progression is accompanied by correlative symptoms.

   In addition, all the following must hold:
   - No intervening anti-cancer therapy between the last course of PD-1 inhibitor treatment and the first dose of study treatment is allowed except for local measures (e.g., surgical excision or biopsy, focal radiation therapy).
   - The interval between last PD-1 inhibitor and start of study treatment should be at least 21 days with no residual anti-PD-1-related immune toxicities in excess of Grade 1 severity.
   - Subjects who had adjuvant anti-PD-1 treatment are eligible if they have either disease recurrence after the end of adjuvant treatment or on-treatment disease recurrence after ≥12 weeks of adjuvant treatment.
   - If BRAF mutation status is unknown, before randomization the subject must have BRAF testing performed using an approved assay method.
   - Patients with BRAF-positive tumor(s) are eligible for the study if they received prior treatment with a BRAF inhibitor (alone or in combination with a MEK inhibitor) or declined targeted therapy.
5. Eastern Cooperative Oncology Group (ECOG) Performance Status ≤1.
6. Adequate baseline organ function as defined by:
   - Absolute neutrophil count (ANC) ≥ 1.5 x 10^9/L (1500/mm^3)

- Platelet count ≥75 x 10^9/L (75,000/mm^3)
- Hemoglobin ≥8.0 g/dL (4.96 mmol/L)
- Serum creatinine ≤1.5 x upper limit of normal (ULN) or calculated creatinine clearance ≥60 mL/minute (≤Grade 1)
- Aspartate aminotransferase (AST) ≤2.5 x ULN; alanine aminotransferase (ALT) ≤2.5 x ULN; AST/ALT <5 x ULN if liver involvement (≤Grade 1)
- Serum bilirubin ≤1.5 x ULN, except in subjects with Gilbert's Syndrome who must have a total bilirubin <3 mg/dL (≤Grade 1)

7. Women of childbearing potential (WOCBP) and men must agree to use effective contraceptive methods from screening until at least 90 days after the last dose of either ipilimumab or IMO-2125, whichever is later.

   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:

   - True abstinence, defined as refraining from heterosexual intercourse, when this is in line with the preferred and usual lifestyle of the subject. 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.
   - Condoms and spermicide
   - Diaphragm and spermicide
   - Oral or implanted hormonal contraceptive (e.g., Implanon™)

   NOTE: For subjects in Sweden, low dose oral contraceptives are not permitted

   - An intra-uterine device

8. WOCBP must have a negative pregnancy test (serum or urine) according to the Schedule of Evaluations (Table 1 and Table 2).

Exclusion criteria

1. Ocular melanoma.
2. Prior therapy with a TLR agonist, excluding topical agents.
3. Prior ipilimumab treatment with the exception of adjuvant treatment completed ≥6 months prior to enrollment.
4. Systemic treatment with IFN-α within the previous 6 months.
5. Known hypersensitivity to any oligodeoxynucleotide.
6. Active autoimmune disease requiring disease-modifying therapy at the time of screening.

7. Subjects with a requirement for receiving more than physiologic doses of systemic steroids (>10 mg/day of prednisone or equivalent) for the 2 weeks preceding start of study treatment.
8. Subjects with another primary malignancy that has not been in remission for at least 3 years with the exception of 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).
9. Active systemic infections requiring antibiotics.
10. Known active, hepatitis A, B, or C infection.
11. Known diagnosis of human immunodeficiency virus (HIV) infection.
12. Women who are pregnant or breast-feeding.
13. Prior anaphylactic or other severe infusion reaction associated with human antibody administration that cannot be managed with standard supportive measures.
14. Presence of known central nervous system, meningeal, or epidural metastatic disease. However, subjects with known brain metastases are allowed if the brain metastases are stable for ≥4 weeks before the first dose of study treatment. Stable is defined as neurological symptoms not present or resolved to baseline, no radiologic evidence of progression, and steroid requirement of prednisone ≤10 mg/day or equivalent.
15. Impaired cardiac function or clinically significant cardiac disease.

Investigational product, dosage, and mode of administration:

IMO-2125 will be supplied as an 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. Ipilimumab is a commercially available product.

Subjects will be randomized (1:1) to receive either:

1. Arm A – ipilimumab 3 mg/kg intravenous (i.v.) Weeks 1, 4, 7, and 10
   or
2. Arm B – IMO-2125, 8 mg intratumorally Weeks 1, 2, 3, 5, 8, 11, 16, 20, and 24 in combination with ipilimumab 3 mg/kg i.v. Weeks 2, 5, 8, and 11

IMO-2125 will be given prior to ipilimumab on days when both are to be administered. IMO-2125 will be administered intratumorally as a 1-4 mL injection to a single designated lesion throughout the study. The injected tumor will be selected from (in order of priority) pathologic draining lymph nodes, superficial or subcutaneous (s.c.) metastases, or deep or visceral metastases, the latter requiring interventional radiology support. The dose will be thoroughly distributed within the injected tumor using a single injection site and a fanning method to ensure even distribution. Dosing volume will be adjusted on a sliding scale and based on the judgment of the investigator as the injected tumor shrinks to maintain a constant total dose. Additional details are described in the Pharmacy Manual. In the event a full dose can no longer be practically administered into the injected tumor, another tumor may be selected. In the event a complete tumor regression occurs prior to completion of therapy, any remaining IMO-2125 doses should be administered into the tumor bed, except in the case of visceral lesions for which injections should be stopped. Treatment following disease progression is at the discretion of the Investigator. Cross-over therapy will not be allowed for subjects assigned to Arm A.

Dose Modification:

The most common adverse events (AEs) following intratumoral administration of IMO-2125 have been non-specific "flu-like" symptoms and mild to moderate injection site reactions. In combination with ipilimumab, IMO-2125 has been associated with immune-related AEs (irAEs) (e.g., hypophysitis) and fever. Subject management guidelines for AEs of key interest, including irAEs and potential class effects seen with other oligonucleotide drugs (e.g., symptomatic thrombocytopenia) are provided. Refer to the current, locally approved ipilimumab package insert for specific guidance in managing irAEs associated with ipilimumab and additional guidance in Section 9.3.4.1 (Table 4). IMO-2125 therapy should be continued if ipilimumab is discontinued early for toxicity.

Dose modification instructions for IMO-2125 are provided in the table below:

Event	Action	Dose Modification
Local or mild systemic reaction (e.g., pyrexia)	Supportive measures as required. Continue treatment with IMO-2125 per clinical discretion.	None
Severe systemic reaction for which more aggressive measures including hospitalization are required (e.g., severe hypotension)	Supportive measures as required. Hold further dosing until the event resolves to baseline or G1 and the re-treatment criteria below are met.	None

Life-threatening AE (e.g., anaphylaxis)	Supportive measures as required.	Discontinue treatment
Serious procedural complication related to deep or visceral injection (e.g. pneumothorax or hematoma formation)	Supportive measures as required	Discontinue visceral injections (treatment may be continued if a superficial lesion or tumor-involved lymph node is available for injection instead)

Conventional supportive medications (including infliximab for immune-related colitis and growth factor support) are permitted.

Criteria for re-initiation of treatment with each dose of study drug include:

- ANC $\geq$1.5 x 10^9/L (1500/µL);
- Platelets $\geq$75 x 10^9/L (75,000/µL);
- Resolution of all clinically significant non-hematologic toxicities for which a causal association to study treatment cannot be ruled out to Grade $\leq$1 or baseline

Duration of study:

The Treatment Phase of the study is 10 weeks for subjects assigned to Arm A and 24 weeks for subjects assigned to Arm B. Subjects who discontinue disease assessments due to disease progression or the start of new anticancer treatment (with or without disease progression), will enter the Survival Follow-up Period (in which they are contacted by telephone according to the Schedule of Evaluations). Subjects who complete or discontinue study treatment for reasons other than disease progression or the start of new anticancer treatment but remain in the study will continue clinical and radiological disease evaluations in the Active Follow-up Period according to the Schedule of Evaluations.

The planned end of study will be approximately 56 months (the projected time for the required number of deaths to support the analysis of OS to occur) after the first subject is randomized.

Endpoints

Primary Endpoint Family:

The primary endpoint family (see Food and Drug Administration [FDA] Guidance for Industry, 2017) includes:

- ORR by blinded independent review using RECIST v1.1
- OS, defined as the time to death from any cause measured from the date of randomization

Secondary:

- ORR by investigator assessment using RECIST v1.1
- Duration of response (DoR) by blinded independent review and by investigator assessment using RECIST v1.1, measured from the time that criteria are first met for

CR or partial response (PR) (whichever is first recorded) until the first date that recurrent or progressive disease is objectively documented

- Durable response rate (DRR) by blinded independent review and investigator assessment using RECIST v1.1, defined as the rate of CR or PR lasting ≥6 months with onset during the first 12 months of treatment
- Time to response (TTR), defined as time to first evidence of a complete or partial response (using RECIST v1.1) measured from the date of randomization, by blinded independent review and investigator assessment
- Progression-free survival (PFS), defined as the time to disease progression or death from any cause measured from the date of randomization, by blinded independent review and investigator assessment (using RECIST v1.1)
- Landmark PFS at 1 and 2 years by blinded independent review and investigator assessment (using RECIST v1.1) and landmark OS at 1 and 2 years
- PRO using the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 (EORTC QLQ-C30)
- Safety, including AEs, laboratory and vital sign tests, electrocardiograms (ECGs), ECOG, and physical examination
- Plasma PK of IMO-2125

Exploratory:

- Immunologic biomarkers (optional tumor biopsies)
- Measurement of anti-IMO-2125 and anti-ipilimumab antibodies

Study Assessments

Efficacy: Tumor assessments will be performed at Screening and Week 12, then every 8 weeks for the first year and every 12 weeks in subsequent years using consistent imaging modality, facilities, and reviewers. Investigators should follow irRECIST guidelines for subject management and provide visit response assessments using RECIST v1.1 and irRECIST. Blinded central reviewers will provide independent assessment of tumor response using RECIST v1.1 and modified irRECIST.

PRO: Periodic assessments will be made using the EORTC-QLQ-C30.

Safety: Assessments will include AEs, physical examination, vital signs, ECOG performance status, laboratory monitoring, periodic ECGs, thyroid function, complement levels, urinalysis, and pregnancy screening.

Pharmacokinetics: Blood samples for IMO-2125 (Arm B only) PK analysis will be drawn according to the Schedule of Evaluations.

Exploratory: Samples for optional tumor biopsies will be obtained in both treatment arms. Anti-IMO-2125 and anti-ipilimumab antibody formation will be assessed in subjects assigned to both arms. Immunologic biomarker evaluations may include flow cytometry for immune cell subsets, immunohistochemistry, and gene expression profiling, among others.

Statistical methods

In this study, ORR and OS comprise a primary endpoint family; both have a priori hypotheses and will be tested for statistical significance. ORR will be tested first followed by OS. The fallback method for the primary endpoint family will be applied to control the study-wise Type I error rate.

Under the fallback method, $\alpha_1 = 0.02$ is assigned to the one-sided ORR test and an alpha of 0.005 is saved for the one-sided OS test.

- If the ORR test is significant at $\alpha_1 = 0.02$, this alpha is unused and will be passed to the OS test as an additional alpha of 0.02, giving a total alpha for the OS test of 0.025. The OS test will then be performed at the significance level of 0.025.

- If the ORR test is not significant at 0.02 level, then this alpha of 0.02 will not be available to be passed on for the OS test. The OS test will be performed at the originally reserved alpha of 0.005.

The analysis of ORR (assessed by blinded independent review using RECIST v1.1) will be performed using a Cochran-Mantel-Haenzsel (CMH) test comparing the ORR for the two treatment groups controlling for the randomization strata. With 454 subjects randomized with a 1:1 ratio, this test will have 90% statistical power (calculated based on chi-square test) to demonstrate an increase in the ORR from the postulated response of 12% for ipilimumab alone in this setting to 24% for the IMO-2125 + ipilimumab combination, at a 0.02 level of significance. The analysis of ORR will take place when all randomized subjects fall within one of the following categories:

- completed scheduled study treatment and completed at least 28 weeks on the study;
- prematurely discontinued study treatment and completed at least 28 weeks on the study;
- withdrew, were lost to follow-up, or died before completing at least 28 weeks on the study.

The analysis of OS will be performed using a stratified log-rank test controlling for the randomization strata. A sample size of 454 subjects provides 90% power to test the alternative hypothesis of hazard ratio (HR) ≤ 0.677 at an α of 0.005 (one-sided). The HR of 0.677 corresponds to an improvement in the median survival from 11.4 months (the historical control for ipilimumab alone) to 16.9 months with the IMO-2125 + ipilimumab combination.

The OS power calculations are based on log-rank test and assume that the trial will have ~20 months of uniform accrual, an overall study duration up to 56 months, and a 10% drop-out rate. If, under the fallback method, a total alpha of 0.025 is available for the OS significance test, then this test will have 90% power to test the alternative hypothesis of HR ≤ 0.72 at an α of 0.025 (one-sided) which corresponds to an improvement in the median survival from 11.4 months (the historical control for ipilimumab alone) to 15.8 months with the IMO-2125 + ipilimumab combination.

The analysis will be performed when the required number of deaths for the OS analysis (392) is reached, or approximately 36 months after the last subject is randomized, whichever occurs first.

Progression-free survival will be assessed centrally and by investigator using RECIST v1.1 and estimated by the Kaplan-Meier method. Subjects who do not have a PFS event at the time of an analysis, including those who have started new anticancer therapy, withdrawn from the study, or been lost to follow-up without disease progression, will be censored at the date of the last valid disease assessment, defined as the latest assessment at which the subject had a RECIST v1.1 response of CR, PR, or stable disease (SD).

Stratification factors will include duration of prior anti-programmed death receptor-1 (PD-1) therapy (≥12 weeks vs <12 weeks), metastasis stage (M1c vs other), and BRAF mutation status and prior targeted therapy (BRAF wild type, BRAF mutation positive with prior targeted therapy, or BRAF mutation positive with no prior targeted therapy) using block randomization. Targeted therapy is the use of an approved BRAF or MEK inhibitor alone or in combination.

Date of Synopsis: 4 June 2020

Table 1: Schedule of Evaluations – Ipilimumab Alone (Arm A)

Evaluation	Screening[1]	Treatment Period[2]						Active F/up[3]	Survival F/up[4]
	Week	1	4	7	10	12	14		
Informed consent[5]	X								
Inclusion/exclusion	X								
Medical history	X								
ECOG	X	X	X	X	X		X		
CBC with diff	X	X[6]	X	X	X		X	X[14]	
Chemistry profile	X	X[6]	X	X	X		X	X[14]	
CH50/C3/C4		X					X		
Coagulation[7]		X					X		
Urinalysis		X					X		
Thyroid function tests		X	X	X	X		X	X[14]	
Vital signs[8]		X	X	X	X	X	X		
ECG		X					X		
Directed physical	X	X	X	X	X	X			
Pregnancy test[9]	X	X					X		
Ipilimumab dosing		X	X	X	X				
Disease assessment	X					X[12]		X[12]	
PRO		X[13]		X[13]		X[13]		X[13]	
AE/conmeds	Continuous[10]								
Serum samples for anti-drug antibodies[16]		X					X		
Tumor biopsies[11]	X[11]			X[11]					
Telephone contact									X
Anticancer treatment information									X[15]

AE=adverse event; aPTT=activated partial thromboplastin time; C3/C4=complement components C3 and C4; CBC=complete blood count; CH50=total hemolytic complement activity 50; diff=differential; ECG=electrocardiogram; ECOG=Eastern Cooperative Oncology Group; eCRF=electronic case report form; F/up=Follow-up; ICF=informed consent form; INR=international normalized ratio; PK=pharmacokinetic(s); PRO=patient-reported outcome; PT=prothrombin time; TSH=thyroid stimulating hormone; USPI=US Prescribing Information; WOCBP=women of childbearing potential

1. All Screening tests and assessments must be performed within 28 days before the date of randomization, except for ECOG and laboratory tests, which should be performed within 10 days before the first dose of study drug, and pregnancy test should be performed within 72 hours, if pregnancy test is not performed within 72 hours prior to randomization, it should be done on the first day of ipilimumab dosing.
2. All assessments will occur within a ±3-day window. Ipilimumab dosing should follow the product label (e.g., USPI).
3. Subjects who discontinue study treatment due to completion of the planned treatment or for reasons other than disease progression or start of new anticancer treatment will enter the Active Follow-up Period. Assessments during the Active Follow-up Period will follow the schedule of the disease assessments and will occur at Week 12 (±1 week), then every 8 weeks (±2 weeks) for the first year and every 12 weeks (±2 weeks) during subsequent years.
4. Subjects who discontinue disease assessments due to either disease progression or the start of new anticancer treatment, with or without disease progression, will enter the Survival Follow-up Period (contacted by telephone every 3 months until death or the end of the study). Assessments will occur within a ±14-day window.
5. Subjects must be randomized within 28 days after signing the ICF; the first dose of study drug should be administered within 2 days after randomization.
6. CBC and chemistries do not have to be repeated if Screening tests are completed within 7 days of start of treatment.
7. PT, aPTT, INR.

8. Vital signs will include systolic and diastolic blood pressure, body temperature, pulse rate, body weight, and height (Week 1 only). Vital signs should be completed prior to treatment administration.
9. WOCBP only. Pregnancy test after randomization should be completed as deemed necessary by the Investigator or required by local law.
10. During the Follow-up Periods, for 90 days after the last dose of study treatment, all SAEs, irAEs, AEs Grade ≥3, and associated concomitant medications for their treatment must be reported. For the remainder of the Follow-up Periods, AE reporting should be limited to Treatment-related Grade ≥3 AEs and SAEs, and the associated concomitant medications.
11. Optional (see Laboratory Manual).
12. To inform treatment management decisions, disease assessments are to be completed at Week 12 (±1 week), then every 8 weeks (±2 weeks) for the first year and every 12 weeks (±2 weeks) during subsequent years.
13. To minimize bias in the PRO data, disease and PRO assessments are to be completed prior to study drug administration and AE evaluations at Weeks 1, 7, and 12 (±1 week), then every 8 weeks (±2 weeks) for the first year and every 12 weeks (±2 weeks) during subsequent years.
14. Per institutional practices following the frequency of active follow-up disease assessments.
15. Follow-on anticancer treatment information will be collected during the telephone calls.
16. Serum samples will be collected for analysis of anti- ipilimumab antibodies; details are provided in the Laboratory Manual. Baseline sample to be collected at Week 1 before the first dose of study treatment.

Table 2: Schedule of Evaluations – Ipilimumab with IMO-2125 (Arm B)

Evaluation	Screening[1]	Combination Treatment[2]							IMO Maintenance			Active F/up[3]	Survival F/up[4]
	Week	1	2	3	5	8	11	12	16	20	24		
Informed consent[5]	X												
Inclusion/Exclusion	X												
Medical History	X												
ECOG	X	X			X	X	X		X	X	X		
CBC with diff	X	X[6]	X	X	X	X	X		X	X	X	X[18]	
Chemistry profile	X	X[6]			X	X	X		X			X[18]	
CH50/C3/C4[7]		X					X						
Coagulation[8]		X							X				
Urinalysis		X							X				
Thyroid function tests		X			X	X	X		X			X[18]	
Vital signs[9]		X	X	X	X	X	X		X	X	X		
ECG		X[22]					X[22]		X		X		
Directed physical	X	X			X	X	X						
Pregnancy test[10]	X	X									X		
IMO-2125 dosing		X	X[11]	X	X[11]	X[11]	X[11]		X[20]	X[20]	X[20]		
Ipilimumab dosing			X		X	X	X						
Disease Assessment	X							X[16]				X	
PRO		X[17]				X[17]		X[17]				X[17]	
AE/Conmeds	Continuous[12]												
IMO-2125 PK samples[13]		X					X						
Serum samples for anti-drug antibodies[14]		X			X		X		X		X	X[19]	
Tumor biopsies	X[15]					X[15]							
Telephone contact													X
Anticancer treatment information													X[21]

AE=adverse event; aPTT=activated partial thromboplastin time; C3/C4=complement components C3 and C4; CBC=complete blood count; CH50=total hemolytic complement activity 50; diff=differential; ECG=electrocardiogram; ECOG=Eastern Cooperative Oncology Group; eCRF=electronic case report form; F/up=Follow-up; ICF=informed consent form; IMO=IMO-2125; INR=international normalized ratio; PK=pharmacokinetic(s); PRO=patient-reported outcome; PT=prothrombin time; TSH=thyroid stimulating hormone; WOCBP=women of childbearing potential

1. All Screening tests and assessments must be performed within 28 days before the date of randomization, except for ECOG and laboratory tests, which should be performed within 10 days before the first dose of study drug, and pregnancy test should be performed within 72 hours, if not performed within 72 hours of randomization, a pregnancy test should be repeated prior to the first dose of IMO-2125.
2. All assessments and IMO-2125 dosing will occur within a ±3-day window. IMO-2125 doses should be at least 5 days apart.
3. Subjects who discontinue study treatment due to completion of the planned treatment or for reasons other than disease progression or start of new anticancer treatment will enter the Active Follow-up Period. Assessments during the Active Follow-up Period will follow the schedule of the disease assessments and will occur at Week 12 (±1 week), then every 8 weeks (±2 weeks) for the first year and every 12 weeks (±2 weeks) during subsequent years.
4. Subjects who discontinue disease assessments due to either disease progression or the start of new anticancer treatment, with or without disease progression, will enter the Survival Follow-up Period (contacted by telephone every 3 months until death or the end of the study). Assessments will occur within a ±14-day window.
5. Subjects must be randomized within 28 days after signing the ICF; the first dose of study drug should be administered within 2 days after randomization.
6. CBC and chemistries do not have to be repeated if Screening tests are completed within 7 days of start of treatment.
7. Samples will be collected pre-dose, and at 1, 2 and 4 hours (±10 minutes) post-dose.
8. PT, aPTT, INR.
9. Vital signs will include systolic and diastolic blood pressure, body temperature, pulse rate, body weight, and height (Week 1 only). Vital signs should be completed prior to treatment administration.
10. WOCBP only. Pregnancy test after randomization should be completed as deemed necessary by the Investigator or required by local law.
11. IMO-2125 should be administered prior to ipilimumab.
12. During the IMO Maintenance Period, all CTCAE Grade ≥2 irAEs and laboratory abnormalities (regardless of relationship to study drug) should be monitored until resolution, stabilization, or return to baseline. During the Follow-up Periods, for 90 days after the last dose of study treatment, all SAEs, irAEs, AEs Grade ≥3, and associated concomitant medications for their treatment must be reported. For the remainder of the Follow-up Periods, AE reporting should be limited to Treatment-related Grade ≥3 AEs and SAEs, and the associated concomitant medications.
13. Blood samples for evaluation of plasma IMO-2125 concentrations will be collected pre-dose and at 1, 2, and 4 h post-dose (± 30 minutes) at Week 1 and Week 11 only.
14. Serum samples will be collected for analysis of anti-IMO-2125 and anti-ipilimumab antibodies; details are provided in the Laboratory Manual. Baseline sample to be collected at Week 1 before the first dose of study treatment.
15. Optional (see Laboratory Manual).
16. To inform treatment management decisions, disease assessments are to be completed at Week 12 (±1 week), then every 8 weeks (±2 weeks) for the first year and every 12 weeks (±2 weeks) during subsequent years.
17. To minimize bias in the PRO data, disease and PRO assessments are to be completed prior to study drug administration and AE evaluations at Weeks 1, 8, and 12 (±1 week), then every 8 weeks (±2 weeks) for the first year and every 12 weeks (±2 weeks) during subsequent years.
18. Per institutional practices following the frequency of active follow-up disease assessments.
19. Every 3 months during the Active Follow-up period and the samples should be collected at the closest Active follow-up visit.
20. Maintenance doses of IMO-2125 should be administered as per dosing instructions (see Section 9.3.3.2).
21. Follow-on anticancer treatment information will be collected during the telephone calls
22. Week 1 performed pre-dose (within 1.5 hours of dosing IMO-2125) and 1 hour (± 30 minutes) post-dose. Week 11 performed pre-dose (within 1.5 hours of dosing IMO-2125) and 1 hour (± 30 minutes) post-dose. ECGs should be done in triplicate.

3. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
βhCG	Beta human chorionic gonadotropin
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 cytosine-guanine dinucleotides
CL/F	Clearance
C_{max}	Maximum plasma concentration
CR	Complete response
CRO	Contract Research Organization
CS	Clinically significant
CTCAE	Common Terminology Criteria for Adverse Events
CTLA-4	Cytotoxic T-lymphocyte antigen 4
DNA	Deoxyribonucleic acid
DRR	Durable response rate
EC	Ethics Committee
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
EDC	Electronic data capture
EORTC QLQ-C30	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30
FDA	Food and Drug Administration
GCP	Good Clinical Practice

Abbreviation	Definition
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
HR	Hazard ratio
ICF	Informed consent form
ICH	International Council for Harmonisation
IDMC	Independent Data Monitoring Committee
IFN	Interferon
IMO	Immune Modulatory Oligonucleotide
IRA	Independent Reviewing Authority
IRB	Institutional Review Board
irAE(s)	Immune-related adverse event(s)
irCR	Immune-related Complete Response
irRECIST	Immune-related Response Evaluation Criteria in Solid Tumors
irPD	Immune-related Progressive Disease
irPR	Immune-related Partial Response
irSD	Immune-related Stable Disease
ITT	Intent-to-Treat
i.v.	Intravenous(ly)
IXRS	Interactive voice/web response system
mAb	Monoclonal antibody
MAPK	Mitogen-activated protein kinase
MedDRA	Medical Dictionary for Regulatory Activities
MRT	Mean residence time
NCI	National Cancer Institute
ORR	Objective response rate
OS	Overall survival
Pap	Papanicolaou
PD	Progressive disease
PD-1	Programmed cell death-1
PD-L1	Programmed death-ligand 1
pDC	Plasmacytoid dendritic cell
PFS	Progression-free survival
PI	Principal Investigator

Abbreviation	Definition
PK	Pharmacokinetic
PR	Partial response
PRO	Patient-reported Outcome
PT	Prothrombin time
QoL	quality of life
RBC	Red blood cell
RECIST	Response Evaluation Criteria in Solid Tumors
RNA	Ribonucleic acid
RP2D	Recommended phase 2 dose
SAE	Serious adverse event
SAP	Statistical Analysis Plan
s.c.	Subcutaneous(ly)
SUSAR	Suspected unexpected serious adverse reaction
$t_{1/2}$	Terminal exponential half-life
TEAE	Treatment-emergent adverse event
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 Prescribing Information
Vd/F	Volume of distribution
WBC	White blood cell
WOCBP	Women of childbearing potential

4. BACKGROUND INFORMATION AND RATIONALE

4.1. Refractory 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. Although melanoma is a rare form of skin cancer, it comprises over 75% of skin cancer deaths. The incidence of melanoma has been increasing steadily over the last four decades. Because melanoma is common in younger individuals, the years of life lost to melanoma are also disproportionately high when compared with other cancers. The American Cancer Society estimates that there were approximately 76,000 new invasive melanoma cases and 10,000 deaths from the disease in the USA in 2016. Fortunately, screening programs have had a major impact and most cases are now diagnosed at an earlier, and potentially curable, stage (Siegel, 2015). However, patients with more advanced disease have a much poorer prognosis; median survival for patients with unresectable or metastatic disease is measured only in months.

Several new drugs have been approved by the Food and Drug Administration (FDA) in recent years for the treatment of melanoma. Ipilimumab was originally approved for the treatment of unresectable or metastatic melanoma in 2011 based on a demonstration of improved survival compared with control. It has since been supplanted as first-line therapy based on superior outcomes (including survival) that have been shown with the programmed cell death-1 (PD-1) inhibitors, pembrolizumab and nivolumab. Kinase inhibitors targeting BRAF or MEK have also had a major impact on outcome for patients whose tumors carry the BRAF V600E mutation. This represents only approximately half of the melanoma population, however, and re-treatment following the development of resistance has been largely ineffective (Simeone, 2017).

For patients relapsing after immunotherapy (and a BRAF or MEK inhibitor if the targetable mutation is present), there are no effective therapeutic options. Retrospective analyses of ipilimumab given as second-line immunotherapy show an objective response rate (ORR) of 10% to 13% (Long, 2016; Bowyer, 2016). A small randomized study of ipilimumab vs the combination of nivolumab with ipilimumab is ongoing in subjects who have progressed or relapsed on PD-1 or programmed death-ligand 1 (PD-L1) inhibitors (NCT02731729). Chemotherapy and biochemotherapy carry significant toxicities and have not been shown to improve survival. Clearly, additional therapeutic options are needed.

4.2. Toll-like Receptor Agonists in the Treatment of Cancer

Toll-like receptors (TLRs) are a family of pattern recognition receptors that can induce potent innate and adaptive immune responses. Toll-like receptor 9 (TLR9) recognizes unmethylated cytosine-phosphate-guanine (CpG) dinucleotide motifs present in bacterial and viral deoxyribonucleic acid (DNA) and synthetic oligodeoxynucleotides and is expressed in endosomal compartments of human plasmacytoid dendritic cell (pDC) and B-cells. Signaling through TLR9 induces cytokine production and secretion, including interferon (IFN)-α and T helper 1 (Th1)-type cytokines, B-cell proliferation, and upregulation of co-stimulatory molecules. Accordingly, TLR9 agonists are being widely studied in the treatment of cancers, infectious diseases, allergy, asthma, and as vaccine adjuvants (Kandimalla and Agrawal, 2012; Struthers, 2010).

The adaptive T-cell response is ultimately dictated by dendritic cells (DCs), whose function is to acquire novel antigens and then direct the activation and expansion of antigen-specific T cells. TLR signaling induces DC activation, a process that is characterized by enhanced expression of costimulatory molecules and increased secretion of cytokines necessary for activation and differentiation of naive T cells (Pulko, 2009). A distinguishing characteristic of TLR9 agonists is their ability to induce strong CD4+ and CD8+ T-cell responses to many types of antigen when used as a vaccine adjuvant (Wang, 2005; Krieg, 2007).

4.3. IMO-2125

IMO-2125 is a synthetic phosphorothioate oligonucleotide that acts as a direct agonist of TLR9 to stimulate the innate and adaptive immune systems. IMO-2125 induces high levels of IFN-α from pDCs along with an array of endogenous cytokines and chemokines. IMO-2125 also promotes B-cell proliferation and differentiation (Yu, 2008; Rodriguez-Torres, 2010).

4.3.1. Nonclinical Experience with IMO-2125

4.3.1.1. Nonclinical Pharmacology

In vivo studies in mouse models of colon carcinoma, lymphoma, and melanoma indicate that intratumoral IMO-2125 monotherapy has been shown to produce abscopal effects in mice, including anti-tumor activity associated with an increase in infiltrating CD8+ T cells, and durable and specific cytotoxic T cell responses against tumor antigens (Jiang, 2015). Intratumoral administration was more effective than s.c. administration. When IMO-2125 was administered in combination with anti-PD-1 mAb or anti-CTLA-4 mAb a complementary effect on reduction in tumor growth was observed (Investigator's Brochure).

The only secondary pharmacologic effect of IMO-2125 identified was activation of the alternative complement pathway in non-human primates (Investigator's Brochure).

4.3.1.2. Nonclinical Toxicology

General toxicology studies were conducted in rats and monkeys administered IMO-2125 by s.c. injection once weekly for 4 and 13 consecutive weeks. Findings in these studies were consistent with immune stimulation, the proposed mechanism of action (Investigator's Brochure).

In chronic twice-weekly administration toxicity studies (26 weeks in rats and 39 weeks in monkeys), findings in the liver (rats) and kidney (monkey) were similar to what has been noted with other oligonucleotides (Investigator's Brochure). Monitoring for these potential effects is included in the ongoing and planned clinical studies using standard safety parameters for liver and kidney function. In addition, lymphomas and leukemias that likely were secondary to chronic immune stimulation and sarcomas at the site of injection that were likely secondary to chronic irritation/inflammation at the injection sites were noted in rats (Investigator's Brochure). Similar findings were not noted in monkeys (Investigator's Brochure).

Due to substantial differences in the pattern of TLR expression in rodents when compared with non-human primates and humans, the pharmacodynamic effects of chronic TLR9 stimulation in cynomolgus monkey may be more representative of the anticipated effects in humans than the effects seen in rodents.

4.3.2. Clinical Experience with IMO-2125

IMO-2125 has been studied previously as a potential treatment for subjects with chronic hepatitis C virus (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 subjects with HCV infection. IMO-2125 was administered subcutaneously (s.c.) at dosages up to 0.48 mg/kg/week in 96 subjects. Study 2125-204 in subjects with melanoma refractory to PD-1 inhibitors is currently ongoing. Full details are provided in the IMO-2125 Investigator's Brochure. The most common adverse events (AEs) were mild to moderate flu-like symptoms and injection site reactions.

4.3.2.1. IMO-2125 in Combination with Checkpoint Inhibitors (Study 2125-204)

Study 2125-204 is an ongoing Phase 1/2 clinical study of intratumoral IMO-2125 in combination with ipilimumab or pembrolizumab in melanoma that is refractory to PD-1 inhibitors. The study is being conducted in two phases. Phase 1 of the study is open-label and is designed to explore escalating dose levels of IMO-2125 (from 4 mg to 32 mg) along with either ipilimumab or pembrolizumab with a primary endpoint of safety (and selection of the recommended phase 2 dose[s] [RP2D(s)]). Subjects in Phase 2 will be assigned to one of the combinations once the RP2D(s) have been determined in Phase 1. The primary endpoint of Phase 2 is clinical activity, defined as objective response as assessed by the Investigator using immune-related Response Evaluation Criteria in Solid Tumors (irRECIST). Other endpoints are ORR by Response Evaluation Criteria in Solid Tumors (RECIST) v1.1, safety, tumor response, pharmacodynamics, and pharmacokinetics (PK). Serial biopsies of both the injected and a distant tumor are performed in all subjects for immunologic assessment. Refer to the Investigator's Brochure for more details.

As of the 05 January 2017 data cut-off, 13 subjects have received IMO-2125 in planned escalating dose cohorts of 4, 8, 16, and 32 mg along with ipilimumab, and another 3 subjects have received 8 mg of IMO-2125 with pembrolizumab (dose escalation is ongoing). Treatment has been generally well-tolerated, with no dose-limiting toxicity observed in any dose cohort to date. One (8%) subject in the 4 mg IMO-2125 + ipilimumab group died due to progressive disease (PD) during the study follow-up period, approximately 5 months after completing all study treatment. Seven (54%) subjects have reported serious adverse events (SAEs); however, none of the SAEs were considered treatment-related by the Investigator. The most commonly reported treatment-emergent adverse events (TEAEs; reported in >5 subjects overall) for the IMO-2125 + ipilimumab combination are anemia, pyrexia, nausea, and vomiting. Four instances of potential immune-related toxicity have been observed: hypophysitis (2 events), adrenal insufficiency, and autoimmune hepatitis, the latter occurring in a subject who had previously experienced dose-limiting immune-related hepatitis while receiving ipilimumab monotherapy (in violation of the protocol eligibility criteria). The outcome for these subjects has been good with routine supportive measures (Uemera 2017).

Clinical activity is promising with 3 investigator-reported responses, including 1 complete response (CR). Tumor biopsies obtained showed maturation of myeloid DC1 subset in the IMO-2125 injected lesion 24 hrs post-treatment compared with pre-treatment biopsy (Uemera 2017).

4.3.2.2. IMO-2125 in Refractory Solid Tumors (Study 2125-RST-101)

This is an open-label, multi-center, Phase 1b study in subjects with refractory solid tumors with a planned enrollment of approximately 40 subjects in the Dose Evaluation Portion of the study. IMO-2125 will be administered intratumorally at dosages of 8, 16, 23, or 32 mg for up to one year. The primary objectives are safety and determination of the RP2D for monotherapy dosing. Additional objectives include evaluation of clinical activity, PK, pharmacodynamics, and immunologic correlates in tumor biopsies.

4.4. Rationale for Study Design

This study is a randomized, multi-center, international, open-label comparison of ipilimumab with and without intratumoral IMO-2125 in subjects with anti-PD-1 refractory melanoma. The primary endpoint family comprises overall survival (OS) and ORR.

4.4.1. Rationale for Population

Immunotherapy has had a major impact on many cancers and PD-1 directed therapy is now recommended as the initial treatment for most patients with advanced melanoma (National Comprehensive Cancer Network [NCCN], 2016). Mitogen-activated protein kinase (MAPK) inhibitors have also proven to be valuable, though their use is limited to settings where a BRAF V600 driver mutation is present. Despite these advances, 67%, 66%, and 50% of patients, respectively, still fail to manifest a response (CR or partial response [PR]) to pembrolizumab, nivolumab, or the ipilimumab/nivolumab combination, respectively (Keytruda USPI, 2015; Opdivo USPI, 2016; Yervoy USPI, 2015). No treatment has been specifically approved for use following failure of PD-L1 directed immunotherapy and treatment options are particularly limited for patients whose tumors lack a BRAF V600 driver mutation. For these patients, clinical trials are recommended as an appropriate option (NCCN, 2016).

4.4.2. Rationale for Ipilimumab Comparator

Ipilimumab is recommended as a second-line immunotherapy option for patients who have not previously received it, and for previously-responding patients who have been off therapy for more than 3 months if they did not experience major toxicity with previous ipilimumab treatment (NCCN, 2016). This recommendation is based on both controlled studies in immunotherapy-naïve patients and uncontrolled retrospective series of ipilimumab as second line immunotherapy (NCCN, 2016). A recent post-hoc analysis of the pembrolizumab KEYNOTE-006 trial confirms that patients do respond to ipilimumab following failure of pembrolizumab treatment, and that clinical outcomes (including safety) are no different than the historical experience in untreated patients (Long, 2016).

4.4.3. Rationale for Combining IMO-2125 with Ipilimumab

Proof of concept for the effectiveness of intratumoral immune stimulation was established many years ago with Coley's demonstration that localized injection of bacterial extracts could on occasion lead to cure (Coley, 1893). Intratumoral BCG is also capable of inducing tumor regression in a substantial proportion of cases (Bast, 1974). More recently, the genetically modified oncolytic virus, talimogene laherparepvec has shown durable clinical responses, including abscopal effects, when injected into cutaneous, s.c., or nodal melanoma lesions (Imlygic®, United States Prescribing Information [USPI]).

Since the immune cells targeted by TLR9 are present within the tumor microenvironment, agonists delivered directly into a single tumor deposit can generate a potent and specific systemic antitumor immune response while potentially inducing less autoimmune toxicity (Marabelle, 2014). Preclinical studies have shown superiority of the intratumoral approach over systemic administration for both IMO-2125 (Jiang, 2015) and other TLR9 agonists (Lou, 2011).

Although intratumoral delivery of pattern recognition receptor agonists like TLR9 is an effective means of creating an adaptive antitumor immune response, this can still be attenuated by dampening mechanisms such as immunosuppressive tumor-infiltrating regulator T cells and anergic/exhausted tumor infiltrating or peritumoral cytotoxic T cells (Conroy, 2008). Therefore, combining a TLR9 agonist with checkpoint inhibitors or other modulators of the immune response to enhance systemic immunity is a logical strategy (Marabelle, 2014).

This hypothesis has been validated in preclinical models. The combination of intratumoral IMO-2125 with either an anti-cytotoxic-T lymphocyte antigen 4 (CTLA-4) or anti-PD-1 antibody results in improved tumor control compared with either agent alone, along with regression of systemic lung metastases and infiltration of tumor infiltrating lymphocytes versus monotherapy with either agent (Wang, 2015a; Wang, 2015b). Preliminary clinical experience is also promising as the combination of IMO-2125 with ipilimumab is well-tolerated and shows encouraging clinical activity in the setting of PD-1 refractory disease (Uemera, 2017).

4.4.4. Rationale for Dose

Previous clinical studies with systemic delivery (s.c.) of IMO-2125 in patients with chronic HCV infection at dose levels up to 0.48 mg/kg/week have shown good tolerability with clinically relevant, dose-dependent induction of IFN-α and other cytokines potentially important to the treatment of cancer (Rodriguez-Torres, 2010). The most common AEs were mild to moderate flu-like symptoms and injection site reactions.

Study 2125-204 is an ongoing Phase 1/2 clinical study designed to evaluate safety and preliminary efficacy of two checkpoint inhibitor combinations. In this study, IMO-2125 is being administered intratumorally at 4, 8, 16, or 32 mg (corresponding to the dose range studied in HCV) in combination with either ipilimumab or pembrolizumab. IMO-2125 injections are given at Weeks 1, 2, 3, 5, 8, and 11. Ipilimumab is administered at the labeled dose of 3 mg/kg intravenously (i.v.) during Weeks 2, 5, 8, and 11. The one week priming interval was chosen to allow migration of activated dendritic cells to the draining lymph nodes (Aarntzen, 2012). As of 28 March 2017, dose finding in the IMO-ipilimumab cohort is complete, while IMO- pembrolizumab dose-finding is ongoing. A total of 18 subjects have been treated in the dose-escalation phase, half of whom received the 8 mg dose of IMO-2125. Enrollment was not limited to superficial disease; thus, some study subjects have received IMO-2125 via deep or visceral injection.

Preliminary data for this study have been reported (Section 4.3.2.1). The RP2D of 8 mg for IMO-2125 was selected from the available options based upon acceptable safety, clinical activity (including one durable CR), and demonstration of early dendritic cell maturation followed by $CD45^+$ tumor-infiltrating lymphocyte (TIL) infiltration in both injected and non-injected tumors. Evidence for systemic Th1 cytokine activation and presence of an IFNα signature in biopsied lesions were also documented (Haymaker, 2017).

The Phase 3 regimen adds maintenance doses of IMO-2125 at 16, 20, and 24 weeks following completion of combination therapy. Prolonging the duration of IMO-2125 therapy provides continued innate immune stimulation in response to neoantigens that may emerge in response to treatment (Schumacher and Schreiber, 2015). Safety follow-up to support this longer dosing period is now available for several 2125-204 study subjects and, along with pre-clinical toxicology assessment of 6 month continued dosing, does not suggest a risk for cumulative toxicity from these additional maintenance doses. Study 2125-204 has recently been amended to assess dosing through 29 weeks; longer-term administration of IMO-2125 (approximately one year) is being evaluated in Study 2125-RST-101. Refer to the Investigator's Brochure for the most updated safety information.

5. STUDY OBJECTIVES

5.1. Primary Objective

The primary objective is to compare the efficacy (measured by ORR and OS) of intratumoral IMO-2125 in combination with ipilimumab versus ipilimumab alone.

5.2. Secondary Objectives

The secondary objectives are to assess other measures of clinical benefit, safety, PK, and patient-reported outcomes (PROs).

5.3. Exploratory Objectives

The exploratory objectives are to investigate potential biomarkers and the incidence of anti-IMO-2125 and anti-ipilimumab antibodies.

6. STUDY ENDPOINTS

6.1. Primary Endpoint Family

The primary endpoint family (see FDA Guidance for Industry, 2017) includes:

- ORR by blinded independent review using RECIST v1.1
- OS, defined as the time to death from any cause measured from the date of randomization.

6.2. Secondary Endpoints

The secondary endpoints include:

- ORR by investigator assessment using RECIST v1.1
- Duration of response (DoR) by blinded independent review and by investigator assessment using RECIST v1.1, measured from the time that criteria are first met for CR or partial response (PR) (whichever is first recorded) until the first date that recurrent or progressive disease is objectively documented
- Durable response rate (DRR) by blinded independent review and investigator assessment (using RECIST v1.1), defined as the rate of CR or PR lasting ≥6 months with onset during the first 12 months of treatment
- Time to response, defined as time to a complete or partial response (using RECIST v1.1) measured from the date of randomization, by blinded independent review and investigator assessment
- Progression-free survival (PFS), defined as the time to disease progression or death from any cause measured from the date of randomization, by blinded independent review and investigator assessment (using RECIST v1.1)
- Landmark PFS at 1 and 2 years by blinded independent review and investigator assessment (using RECIST v1.1) and landmark OS at 1 and 2 years
- PRO using the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 (EORTC QLQ-C30)
- Safety, including AEs, laboratory and vital sign tests, electrocardiograms (ECGs), ECOG, and physical examination
- Plasma PK of IMO2125

6.3. Exploratory Endpoints

The exploratory endpoints include:

- Immunologic biomarkers (optional tumor biopsies)
- Measurement of anti-IMO-2125 and anti-ipilimumab antibodies

7. SUBJECTS TO BE RECRUITED

7.1. Subject Recruitment

Subject selection and recruitment will be organized and overseen by the Investigator at each site following approval of the study protocol by the respective Institutional Review Board (IRB) or Ethics Committee (EC). All subjects 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 subject to participate and consent to the conduct of the study before initiating any study-related procedures.

An interactive voice/web response system (IXRS) will be used to register and randomize subjects into the study.

7.2. Inclusion Criteria

To be eligible for this study, subjects must meet all of the following inclusion criteria.

1. Subjects must be willing and able to sign the informed consent and comply with the study protocol.
2. Must be ≥18 years of age.
3. Histologically confirmed metastatic melanoma with measurable (by RECIST v1.1), stage III (lymph node or in transit lesions) or stage IVA, IVB, or IVC disease that is accessible for injection. Stage should be determined using the American Joint Committee on Cancer (AJCC) Cancer Staging Manual, Seventh Edition (Edge, 2010).
4. Confirmed progression during or after treatment with a PD-1 inhibitor (cannot be part of bi-specific antibody) e.g. nivolumab or pembrolizumab. Confirmed progression is defined as:

   - Radiological progression (confirmed at least 4 weeks after the initial scan showing PD); or
   - For progression based solely on worsening of non-target or new, non-measurable disease, confirmation by an additional scan at least 4 weeks after the initial scan *unless* progression is accompanied by correlative symptoms.

   In addition, all the following must hold:

   a) No intervening anti-cancer therapy between the last course of PD-1 inhibitor treatment and the first dose of study treatment is allowed except for local measures (e.g., surgical excision or biopsy, focal radiation therapy).
   b) The interval between last PD-1 inhibitor and start of study treatment should be at least 21 days with no residual anti-PD-1-related immune toxicities in excess of Grade 1 severity.
   c) Subjects who had adjuvant anti-PD-1 treatment are eligible if they have either disease recurrence after the end of adjuvant treatment or on-treatment disease recurrence after ≥12 weeks of adjuvant treatment.
   d) If subject BRAF mutation status is unknown, before randomization the subject must have BRAF testing performed using an approved assay method.

e) Patients with BRAF-positive tumor(s) are eligible for the study if they received prior treatment with a BRAF inhibitor (alone or in combination with a MEK inhibitor) or declined targeted therapy.

5. ECOG Performance Status ≤1.
6. Adequate baseline organ function as defined by:
   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 (≤Grade 1)
   e) Aspartate aminotransferase (AST) ≤2.5 x ULN; alanine aminotransferase (ALT) ≤2.5 x ULN; AST/ALT <5 x ULN if liver involvement (≤Grade 1)
   f) Serum bilirubin ≤1.5 x ULN, except in subjects with Gilbert's Syndrome who must have a total bilirubin <3 mg/dL (≤Grade 1)
7. Women of childbearing potential (WOCBP) and men must agree to use effective contraceptive methods from screening until at least 90 days after the last dose of either ipilimumab or IMO-2125, whichever is later.

   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 subject. 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™)

      NOTE: For subjects in Sweden, low dose oral contraceptives are not permitted
   e) An intra-uterine device
8. WOCBP must have a negative pregnancy test (serum or urine) according to the Schedule of Evaluations (Table 1 and Table 2).

7.3. Exclusion Criteria

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

1. Ocular melanoma.
2. Prior therapy with a TLR agonist, excluding topical agents.

3. Prior ipilimumab with the exception of adjuvant treatment completed ≥6 months prior to enrollment.
4. Systemic treatment with IFN-α within the previous 6 months.
5. Known hypersensitivity to any oligodeoxynucleotide.
6. Active autoimmune disease requiring disease-modifying therapy at the time of screening.
7. Subjects with a requirement for receiving more than physiologic doses of systemic steroids (>10 mg/day of prednisone or equivalent) for the 2 weeks preceding start of study treatment.
8. Subjects with another primary malignancy that has not been in remission for at least 3 years with the exception of 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).
9. Active systemic infections requiring antibiotics.
10. Known active, hepatitis A, B, or C infection.
11. Known diagnosis of human immunodeficiency virus (HIV) infection.
12. Women who are pregnant or breast-feeding.
13. Prior anaphylactic or other severe infusion reaction associated with human antibody administration that cannot be managed with standard supportive measures.
14. Presence of known central nervous system, meningeal, or epidural metastatic disease. However, subjects with known brain metastases are allowed if the brain metastases are stable for ≥4 weeks before the first dose of study treatment. Stable is defined as neurological symptoms not present or resolved to baseline, no radiologic evidence of progression, and steroid requirement of prednisone ≤10 mg/day or equivalent.
15. Impaired cardiac function or clinically significant cardiac disease.

8. STUDY DESIGN

8.1. Overview

This is a randomized Phase 3 global, multi-center, open-label comparison of ipilimumab with and without intratumoral IMO-2125 in subjects with advanced melanoma who had disease progression while on PD-1 directed therapy. Confirmed progression is defined by irRECIST criteria (see Section 20.3). Subjects will be randomized 1:1 to Arm A or B. Randomization is stratified on the duration of prior anti-PD-1 therapy (≥12 weeks vs <12 weeks), metastasis stage (M1c vs other), and BRAF mutation status and prior targeted therapy (BRAF wild type, BRAF mutation positive with prior targeted therapy, or BRAF mutation positive with no prior targeted therapy) using block randomization. Targeted therapy is the use of an approved BRAF or MEK inhibitor alone or in combination. The primary endpoint family of the study comprises OS and ORR.

8.1.1. Independent Review Facility

Blinded independent review of all clinical and imaging results for response assessment will be performed centrally. The composition and duties of the blinded, independent reviewers are described in a separate charter.

8.1.2. Independent Data Monitoring Committee

The Independent Data Monitoring Committee (IDMC) composition and duties are described in a separate charter. Periodic data reviews will be performed by an IDMC as described in the IDMC Charter. The first IDMC meeting will occur after approximately 20 subjects on each arm have been treated with two doses of ipilimumab, and subsequent meetings occurring at regular intervals after the initial meeting until the database lock for the final analysis of OS. The initial meeting will review safety only. The IDMC will assess benefit:risk on an ongoing basis and will recommend early stopping if the safety profile is not acceptable given the efficacy of the study treatment.

8.2. Duration of Study

8.2.1. Treatment Duration

The Treatment Phase of the study is 10 weeks for subjects assigned to Arm A and 24 weeks for subjects assigned to Arm B.

8.2.2. Study Duration

The study is complete and final analysis will occur when approximately 392 randomized subjects have died, or approximately 36 months after the last subject is randomized, whichever occurs first; it is assumed this will take approximately 56 months after the first subject is randomized.

8.3. Study Drug Discontinuation and Study Withdrawal

8.3.1. Subject Discontinuation of Study Drug

Failure to complete Week 10 of study drug (Arm A) or Week 24 (Arm B) for any reason will be considered premature study drug discontinuation. Reasons for premature study drug discontinuation include PD (by irRECIST or by clinical progression), death, intolerable AE, withdrawal of consent, lost to follow up, Investigator discretion, Sponsor decision, and premature termination of the study.

Subjects who discontinue treatment prematurely prior to progression should continue to be followed according to the SOE (Active Follow-up). The Investigator will document the date of and reason(s) for study treatment discontinuation on the electronic case report form (eCRF). Once a subject discontinues study treatment permanently, they will not be able to be retreated.

Subjects who complete the planned study treatment and who have not progressed or started new anti-cancer therapy will enter the Active Follow-up Period and be followed according to the SOE. Subjects will enter the Survival Follow-up Period at disease progression or the start of new anti-cancer therapy (with or without disease progression).

8.3.2. Subject Withdrawal from the Study

Subjects are free to withdraw consent from participation in the study at any time. For any subject who withdraws consent due to an AE, the Investigator should arrange for the subject to be followed appropriately until the AE has resolved or stabilized (in the opinion of the Investigator).

The Investigator will document the reason(s) for study withdrawal on the eCRF. Idera and the Contract Research Organization (CRO) Medical Monitor should be informed when a subject is withdrawn from the study.

8.3.3. Study and Subject Completion

The study is complete when approximately 392 randomized subjects have died or approximately 36 months after the last subject is randomized, whichever occurs first.

A subject has completed the study at death. Subjects who withdraw from the study (including withdrawal of consent for study participation, lost to follow-up, premature termination of the study, or withdrawal at the discretion of the Investigator) will not be considered to have completed the study.

8.3.4. Lost to Follow-up

Subjects are considered lost to follow-up if they cannot be contacted after at least 3 attempts over a 6-month period and it cannot be determined whether death has occurred.

8.4. Number of Subjects

The study will enroll approximately 454 subjects.

8.5. 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 TREATMENTS

9.1. 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 drug product is supplied as an 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.

9.2. Ipilimumab

Ipilimumab is a commercially available product.

9.3. Drug Handling and Administration

9.3.1. Drug Delivery to Site

After the research site has submitted all approved regulatory and study start-up documents, an IXRS will be used to manage drug supply. All IMO-2125 shipments are sent refrigerated. Upon receipt, the pharmacist or appropriate technician/designee must inspect the contents, verify temperature conditions, and confirm receipt of goods.

Drug inventory will be maintained by the site. Resupply of IMO-2125 to the sites is detailed in the Pharmacy Manual.

9.3.2. Drug Storage

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

9.3.2.2. Ipilimumab Storage

Refer to locally issued ipilimumab package insert for subjects receiving this agent.

9.3.3. Administration

Subjects will be randomized (1:1) to receive either:

1. Arm A – ipilimumab 3 mg/kg i.v. at Weeks 1, 4, 7, and 10

   or

2. Arm B – IMO-2125, 8 mg intratumorally at Weeks 1, 2, 3, 5, 8, 11, 16, 20, and 24 in combination with ipilimumab 3 mg/kg i.v. at Weeks 2, 5, 8, and 11

9.3.3.1. Ipilimumab- Arm A

Ipilimumab will be administered i.v. using a 90-minute infusion duration at 3 mg/kg on Weeks 1, 4, 7, and 10 (Arm A) or Weeks 2, 5, 8, and 11 (Arm B). Cross-over therapy will not be allowed for subjects assigned to Arm A.

9.3.3.2. IMO-2125 + Ipilimumab- Arm B

IMO-2125 will be given prior to ipilimumab on days when both are to be administered. IMO2125 will be administered intratumorally as a 1-4 mL injection to a single designated lesion throughout the study. Subjects will remain at the study site for observation for a minimum of 30 minutes following each administration of IMO2125.

The injected tumor will be selected from (in order of priority) pathologic draining lymph nodes, superficial or s.c. metastases, or deep or visceral metastases, the latter requiring interventional radiology support for both IMO-2125 administration and selection of a lesion that can be safely injected multiple times. The dose will be thoroughly distributed within the injected tumor using a single injection site and a fanning method to ensure even distribution.

Dosing volume will be adjusted on a sliding scale and based on the judgment of the investigator as the injected tumor shrinks to maintain a constant total dose. Additional details are described in the Pharmacy Manual. In the event a full dose can no longer be practically administered into the injected tumor, another tumor may be selected. In the event a complete tumor regression occurs prior to completion of therapy, any remaining IMO-2125 doses should be administered into the tumor bed, except in the case of visceral lesions for which injections should be stopped. Treatment following disease progression is at the discretion of the Investigator. More details on IMO-2125 dose preparation can be found in the Pharmacy Manual.

9.3.4. Dose Modification

The most common AEs following intratumoral administration of IMO-2125 have been non-specific “flu-like” symptoms and mild to moderate injection site reactions. In combination with ipilimumab, IMO-2125 has been associated with irAEs (Section 10.1.3.4) and fever. Ipilimumab dosing will follow the local package insert. IMO-2125 therapy should be continued if ipilimumab is discontinued early for toxicity.

Dose modification instructions for IMO-2125 including its use in combination with ipilimumab are provided in Table 3.

Table 3: Dose Modification Instructions for IMO-2125

Event	Action	Dose Modification
Local or mild systemic reaction (e.g., pyrexia)	Supportive measures as required. Continue treatment with IMO-2125 per clinical discretion.	None
Severe systemic reaction for which more aggressive measures including hospitalization are required (e.g., severe hypotension)	Supportive measures as required. Hold further dosing until the event resolves to baseline or Grade 1 and the re-treatment criteria below are met.	None.
Life-threatening AE (e.g., anaphylaxis)	Supportive measures as required.	Discontinue treatment
Serious procedural complication related to deep or visceral injection (e.g. pneumothorax or hematoma formation)	Supportive measures as required	Discontinue visceral injections (treatment may be continued if a superficial lesion or tumor-involved lymph node is available for injection instead)

Conventional supportive medications (including infliximab for immune-related colitis and growth factor support) are permitted.

Criteria for re-initiation of treatment with each dose of study drug include:

- ANC $\geq$1.5 x 10^9/L (1500/µL);
- Platelets $\geq$75 x 10^9/L (75,000/µL);
- Resolution of all clinically significant non-hematologic toxicities for which a causal association to study treatment cannot be ruled out to Grade $\leq$1 or baseline.

If the subject does not meet these criteria, dosing will be delayed, and the subject should be re-evaluated within 48 to 72 hours. If the next dose is delayed by more than 21 days for toxicity, the subject should be removed from study treatment unless approved by the medical monitor.

9.3.4.1. Dose Modifications for Ipilimumab-Related Toxicities

Please refer to the current, locally approved ipilimumab package insert for specific guidance in managing irAEs associated with ipilimumab. Table 4 provides guidance on modifications to ipilimumab dosing for selected toxicities.

Table 4: Recommended ipilimumab dose modifications for selected toxicities

Organ system	Adverse reaction	Treatment modification
Endocrine	Symptomatic endocrinopathy	Withhold ipilimumab Resume ipilimumab in patients with complete or

Organ system	Adverse reaction	Treatment modification
		partial resolution of adverse reactions (Grade 0 to 1), and who are receiving no more than physiologic doses of systemic steroids per local prescribing information.
	• Symptomatic reactions lasting 6 weeks or longer • Inability to reduce corticosteroid dose to physiologic doses per local prescribing information	Permanently discontinue ipilimumab
Ophthalmologic	Grade 2 through 4 reactions • not improving to Grade 1 within 2 weeks while receiving topical therapy or • requiring systemic treatment	Permanently discontinue ipilimumab
Enterocolitis	Grade ≤2 Grade 3 or 4	Withhold ipilimumab; administer anti-diarrheal treatment and, if persistent for more than 1 week, initiate systemic corticosteroids at a dose of 0.5 mg/kg/day prednisone or equivalent. The use of infliximab is also permitted per institutional policies. Permanently discontinue ipilimumab
Hepatitis Dermatitis Neuropathies Other immune-related toxicities	Grade 2	Withhold ipilimumab Resume ipilimumab in patients with complete or partial resolution of adverse reactions (Grade 0 to 1), and who are receiving no more than physiologic doses of systemic steroid per local prescribing information.
	• Grade 2 reactions lasting 6 weeks or longer	Permanently discontinue ipilimumab

Organ system	Adverse reaction	Treatment modification
	• Inability to reduce corticosteroid dose to physiologic doses per local prescribing information • Grade 3 or 4	

If the subject does not meet the criteria for resuming treatment, dosing will be delayed, and the subject should be re-evaluated within 48 to 72 hours. If the next dose is delayed for toxicity by more than the period specified per the locally approved ipilimumab package insert, the subject should be discontinued from study treatment unless approved by the medical monitor.

9.3.4.2. Procedures for Assessment of Subjects with Changes in Complement Levels

Activation of complement in non-human primates is a well-described effect of phosphorothioate oligonucleotides, including IMO-2125. Monkeys are thought to be particularly sensitive to oligonucleotide-induced complement activation and a similar direct oligonucleotide-induced complement activation has not been observed in humans or other species.

Complement samples will be collected at Weeks 1 and 14 for Arm A and Weeks 1 and 11 for Arm B, according to the Schedule of Events table (see Table 1), and will be analyzed at a central laboratory (Medpace Reference Laboratories). If at any time during study participation, a subject experiences an acute drop in complement (total hemolytic complement assay, complement component 3, or complement component 4) levels ≥50% or a drop to an absolute value below the lower limit of normal with reference to baseline testing or most recent values on study, the Sponsor will notify the site and the following procedures should be performed by the investigator:

1. Perform a safety evaluation and any necessary testing for the subject as clinically indicated.
2. If the results of the safety evaluations suggest any safety concerns associated with the drop in complement levels, hold the study drug treatment.
3. The patients should return to the clinic to have another serum sample drawn and sent to the central laboratory to confirm decreased complement levels.

Based on the results of this work-up and the subject's disease assessment/response to study drug, the Investigator, in discussion with the Sponsor's Medical Monitor, will determine the subject's risk/benefit profile and discuss appropriate next steps regarding the subject's continued treatment with study drug.

9.3.4.3. Procedures for Assessment of Subjects with Symptomatic Thrombocytopenia

Severe thrombocytopenia has been reported in clinical studies with another oligonucleotide (FDA Briefing Document, 2015). Most of these subjects had confirmed anti-platelet antibodies. These cases occurred 14 to 26 months after the onset of treatment, suggesting that risk increases with duration of exposure. In the event of a precipitous drop in platelet counts (i.e., to $<25 \times 10^9$/L), treatment with IMO-2125 should be held and an anti-platelet antibody count

obtained. Treatment may be resumed once administration criteria (Section 9.3.4) are met. Anti-platelet, thrombolytic, or anticoagulant drugs should be used with caution.

9.4. 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.

9.5. Drug Accountability

The Investigator is responsible for study drug accountability, reconciliation, and record maintenance. In accordance with all applicable regulatory requirements, the Investigator or designated study personnel (e.g., Pharmacy) must maintain study drug accountability records throughout the study. Further details are provided in the Pharmacy Manual.

9.6. Concomitant and Prohibited Medications

9.6.1. Concomitant Medications

With the exception of the prohibited drugs listed in Section 9.6.2, concomitant prescription medications and over-the-counter drugs are permitted, including infliximab and growth factor support. These should be recorded on the eCRF.

9.6.2. Prohibited Medications

The following medications are prohibited while the subject is in this study:

- Anti-cancer therapies other than those specified in the protocol (see Section 7.2 for inclusion criteria related to anti-cancer therapies)
- Oncolytic tumor viral therapies (e.g., Imlygic®)
- Investigational/experimental medicines or vaccines

10. ADVERSE EVENT REPORTING

10.1. Adverse Events

Adverse events should be assessed continuously throughout the study and recorded on the eCRF. During the Follow-up Periods, for 90 days after the last dose of study treatment, all SAEs, irAEs (Section 10.1.3.4), AEs Grade ≥3, and associated concomitant medications for their treatment must be reported. For the remainder of the Follow-up Periods, AE reporting may be limited to treatment-related Grade ≥3 AEs and SAEs, and the associated concomitant medications (see Table 1 and Table 2).

10.1.1. Definition of Adverse Events

10.1.1.1. Adverse Event

An AE is any untoward medical occurrence temporally associated with the use of a medical product in a subject, ***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.

10.1.1.2. Serious Adverse Event

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

- Death.
- Life-threatening, meaning that the subject 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).

10.1.1.3. 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 10.1.3.3);
- *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 10.1.3.5);
  - The event is now characterized more specifically (e.g., an event of "interstitial nephritis" in a subject receiving an agent previously described as associated with "acute renal failure").

In clinical trials involving ill subjects, 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."

10.1.2. Recording Adverse Events

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

- AEs are captured from the time of informed consent. 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 TEAEs.
- After the Active Follow-up Period, 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 10.1.1.3).
- In accordance with the FDA guidance document – Safety Reporting Requirements for Investigational New Drugs and Bioavailability/Bioequivalence 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.

10.1.3. Characterizing Adverse Events

For each AE recorded the following characteristics will be noted.

10.1.3.1. 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."

10.1.3.2. 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 subject and Investigator independently, and information from each may contribute to the final report. For example, a subject may report the onset of a rash 2 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 subject and a specific description (herpes zoster) based on the clinical exam and tests.

10.1.3.3. 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 subject's underlying disease or comorbid 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 holding 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 (an)other 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 from the use of the study drug as planned (per protocol), or from abuse, withdrawal, or over-dosage of the agent.

10.1.3.4. Immune-related AEs

Immune-related AEs (irAEs) are side effects associated with the increased activity of the immune system by immunotherapy agents such as checkpoint inhibitors, which can affect multiple organs of the body including the skin, gastrointestinal tract, endocrine system, liver, lungs, nervous system, and musculoskeletal system. 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
- Hypothyroidism
- Hyperthyroidism
- Other endocrinopathies
- Colitis
- Enterocolitis
- Dermatitis
- Autoimmune dermatitis
- GuillainBarre syndrome
- Hepatitis
- Myasthenia gravis
- Pneumonitis
- StevensJohnson Syndrome
- Toxic epidermal necrolysis
- Uveitis
- Iritis
- Myocarditis
- Any AEs that the Sponsor or investigator considers to be of autoimmune or immune-related origin.

Immune-related AEs will be identified as such in the eCRF, and the associated treatment for these AEs should be recorded including the drugs, doses, duration, and AE(s) being treated. Any dose modifications to either study treatment should also be recorded including the start and end dates of the modification, the study drug doses, and any dose reductions. See Section 9.3.4 for additional information about dose modifications.

10.1.3.5. Severity

The severity of clinical AEs (i.e., symptoms reported by the subject and/or signs observed by the Investigator) will be assessed using the guidelines summarized in Table 5 based on National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) v4.03.

Table 5: 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 [a]
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 [b]
Grade 4/Life-threatening	Life-threatening consequences; urgent intervention indicated
Grade 5/Death	Death related to adverse event

[a.] Instrumental activities of daily living refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

[b.] Self-care activities of daily living refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

10.1.3.6. 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
- Reported as AEs when assessed as clinically significant ("CS") using the procedures and criteria detailed in Section 10.1.2.

All relevant and clinically significant laboratory results from hospitalizations occurring during the study must be entered into the EDC on an Unscheduled Visit eCRF.

10.1.3.7. 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 or dosing was skipped; i.e., one or more doses were not administered, but drug was not stopped permanently.
- ***Dose Reduced*** — study drug regimen was modified by subtraction; i.e., by decreasing the frequency.
- ***Dose Not Changed*** — no change in the administration of study drug.

For subjects whose treatment is paused due to events requiring dose modification (see Section 9.3.4) and then resumed at a decreased frequency, the management of study drug will be recorded as "Dose Reduced."

10.1.3.8. 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.

10.1.3.9. 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 subjects who prematurely discontinue study participation. For the purpose of SAE reporting, the end date of an SAE is the date that it no longer met the serious criteria, e.g. the discharge date is the end date for SAEs considered serious on the basis of hospitalization. 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.

For subjects in Arm B (ipilimumab + IMO-2125), during the IMO Maintenance Period, all CTCAE Grade ≥2 irAEs and laboratory abnormalities (regardless of relationship to study drug) should be monitored until resolution, stabilization, or return to baseline (see Table 2).

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

- ***Resolved without sequelae*** — the event resolved and subject returned to baseline.
- ***Resolved with sequelae*** — the event resolved but the subject 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 subject died, but were *not* assessed as the primary cause of death. For the purpose of SAE reporting, these categories are to be filled out as appropriate as of the date that the SAE form is filled out by the site.

10.1.3.10. Date and Time of Outcome

For each class of outcome as defined above, Table 6 indicates the date and time to be recorded. As discussed in detail for date/time of onset (see Section 10.1.3.2), determining the date/time an event resolved (ended) should reflect the type of event and the source of the information.

Table 6: 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)

For the purpose of SAE reporting, these categories are to be filled out as appropriate as of the date that the SAE form is filled out by the site.

10.1.4. Reporting Adverse Events

10.1.4.1. Where to Report Serious Adverse Events

Serious AE reporting will be performed by the site via submission of a paper SAE form sent as a PDF by e-mail or fax to the pharmacovigilance vendor (see Emergency contact page for details); detailed training will be provided during site initiation. Contact information for the Medical Monitor is provided in the Emergency Contact Information section of this protocol.

10.1.4.2. Procedures for Reporting Serious Adverse Events to the Sponsor

The SAE will be submitted by e-mail or fax to the pharmacovigilance vendor ***within 24 hours*** of the time the Investigator (or the Investigator's designee) becomes aware that the event has occurred. The study specific SAE form should be used and each box/question should be filled out as pertinent to the date that the SAE form was filled out.

Copies of relevant medical reports — including diagnostic procedures (e.g., laboratory, ECG, xray), surgical procedures, and consultations may be sent as accompanying documentation and may be requested if not available. However, the relevant information from these documents needs to be included in the appropriate section of the study-specific SAE form, including the narrative as appropriate.

10.1.4.3. 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 (subject becomes pregnant while taking study drug). Should a female subject or partner of a male subject become pregnant during the study, the subject will inform the Investigator. The subject 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 (subject was taking study drug while nursing an infant).
- Accidental exposure (someone other than the subject was exposed to study drug).
- Overdose (subject received more than the prescribed dose of study drug within a given timeframe).
- Other medication errors that potentially place subjects at greater risk of harm than was previously known or recognized (e.g., study drug was administered via incorrect route).

10.1.4.4. 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 (typically within 7 days of receipt by Idera or designated vendor for fatal or life-threatening SUSARs; within 15 days for all other SUSARs). Therefore, as with all SAEs, the site must submit an SAE form with relevant information to the pharmacovigilance vendor within 24 hours of being made aware of the event. The Sponsor and the Investigator will work together to meet these reporting requirements.

11. ASSESSMENT OF EFFICACY

11.1. Tumor Response

Tumor assessments will be performed at Screening and Week 12 (±1 week), then every 8 weeks (±2 weeks) for the first year and every 12 weeks (±2 weeks) in subsequent years using consistent imaging modality. Investigators should follow modified irRECIST guidelines for patient management and provide visit response assessments using RECIST v1.1. Blinded central reviewers will provide independent assessment of tumor response using RECIST v1.1 and modified irRECIST (see Section 20.2 and Section 20.3, respectively), as described in a charter.

Efficacy evaluations should include clinical examination, assessment of cutaneous lesions with photography, and computed tomography (CT) or magnetic resonance imaging (MRI) scanning of known sites of disease. Injected lesions will contribute to the assessment of overall tumor burden and may be selected as target lesions if appropriate. Ultrasound studies performed for needle biopsy localization or IMO-2125 dosing should not be used as the sole means of assessing response. Similarly, lesions that will be biopsied for exploratory analyses should generally not be considered target lesions for purposes of disease assessment when other measurable lesions are present.

If present, skin lesions may be considered RECIST v1.1 (or irRECIST) target lesions when they are superficial and ≥10 mm diameter as assessed using calipers. Documentation by color photography including a ruler to measure the size should be done and sent to the independent review facility for response assessment evaluation.

The same method(s) of assessment should be used throughout the study for consistency. For irRECIST, response assessments of immune-related CR (irCR), immune-related PR (irPR), and immune-related PD (irPD) must be confirmed by imaging ≥4 weeks after the initial documentation of response except progression based solely on substantial, unequivocal worsening of non-target or new, non-measurable disease accompanied by correlative symptoms (see Section 20.3). For RECIST v1.1, response assessments of CR or PR must be confirmed by imaging ≥4 weeks after the initial documentation of response.

Patients will be allowed to be treated until confirmed progression and per Investigator discretion.

11.2. Patient-Reported Outcomes (EORTC QLQ-C30)

The EORTC QLQ 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 five functional scales (physical, role, emotional, social, and cognitive), three symptom scales (fatigue, nausea and vomiting, and pain) and a global health status/ QoL scale, and six single items (dyspnoea, insomnia, appetite loss, constipation, diarrhoea, 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 (see Table 1 and Table 2). To minimize bias in the PRO data, the PRO assessments are to be completed before study drug administration and AE assessments.

12. SAFETY ASSESSMENTS

Adverse events will be continuously assessed during the study (see Section 10.1).

12.1. Vital Signs

Vital sign measurements will be taken at intervals as specified in the Schedule of Evaluations (Table 1 and Table 2). Vital signs will include systolic and diastolic blood pressure, body temperature, pulse rate, body weight, height (Screening only). Vital signs should be done prior to treatment administration.

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 Schedule of Evaluations (Table 1 and Table 2). Blood and urine samples will be analyzed for the analytes presented in Table 7.

Table 7: Safety Laboratory Measurements

Hematology	Chemistry	Urinalysis by 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	Blood	PT
Hemoglobin	Calcium	Specific gravity	aPTT
MCH	CO_2	Ketones	INR
MCHC	Sodium, chloride, and potassium	Bilirubin	
MCV	Cholesterol		**Complement**
Platelet count	Glucose	**Microscopy**	CH50
RBC count	Lactate dehydrogenase	Bacteria	C3
WBC count	Phosphate	Crystals	C4
	Total protein	Casts (cellular, granular, and hyaline)	
	Triglycerides	RBC	
	Uric acid	WBC	
	βhCG for WOCBP	Epithelial cells	

ALT=alanine aminotransferase; aPTT= activated partial thromboplastin time; AST=aspartate aminotransferase; βhCG=beta human chorionic gonadotropin; BUN=blood urea nitrogen; C3=complement component 3; C4=complement component 4; CH50=total complement activity 50; CO2=carbon dioxide; 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; T3=triiodothyronine; T4=thyroxine; TSH=thyroid-stimulating hormone; WBC=white blood cell; WOCBP=women of childbearing potential.

12.3. Other Safety Assessments

12.3.1. Physical Examination

A directed physical examination with clinical disease assessment will be performed as outlined in the Schedule of Evaluations (Table 1 and Table 2). A medical history will be done at the Screening Visit and any clinically significant findings should be recorded as part of the medical history. During the study, any new physical examination findings that the Investigator deems clinically significant should be recorded as AEs.

12.3.2. Electrocardiogram Monitoring

A resting 12-lead ECG will be performed (in triplicate for Arm B only) at intervals as specified in the Schedule of Evaluations (Table 1 and Table 2). Any clinically significant findings during the Screening Visit should be recorded as part of the medical history.

12.3.3. ECOG Performance Status

The subject's ECOG performance status will be evaluated per guidance in Section 20.1 as outlined in the Schedule of Evaluations (Table 1 and Table 2).

13. PHARMACOKINETICS

The timing of sample collection is provided in the Schedule of Evaluations (Table 1 and Table 2). Plasma samples for analysis of IMO-2125 concentrations will be collected from subjects in Arm B only. Samples for IMO-2125 analysis will be collected pre-dose and at 1, 2, and 4 hours post-dose at Week 1 and Week 11.

Detailed instructions and materials for all blood sampling will be provided in a separate study manual and kits.

14. EXPLORATORY ASSESSMENTS

14.1. Tumor Biomarkers

The RNA from optional biopsies obtained from the subjects will have NanoString analyses performed using the NanoString nCounter® system for identification of putative prognostic and predictive biomarkers. The nCounter® PanCancer Immune panel measures 770 genes representing 24 different immune cell types and 30 common cancer antigens. The assessment of tumor genetic markers will be used to identify gene patterns that might be correlated to clinical response and gene pattern changes after IMO-2125 treatment compared to untreated samples (where available). Putative biomarker(s) of response identified from these samples may be applicable for other tumor types.

14.2. Anti-Drug Antibodies

The development of antibodies to IMO-2125 and ipilimumab will be assessed in subjects at the timepoints indicated in the Schedule of Evaluations (Table 1 and Table 2).

15. STATISTICAL ANALYSIS METHODS

15.1. Determination of Sample Size

In this study, ORR and OS comprise a primary endpoint family; both have a priori hypotheses and will be tested for statistical significance. ORR will be tested first followed by OS. The fallback method for the primary endpoint family will be applied to control the study-wise Type I error rate. Under the fallback method, $\alpha_1 = 0.02$ is assigned to the one-sided ORR test and an alpha of 0.005 is saved for the one-sided OS test. If the ORR test is significant at $\alpha_1 = 0.02$, this alpha is unused and will be passed to the OS test as an additional alpha of 0.02, giving a total alpha for the OS test of 0.025.

With 454 subjects randomized with a 1:1 ratio, this test will have 90% statistical power (calculated based on chi-square test) to demonstrate an increase in the ORR from the postulated response of 12% for ipilimumab alone in this setting to 24% for the IMO-2125 + ipilimumab combination, at a 0.02 level of significance.

A sample size of 454 subjects provides 90% power to test the alternative hypothesis of hazard ratio (HR) for OS ≤ 0.677 at an α of 0.005 (one-sided). The HR of 0.677 corresponds to an improvement in the median survival from 11.4 months (the historical control for ipilimumab alone) to 16.9 months with the IMO-2125 + ipilimumab combination. The OS analysis will be performed when 392 deaths are reached.

The OS power calculations are based on log-rank test and assume that the trial will have ~20 months of uniform accrual, an overall study duration up to 56 months, and a 10% drop-out rate. If under the fallback method a total alpha of 0.025 is available for the OS significance test, then this test will have 90% power to test the alternative hypothesis of HR ≤ 0.72 at an α of 0.025 (one-sided) which corresponds to an improvement in the median survival from 11.4 months (the historical control for ipilimumab alone) to 15.8 months with the IMO-2125 + ipilimumab combination.

15.2. Analysis Populations

15.2.1. Screened Population

The Screened Population consists of all subjects who provided written informed consent and who undergo study screening procedures.

15.2.2. Intent-to-Treat Population

The Intent-to-Treat (ITT) Population comprises all subjects in the Screened Population who were randomized. This population will be analyzed using the treatment to which the subject was randomized regardless of the treatment actually received and will be the primary analysis set for efficacy analyses. Any subject who receives a treatment randomization number will be considered to have been randomized.

15.2.3. Safety Population

The Safety Population comprises all subjects in the ITT Population who receive at least one dose of study treatment and will be based on the actual treatment received.

15.2.4. Pharmacokinetic Population

The PK Population comprises all subjects who receive at least one dose of IMO-2125 with at least one measurable concentration of IMO-2125.

15.3. Missing Data

Missing data occurs when any requested data is not provided, leading to blank fields on the collection instrument. These data will be indicated by the use of a "blank" in subject listing displays. Answers such as "Not applicable" and "Not evaluable" are not missing.

All available OS, PFS, and duration of response data will be analyzed using suitable statistical methods; subjects with shorter treatment and follow-up due to the natural history of their disease, or medical necessities of the treatment of their disease will not be considered to have missing time-to-event data. For ORR and DRR, all subjects in the ITT population will be included in the denominator when calculating the percentages; that is, the imputed response will be negative. Missing QoL data from the EORTC QLQ-C30 will be imputed using the methods prescribed for EORTC QLQ instruments.

Subjects with the designation of treatment relationship for AEs and SAEs missing will have the worst case assumed to impute the relationship: if relationship to study treatment is missing it will be assumed to be "Yes".

Partial dates will be imputed for AEs and concomitant medications. Imputed dates are will not be used for deriving the last contact date for OS. Imputed dates will be displayed in listings and identified as imputed. Full details of imputing missing data and rules for analysis of measures with missing data will be included in the Statistical Analysis Plan (SAP).

15.4. Analysis of Efficacy

In this study, ORR and OS comprise a primary endpoint family; both have a priori hypotheses and will be tested for statistical significance. ORR will be tested first followed by OS. The fallback method for the primary endpoint family will be applied to control the study-wise Type I error rate.

Under the fallback method, $\alpha_1 = 0.02$ is assigned to the one-sided ORR test and an alpha of 0.005 is saved for the one-sided OS test.

- If the ORR test is significant at $\alpha_1 = 0.02$, this alpha is unused and will be passed to the OS test as an additional alpha of 0.02, giving a total alpha for the OS test of 0.025. The OS test will then be performed at the significance level of 0.025.

- If the ORR test is not significant at 0.02 level, then this alpha of 0.02 will not be available to be passed on for the OS test. The OS test will be performed at the originally reserved alpha of 0.005.

Full details of all efficacy analyses will be in the SAP. All efficacy analyses will use the ITT Population.

15.4.1. Analysis of the Family of Primary Endpoints

15.4.1.1. Analysis of Objective Response Rate

The analysis of ORR (assessed by blinded independent review using RECIST v1.1) will be performed using a CMH test comparing the ORR for the two treatment groups controlling for the randomization strata. This is the only test of RECIST v1.1 ORR that will be done. The analysis of ORR will take place when all randomized subjects fall within one of the following categories:

- completed scheduled study treatment and completed at least 28 weeks on the study;
- prematurely discontinued study treatment and completed at least 28 weeks on the study;
- withdrew, were lost to follow-up, or died before completing at least 28 weeks on the study.

15.4.1.2. Primary Analysis of Overall Survival

Overall survival, defined as the time in months from randomization to death from any cause, will be analyzed using the Kaplan-Meier method after approximately 392 deaths have occurred, or approximately 36 months after the last subject is randomized, whichever occurs first. Sensitivity analyses will be detailed in the SAP.

The study hypotheses will be tested using a one-sided, stratified log-rank test. If the null hypothesis is rejected at the appropriate alpha level in accordance with the fallback method, it will be concluded that OS in the IMO-2125 + ipilimumab combination arm is statistically significantly superior to the OS in the ipilimumab alone arm.

Stratification factors will include duration of prior anti-programmed death receptor-1 (PD-1) therapy (≥12 weeks vs <12 weeks), metastasis stage (M1c vs other), and BRAF mutation status and prior targeted therapy (BRAF wild type, BRAF mutation positive with prior targeted therapy, or BRAF mutation positive with no prior targeted therapy) using block randomization. Targeted therapy is the use of an approved BRAF or MEK inhibitor alone or in combination. Stratification will use block randomization. Depending on the distribution of the strata with the ITT, strata may be collapsed as appropriate. The full details will be specified within the SAP.

Subjects who have not died or who are lost to follow up at the data cut-off date will be censored at the last date they were known to be alive.

15.4.2 Analysis of Secondary Efficacy Endpoints

The ORR assessed by investigator assessment using RECISTv1.1 will be summarized descriptively by treatment arm. ORR will be estimated at each level of the stratification factors.

Duration of response (DoR) by blinded independent review and investigator assessment using RECIST v1.1, measured from the time that criteria are first met for CR or PR (whichever is first recorded) until the first date that recurrent or progressive disease is objectively documented, will be summarized descriptively by the Kaplan-Meier method. If supported by the data, quartiles with corresponding 95% two-sided confidence intervals will be reported. There will be no statistical tests of DoR.

Durable response rate, defined as CR or PR lasting ≥6 months with onset during the first 12 months of treatment, will be estimated for the subjects with at least a PR using the same methods as for ORR. The DRR will be reported for both blinded independent review and investigator assessment using RECIST v1.1. There will be no statistical tests of DRR.

Time to response (TTR), defined as time to a CR or PR (using RECIST v1.1) measured from the date of randomization, by blinded independent review and investigator assessment will be summarized descriptively. There will be no statistical tests of TTR.

Progression-free survival, defined as the time from randomization to disease progression or death from any cause, will be assessed using RECIST v1.1 by blinded independent review and investigator assessment and estimated by the Kaplan-Meier method. Quartiles with corresponding 95% two-sided confidence intervals will be reported. There will be no statistical tests of PFS. Subjects who do not have a PFS event at the time of an analysis, including those who have started new anticancer therapy, withdrawn from the study, or been lost to follow-up without disease progression, will be censored at the date of the last valid disease assessment, defined as the latest assessment at which the subject had progressed RECIST v1.1 response of CR, PR, or stable disease.

In addition, PFS by blinded independent review and investigator assessment using RECIST v1.1 and OS will be estimated at 1 and 2 years. Overall survival will be estimated at each level of the stratification factors.

Amounts and patterns of missing PRO data from the EORTC QLQ-C30 instrument in the two arms will be described using counts and percentages and with appropriate figures. Scores and changes from baseline in scores will be reported by visit. A mixed model for repeated measures data will be used with treatment arm and stratification factors (as used in the primary analysis of OS) included as independent variables. There will be no statistical tests of EORTC QLQ-C30 data; all analyses will be descriptive.

15.5. Analysis of Safety

All safety analyses will use the Safety Population.

All safety measures, including vital signs, laboratory values, ECOG performance status, and ECG values will be summarized descriptively; no formal statistical hypotheses will be tested.

For laboratory values that are continuous, shift tables from baseline by scheduled visit and to worst case on study will be produced. Worst case will be relative to the normal range for laboratory values that are not in the CTCAE; otherwise, the worst case will be the highest CTCAE grade. For laboratory values that are bi-directional, separate shift summaries will be produced; for example, for shifts in CTCAE grade, both hypokalemia and hyperkalemia shifts will be shown. Only scheduled visits will be included in the shift tables by visit; all visits will be included when determining the worst case on study.

Adverse events will be tabulated by Medical Dictionary for Regulatory Activities (MedDRA) System Organ Class and Preferred Term for each treatment arm. Adverse event summaries will include: overall, by severity, related AEs, SAEs, irAEs, and AEs leading to discontinuation of study treatment.

Concomitant medications will be coded by World Health Organization drug class and Anatomical Therapeutic Chemical text and summarized by treatment arm.

15.6. Analysis of Pharmacokinetics

Plasma concentration of IMO-2125 will be monitored for subjects in Arm B at Weeks 1 and 11. Plasma concentration data will be summarized using descriptive statistics.

The relationship between PK parameters, safety, efficacy, and pharmacodynamics variables will be explored whenever possible in analyses independent from this protocol. Complete details of the analyses of plasma IMO-2125 concentrations will be given in a separate PK SAP.

15.7. Analysis of Patient-Reported Outcomes

Patient-reported outcomes will be assessed using the EORTC QLQ-C30. The number and percentage of subjects with each pattern of missing PRO data will be described for each treatment arm. Changes from baseline in PRO scores will be summarized by visit and treatment arm. If supported by the data, changes from baseline will be described using a mixed model for repeated measures. Analyses will be prioritized by the most important patient-reported symptoms and functional impacts (i.e., physical function) that are responsive to treatment.

All analyses of PRO data will be descriptive. Full details of the analysis of PRO data will be in the SAP.

15.8. Exploratory Analyses

Ribonucleic acid from optional biopsies will be subjected to NanoString analysis. NanoString nCounter system is used for identification of putative prognostic and predictive biomarker. The nCounter PanCancer Immune panel is comprised of 770 genes representing 24 different immune cell types and 30 common cancer antigens. Exploratory analysis will identify gene patterns associated with clinical response as well as gene pattern changes after IMO-2125 treatment compared with untreated samples (where available).

Full details of the analyses of exploratory data will be described in a separate biomarker SAP.

16. DATA COLLECTION

16.1. Required Data

The full study dataset will be collected for all randomized subjects.

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

16.2. Data Collection and Tracking

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

Laboratory and ECG data from the Screening Visit through the Active Follow-up Period will be collected at the participating site. Central Laboratories may be used to track and analyze the complement, PK, and anti-drug antibody testing.

Site staff will enter data into an eCRF. The frequency and procedures for the handling of data within the clinical database will be documented in detail in the Data Management Plan.

17. ADDITIONAL STUDY RESPONSIBILITIES

17.1. 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 (or its designees) and the IRB in writing regarding the type of emergency and the course of action taken.

17.2. 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.

17.3. Training

The training of appropriate clinical site personnel will be the responsibility of Idera or its designees. 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, Idera or its designees 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 Idera or its designees in the course of regular site monitoring.

17.4. Monitoring the Investigational Site

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

17.5. 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 subject 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 federal, state, and local laws, rules, and regulations; and, for each subject 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.

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 Idera and its designees (if applicable) 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 or responsible government agencies as required by law. The Investigator agrees to promptly take any reasonable steps that are requested by Idera or its designees as a result of an audit to cure deficiencies in the study documentation and eCRFs.

17.6. 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, subject diaries, biopsy reports, ultrasound photographs, subject 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 subject'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 subject before involvement in the study sufficient to verify protocol entry criteria
2. Medical record documenting that informed consent was obtained for the subject's participation in the study
3. Dated and signed notes for each subject 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. Subject's condition upon completion of or withdrawal from the study

17.7. 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.

17.8. Study Supply Accountability

The Investigator will maintain complete and accurate records of the receipt and disposition of all investigational agents. During the study, used, unused, or expired study drug vials may be destroyed according to local practice. When the enrollment is complete, the Investigator will be notified by Idera and, in a timely manner, will destroy the remaining study drug in a documented fashion, as directed by Idera. Please refer to the Pharmacy Manual for details about study drug accountability and destruction.

17.9. 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 subject visit or the availability of test results. All completed eCRFs will be reviewed 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 that records may be destroyed.

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

The Investigator must obtain written permission from Idera or its designees before disposing of any records. In order to avoid any possible errors, the Investigator will contact Idera or its designees prior to the destruction of any study records. The Investigator will promptly notify Idera or its designees in the event of accidental loss or destruction of any study records. If the Investigator relocates, retires, or for any reason withdraws from the study, the study records may be transferred to an acceptable designee, such as another Investigator, another institution, or to Idera or its designees.

17.10. Study Closeout

Upon completion of the study (defined as all subjects have completed all follow-up visits, all eCRFs are complete, and all queries have been resolved), Idera or its designees 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 or its designees. 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 of study closure.

17.11. Audit/Inspections

The designated Idera or its designee's quality assurance personnel 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 also audit the Investigator during or after the study. The Investigator should contact Idera immediately if this occurs and must fully cooperate with governmental audits conducted at a reasonable time in a reasonable manner.

18. ETHICAL CONSIDERATIONS

By signing this protocol, the Investigator agrees to conduct the study in compliance with the protocol, the 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.

18.1. Role of Sponsor

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

18.2. Informed Consent

The Investigator has both ethical and legal responsibility to ensure that each subject being considered for inclusion in this study is given a full explanation of the study. Written informed consent will be obtained from all subjects (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 informed consent form (ICF) approved by the same Independent Reviewing Authority (IRA) 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 of any ICF intended for use in the study, prior to submission for IRB approval.

The ICF will be reviewed with the prospective study subject 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 subject and fully explained by the Investigator or qualified designee, and it is felt that the subject understands the implications of participating, the subject and the Investigator or designee will sign and date the IRB-approved written ICF. The subject 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 subject's informed consent for and participation in this study will be noted in the subject's medical record.

If the subject is illiterate, an impartial witness is required to be present during the entire informed consent reading and discussion. Afterward, the subject 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 subject 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 subject's willingness to continue participation in the trial. The communication of this information to the subject will be documented.

18.3. Confidentiality of Subjects

The Investigator and his/her staff will be required to manage subject data collected for the study in accordance with applicable laws and regulations on personal data protection.

Monitors, auditors, and other authorized representatives of Idera, the IRA approving the study, as well as any applicable regulatory authorities, will be granted access to the study subject's original medical records for permitted study purposes, in accordance with applicable laws and regulations. In any presentation of study results at meetings or in publications, subject identity will remain confidential.

18.4. Institutional and Ethics Review

This protocol and a subject 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 subjects and release of investigational product. Documentation of IRB/EC approval and the approved consent form must be received by Idera or its designees prior to obtaining the subject'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. Any updates to the protocol by means of protocol amendment that impacts patient safety or changes the interpretation of scientific documents in support of conduct of the trial will be submitted as substantial amendment to competent authorities and health agencies in all countries where trial is open.

18.5. 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 subjects will disclose the following information for the time period during which the Investigator is participating in the study and for 1 year following completion of the study:

1. Any financial arrangement entered into between Idera and the Investigator whereby the value of the compensation to the Investigator for conducting the study could be influenced by the outcome of the study.
2. Any other significant payments totaling > $10,000.00, exclusive of the costs of conducting this or other clinical studies, by Idera, such as a grant to fund ongoing research, compensation in the form of equipment, retainer for ongoing consultation, or honoraria.
3. Any proprietary interest held by the Investigator in the product being evaluated.

Any significant equity interest in Idera, including ownership interest, stock options, or other financial interest whose value cannot be determined through reference to public prices that exceeds $10,000.

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20. APPENDICES

20.1. ECOG

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

20.2. 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.

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 1: 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 2: Objective Response Status at Each Evaluation for Subjects 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

20.3. The use of irRECIST (Immune-Related Response Evaluation Criteria in Solid Tumors) in this study

Throughout the study, subject management will be performed according to irRECIST (with the modification described below). irRECIST is based on the established RECIST (see Section 20.2) with changes that have been recommended as being better suited for assessing response to immunotherapeutic agents (Nishino, 2013; Bohnsack, 2014). irRECIST differs from conventional RECIST in that the development of new lesions is not automatically scored as PD, since atypical response patterns can occur. This reduces the risk of declaring a treatment to be ineffective based upon "pseudoprogression," as has been well-documented for other immunotherapies (Hodi, 2016; Wolchok, 2009).

Blinded central reviewers will assess tumor response rates using irRECIST with modifications according to Appendix Table 3. In this study, irRECIST is modified as follows:

For purposes of determining progression based solely on worsening of non-target or new, non-measurable disease, "substantial, unequivocal worsening" requires confirmation by an additional scan (at least 4 weeks apart) unless it is accompanied by correlative symptoms.

Appendix Table 3: Objective 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