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Statistical Analysis Plan

Sponsor Idera Pharmaceuticals, Inc.

Protocol Number: 2125-204

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

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Approval

Upon review of this document, including table, listing, and figure shells, the undersigned approves the Statistical Analysis Plan. The analysis methods and data presentation are acceptable.

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LIST OF ABBREVIATIONS

δ	Dose-limiting toxicity rate
ADaM	Analysis data model
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
CH50	Total hemolytic complement activity 50
CL/F	Clearance
C_{max}	Maximum plasma concentration
CR	Complete response
CRC	Cohort Review Committee
CS	Clinically significant
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTLA-4	Cytotoxic T lymphocyte antigen-4
DCR	Disease control rate
DLT	Dose-limiting toxicity
DoR	Duration of response
DRR	Durable response rate
ECG	Electrocardiogram

List of abbreviations continued

ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
EE	Efficacy Evaluable
FDA	Food and Drug Administration
ICH	International Council for Harmonisation
IMO	Immune Modulatory Oligonucleotide
irAE	Immune-related adverse event
irRC	Immune-related response criteria
irRECIST	Immune-related reponse evaluation criteria solid tumors
ISR	Injection site reaction
LFT	Liver function test
MLE	Maximum Least-square Estimation
MTD	Maximum tolerated dose
NCI	National Cancer Institute
ORR	Objective response rate
OS	Overall survival
PD	Progressive disease
PFS	Progression-free survival
PI	Principal Investigator
PK	Pharmacokinetic
PR	Partial response
Pr	Probability
PRO	Patient reported outcome
PT	Prothrombin time
RBC	Red blood cell
RP2D	Recommended Phase 2 dose

SAE	Serious adverse event
SD	Stable disease
ULN	Upper limit of normal
WBC	White blood cell

DEFINITIONS

Adverse Event	An adverse event (AE) is any reaction, side effect, or other untoward event, regardless of relationship to study drug, which occurs anytime during the study.
DLT Evaluable Population	All subjects in the Safety Population who continue participation in the study for the entire DLT evaluation period, or who discontinue prematurely due to a DLT.
DLT Evaluation Period	The DLT evaluation period will be Cycle 1 (Weeks 1 through 4).
Safety Population	All subjects who received at least one dose of IMO-2125.
Serious AE	An AE occurring at any dose that: results in death; is a life-threatening experience; requires hospitalization or prolongation of an existing hospitalization; results in a persistent or significant disability/incapacity; or is a congenital anomaly/birth defect in the offspring of a subject who received study drug; or important medical event that, although not immediately life-threatening, requires intervention in order to prevent one of the listed serious outcomes listed.
Study Drug	IMO-2125 in combination with ipilimumab or pembrolizumab
Treatment-emergent AE	AEs with an onset date on or after the date of the initial dose of study drug, or an AE that worsens after the date of the initial dose of study drug.

1. INTRODUCTION

This document outlines the statistical methods to be implemented during the analyses of data collected within the scope of Idera Protocol Number: 2125-204 [A Phase 1/2 Study to Assess the Safety and Efficacy of Intratumoral IMO-2125 in Combination with Ipilimumab or Pembrolizumab in Subjects with Metastatic Melanoma]. The purpose of this plan is to provide specific guidelines from which the statistical analyses will proceed. Any deviations from this plan will be documented in the clinical study report (CSR).

2. STUDY OBJECTIVES

2.1 Primary Objective

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

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

2.2 Secondary Objectives

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

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

2.3 Exploratory Objectives

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

3. STUDY DESIGN AND PLAN

3.1 Overview

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

3.1.1 Phase 1

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

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

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

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

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

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

Each cohort will be monitored for the occurrence of DLTs. The DLT evaluation period will be Cycle 1 (Weeks 1 through 4). If a subject discontinues study participation before the DLT evaluation period is finished due to reasons other than experiencing a DLT, that subject must be replaced so that the cohort may be properly evaluated. More information about the review of DLTs and the escalation of dose levels between cohorts is provided in Section 3.1.3, Section 3.1.4, and Section 3.1.5.

There are 3 subjects planned per cohort. During Phase 1, the sponsor will assign subjects to a treatment arm (IMO-2125 + ipilimumab or IMO-2125 + pembrolizumab) by cohort.

After completing the DLT evaluations for all planned IMO-2125 doses in either combination, supplemental cohorts of up to 5 subjects each may be enrolled with either combination at doses up to and including the MTD. After completion of either Phase 1 treatment arm and determination of the RP2D for that arm, the Phase 2 portion for the

completed treatment arm may be initiated. It is not necessary for Phase 1 to be completed in both treatment arms before Phase 2 is started.

3.1.2 Phase 2

The Phase 2 portion of the study will assess preliminary efficacy, using investigator-assessed RECIST v1.1, of IMO-2125 + ipilimumab, IMO-2125 + pembrolizumab, and any additional combinations that are studied in Phase 1. The dose level of IMO-2125 to be administered for each treatment arm will be the RP2D for the combination, as determined in Phase 1. Phase 2 will enroll up to 60 subjects treated at the IMO-2125 + ipilimumab RP2D. This will include at least 21 subjects in the primary IMO-2125 + ipilimumab efficacy-evaluable population and up to 20 subjects in the secondary IMO-2125 + ipilimumab efficacy-evaluable population. In the IMO-2125 + pembrolizumab Phase 2 cohort, enrollment will continue until 21 subjects in the IMO-2125 + pembrolizumab efficacy-evaluable population have been treated at the the IMO-2125 + pembrolizumab RP2D. Phase 1 subjects treated at the RP2D for either combination may contribute to these totals. A two-stage design will be used to test for clinically and statistically relevant clinical activity. A treatment arm will stop if an interim futility analysis shows there is insufficient evidence of a clinically relevant response rate after 10 subjects (Stage 1).

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

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

3.1.3 Dose Escalation and Stopping Rules

Up to five dose levels for IMO-2125 are initially planned (**Table 2**).

Table 2: Treatment Doses to be investigated

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

In Phase 1, the study will enroll subjects in planned cohorts of 3, beginning at Dose Level +1 for the ipilimumab treatment arm and beginning at Dose Level +2 for the pembrolizumab treatment arm once safety of the IMO-2125 + ipilimumab combination has been established for that level.

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

The MTD will be determined from the assessment of DLTs during the first treatment cycle of each cohort (Section 3.1.5). Using a prior beta(1,1) distribution of the DLT rate δ_i for each dose level i, the MTD is defined as the highest dose level for which the mean of the posterior distribution of toxicity is closest to 25% among all the evaluated doses i for which Pr ($\delta_i > 0.25$ | data) < 0. 80.

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

3.1.3.1 Phase 2 Stopping Rules

Additional subjects will be enrolled at the RP2D level(s) established in the Phase 1 portion of the study for a total of approximately 90 to 100 subjects enrolled in the study. DLTs will be continuously monitored throughout the study. Assuming a prior beta (0.6, 1.4) distribution for the overall toxicity rate for a treatment, a Phase 2 arm will terminate if the Pr ($\delta_t > 0.25$ | data) > 0.80, where δ_t is the DLT rate attributable to the treatment. The decision rule for terminating due to toxicity is presented in **Table 3**. The method used to produce the decision rule and operating characteristics was designed by Thall (2006).

Table 3: Phase 2 Stopping Boundaries

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

3.1.4 Cohort Review Committee

The CRC composition and duties are described in a separate Charter. A CRC meeting will be convened to review all safety data and decide whether DLTs were observed. Based on the CRC's adjudication of DLTs observed in a cohort, they will guide decisions on the dose level that the subsequent cohort will be administered.

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

3.1.5 Definition of Dose-limiting Toxicities

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

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

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

Protocol-defined hematologic DLTs include:

CTCAE Grade 4 neutropenia ≥ 7 days;

CTCAE Grade 3 or 4 neutropenia with fever ≥ 38.5°C;

CTCAE Grade 3 thrombocytopenia with bleeding;

CTCAE Grade 4 thrombocytopenia ≥7 days.

Protocol-defined non-hematologic DLTs include:

Grade ≥3 vomiting or nausea ≥ 14 days despite the use of optimal anti-emetic treatments;

Grade ≥3 diarrhea ≥ 14 days despite the use of optimal anti-diarrheal treatments which should include infliximab as per institutional guidelines;

Serum creatinine > 3.0 x ULN;

AST or ALT > 5 x ULN; in subjects with liver metastasis who entered the study with Grade 2 elevation of AST or ALT, an AST or ALT increase ≥50% relative to baseline and lasting ≥1 week;

Bilirubin ≥ 3.0 x ULN;

Bilirubin ≥ 2.0 x ULN with ALT > 3 x ULN in subjects without liver metastases;

Other non-hematologic toxicities of Grade ≥3, except for the following:

AEs related to underlying disease;

CTCAE Grade 3 fatigue < 14 days;

Alopecia;

Isolated, asymptomatic elevations in biochemistry laboratory values lasting ≤ 14 days. This includes electrolyte abnormalities that respond to medical intervention.

Ipilimumab-related DLTs:

Grade ≥4 immune-mediated dermatitis (except skin reaction at site of injection);

Grade ≥3 immune-mediated endocrinopathy (with the exception of Grade 3 autoimmune thyroiditis that resolves to Grade 1 or baseline within 28 days of onset);

Grade ≥3 immune-mediated enterocolitis;

Grade ≥3 immune-mediated hepatitis with the exception of Grade 3 immune-mediated hepatitis that resolves to Grade 1 or baseline within 28 days of onset;

Grade ≥3 immune-mediated neuropathy, pancreatitis, meningitis, nephritis, and pneumonitis that are considered to be possibly, probably, or definitely related to study therapy as determined by the Investigator;

Any persistent IMO-2125-related toxicity that leads to a delay of scheduled (per standard of care) ipilimumab > 14 days.

Pembrolizumab-related DLTs:

Grade ≥3 pneumonitis or recurrent Grade 2 pneumonitis;

Grade ≥3 nephritis;

Grade ≥3 infusion-related reactions;

Inability to reduce corticosteroid dose to 10 mg or less of prednisone or equivalent per day within 12 weeks;

Any Grade ≥3 treatment-related AE that recurs.

If at any time during the study, a subject experiences a DLT as outlined above, the toxicity in question must be assessed for attribution based on the known toxicity profiles for ipilimumab, pembrolizumab, and IMO-2125. If assessment can be clearly attributed to one of the drugs in the combination, then dosing should be interrupted and the toxicity should be followed until resolution, stabilization, or return to baseline. Treatment with the other agent may continue during this time period. If attribution cannot be clearly ascribed to one agent versus the other, then both IMO-2125 and ipilimumab (or pembrolizumab) should be stopped and the toxicity should be followed until resolution, stabilization, or return to baseline. If treatment is to be resumed, then re-initiation criteria must be met. If the DLT was clearly related to IMO-2125 or if attribution cannot be clearly determined, then IMO-2125 must be administered at a lower dose level (a minimum reduction of at least 1 dose level). If the DLT recurs after a dose level reduction, then treatment should be discontinued.

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

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

ANC must be ≥ 1.5 x 10^9/L (1500/μL);

Platelets must be ≥ 75 x 10^9/L (75,000/μL);

All clinically significant non-hematologic toxicities for which a causal association to study treatment cannot be ruled out must be Grade ≤1 (except alopecia) or returned to baseline.

If the 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 cycle is delayed by more than 21 days for toxicity, the subject should be removed from study treatment. In these situations, if the subject is experiencing clinical benefit and has a favorable risk/benefit profile, study treatment with IMO-2125 may be continued if agreed upon by the Sponsor and the Investigator.

3.1.6 Safety Assessment for Immunologically Related Toxicity

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

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

If more than one subject experiences a Grade ≥3, immune-related adverse event (irAE) in a cohort of 3 subjects;

If more than two subjects experience a Grade ≥3 irAE in cohorts of 6 subjects.

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

3.2 Duration of Study

3.2.1 Treatment Duration

The study treatment period is 29 weeks (as per Table 1) in the absence of intolerable toxicity or unequivocal disease progression. Continued treatment with pembrolizumab

following the completion of study treatment is at the discretion of the Investigator for subjects in the IMO-2125 + pembrolizumab treatment arm.

3.2.2 Study Duration and Study Completion

The study ends approximately 1 year after the last subject in Phase 2 has commenced study treatment. Subjects who complete or discontinue study treatment prior to progression will be followed for clinical and radiological evidence of progression and immunogenicity assessment at least every 3 months until documentation of RECIST v1.1 progressive disease (PD), start of a subsequent anti-cancer treatment regimen, withdrawal of consent, death, or Sponsor notification that follow-up is no longer required, whichever comes first. Best response to first subsequent therapy, AEs which are Grade ≥3, and concomitant medications used to treat these AEs, will also be captured during the follow-up phase of the study (Table 4 and Table 5).

After documentation of PD or use of a subsequent anti-cancer treatment regimen, all subjects will be contacted by telephone every 3 months for a survival follow-up until the site is notified by the Sponsor that survival follow-up is no longer required. A subject has completed the study at the earliest of death or study end.

3.3 Number of Subjects

The study will enroll up to approximately 90 to 100 subjects. It is estimated that approximately 30 subjects will be treated in Phase 1 and approximately 60 to 70 subjects will be treated in the Phase 2 portion of the study.

3.4 Schedules of Evaluations

Table 4: Phase 1: Schedule of Evaluations

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

Week [4]	Screen [5]	Treatment Period (Cycle[1])												Follow-up	
		1			2	3	4			5		6		7	Safety[2]	Ongoing [3] (every 3 months)
		1	2	3	5	8	11	13	14	17	20	23	26	29/EOT	32	
Ipilimumab dosing			X		X	X	X									
Pembrolizumab dosing			X		X	X	X	X	X	X	X	X	X	X	X [22]	X [22]
PK testing [23]		X	X	X	X	X	X			X [24]			X [24]	X [24]	X[24]	
Immunogenicity [25]		X			X		X			X			X	X	X	X[26]

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

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

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

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

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

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

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

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

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

[9] CBC with differential should be done 24 to 48 hours after the IMO-2125 injection, to coincide with the post-injection biopsy. Chemistry profile and coagulation tests do not have to be conducted if Screening tests were conducted within 7 days of the Cycle 1 Week 1 Visit.

[10] PT, aPTT, INR.

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

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

[13] Including assessment of melanoma lesions.

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

[15] Biopsy of the injected tumor should occur within 24 to 48 hours after injection (no more than 48 hours). Collection of blood for biomarkers should occur on Day 1 pre-IMO-2125 administration, 4 hours after IMO-2125

administration, and 24 to 48 hours after injection (coinciding with the 24-hour PK sample). At Week 2, collect before ipilimumab or pembrolizumab dosing.

[16] Optional biopsy.

[17] At Weeks 5 and 8, collect pre-ipilimumab or pre-pembrolizumab dosing and post-IMO-2125 dosing. At Week 29/EOT collect pre-pembrolizumab dosing (for subjects in that arm who have pembrolizumab continued) and post-IMO-2125 dosing. If no ipilimumab or pembrolizumab is given at the specified visit(s) collect the samples pre- and post-IMO-2125 dosing. If no IMO-2125 if given, then collect pre- and post- ipilimumab or pembrolizumab.

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

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

[20] In Phase 1, response assessed using irRC and RECIST v 1.1. Best response to first subsequent treatment should also be captured. Confirmatory scans for CR, PR, and progressive disease should be performed ≥4 weeks after the date the response was first documented.

[21] To minimize bias in the PRO data, the PRO assessments should be completed before study drug administration and AE assessments.

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

[23] PK: blood sampling for analysis of plasma concentrations of IMO-2125 and serum concentrations of ipilimumab, and pembrolizumab (See Table 3 of the protocol for specific collection times).

[24] For patients who continue pembrolizumab treatment, pembrolizumab pre-dose PK samples should be collected before dosing at all visits. A post-dose pembrolizumab PK sample should be collected 30 minutes after initiation of pembrolizumab infusion at Week 23. Pharmacokinetic samples at Week 33 are optional.

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

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

Table 5: Phase 2 Schedule of Evaluations

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

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

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

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

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

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

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

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

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

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

[9] CBC with differential should be done 24 to 48 hours after the IMO-2125 injection, to coincide with the post-injection biopsy (if the biopsy is conducted). Chemistry profile and coagulation tests do not have to be conducted if Screening tests were conducted within 7 days of the Cycle 1 Week 1 Visit.

[10] PT, aPTT, INR.

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

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

[13] Including assessment of melanoma lesions.

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

[15] Biopsy of the injected tumor should occur within 24 to 48 hours after injection (no more than 48 hours).

[16] In Phase 2, blood biomarker samples will be collected from at least 20 patients treated at the IMO-2125 RP2D after which the Sponsor will determine if additional samples are needed. The blood biomarker samples will be collected on Day 1 before IMO-2125 administration, 4 hours after IMO-2125 administration, and 24 to 48 hours (coinciding with the 24-hour PK sample) after the injection. At Week 2 and Cycle 3 Week 8, collect before ipilimumab or pembrolizumab dosing.

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

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

[19] In Phase 2, response assessed using irRECIST and RECIST v 1.1. Best response to first subsequent treatment should also be captured. Confirmatory scans for CR, PR, and progressive disease should be performed ≥4 weeks after the date the response was first documented.

[20] To minimize bias in the PRO data, the PRO assessments should be completed before study drug administration and AE assessments.

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

[22] PK: blood sampling for analysis of plasma concentrations of IMO-2125 and serum concentrations of ipilimumab, and pembrolizumab (See **Error! Reference source not found.**Table 3 of the protocol for specific collection

times). For each combination in Phase 2, the collection of plasma concentration samples will be done on at least 20 patients treated at the IMO-2125 RP2D after which the Sponsor will determine if additional samples are needed.

[23] For patients who continue pembrolizumab treatment, pembrolizumab pre-dose PK samples should be collected before dosing at all visits. A post-dose pembrolizumab PK sample should be collected 30 minutes after initiation of pembrolizumab infusion at Week 23. Pharmacokinetic samples at Week 33 are optional.

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

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

Table 5.1: Schedule of PK Blood Sampling for IMO-2125, Ipilimumab, and Pembrolizumab

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

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

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

4. DETERMINATION OF SAMPLE SIZE

The primary objective of Phase 2 is to assess the preliminary clinical activity, defined as the investigator assessed RECIST v1.1 ORR, of IMO-2125 in combination with ipilimumab or of IMO-2125 in combination with pembrolizumab in subjects with progression on or following PD-(L)1 therapy for metastatic melanoma. Given that two primary hypotheses are being tested (regarding the ORR of IMO-2125 and ipilimumab and the ORR of IMO-2125 and

pembrolizumab), a Bonferroni correction has been applied to the alpha to control for Type I error for the trial.

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

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

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

5. GENERAL ANALYSIS CONSIDERATIONS

The statistical analyses will be reported using summary tables, listings, and figures (TLFs). The International Conference on Harmonisation (ICH) numbering convention will be used for all TLFs. Unless otherwise noted, all statistical testing will be one-sided and will be performed at the 0.025 significance level. Tests will be declared statistically significant if the calculated p-value is less than or equal to the significance level of the test, usually 0.025. Continuous variables will be summarized with means, standard deviations, medians, minimums, and maximums. For continuous variables, descriptive statistics will include the number of non-missing values, mean, standard deviation, median, 25^{th} and 75^{th} percentile, minimum, maximum, and 95% confidence intervals (CIs) as appropriate. All durations will be reported in months.

For categorical variables, descriptive statistics will include counts and percentages per category. Statistics describing time-to-event variables will use the Kaplan-Meier method. Individual subject data obtained will be presented by subject in data listings. Dose group will be used to identify the dose and study treatment cohort in the Phase 1 portion of the trial; treatment arm will identify the treatment arm in the Phase 2 portion of the study. All analysis will be done using these descriptors.

The analyses described in this plan are considered *a priori*, in that they have been defined prior to database lock. All analyses and tabulations will be performed using SAS® Version 9.2 or higher. Tables and listings will be presented in RTF format. All SAS® programs will be validated by an independent programmer. In addition, all program output will undergo a senior level statistical review. The validation process will be used to confirm that statistically valid methods have been implemented and that all data manipulations and calculations are accurate. Checks will be made to ensure accuracy, consistency with this plan, consistency within tables, and consistency between tables and corresponding data listings. Upon completion of validation and quality review procedures, all documentation will be collected and filed by the project statistician or designee.

6. ANALYSIS POPULATIONS

The following analysis population will be used for safety analyses:

- Safety Population: all patients who received at least one dose of IMO-2125.

The following analysis population will be used only for Cohort Review Committee meetings to determine if the dose may be escalated.

- DLT Evaluable Population: all patients in the Safety Population who continue participation in the study for the entire DLT evaluation period, or who discontinue prematurely due to a DLT.

The following analysis populations will be used for efficacy analyses:

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

7. STUDY POPULATION

7.1 Subject Disposition

Subject disposition will be summarized for all subjects. Summaries will include: the number of subjects screened, the number of enrolled subjects, the number of subjects in each analysis population, the number of subjects completing or withdrawing from the study, and the primary reason for discontinuation.

7.2 Protocol Deviations

Major protocol deviations will be summarized by deviation category and treatment group. All protocol deviations will be listed.

7.3 Demographic and Baseline Characteristics

Demographic variables include: age, sex, ethnicity, and race. Age will be calculated in years relative to the informed consent date. Other baseline characteristics include: medical history, baseline melanoma disease characteristics, selected previous melanoma treatment, height, weight, body mass index (BMI), etc. Descriptive statistics will be presented for demographic and baseline characteristics for the Safety Population.

7.4 Concomitant Medications

Concomitant medication verbatim terms on electric case report forms (eCRFs) will be mapped to Anatomical/Therapeutic/Chemical (ATC) class and Preferred Names using the World Health Organization (WHO) Drug Dictionary Enhanced (version March 1, 2015).

Concomitant medications will be summarized for each dose group as well as for all subjects in each treatment arm by WHO ATC class and preferred name. These summaries will present the number and percentage of subjects using each medication. Subjects may have more than one medication per ATC class and preferred name. At each level of subject summarization, a subject is counted once if he reported one or more medications at that level. Each summary will be ordered by descending order of incidence of ATC class and preferred name within each ATC class.

Any concomitant medications identified as sensitive and narrow therapeutic range CYP substrates will be listed including any adverse event(s) that started during the duration of the IMO-2125 treatment. The medications of interest are as follows:

Drug Category	Preferred Term
Sensitive CYP3A4 substrates	budesonide, buspirone, eplerenone, eletriptan, felodipine, fluticasone, lovastatin, midazolam, saquinavir, sildenafil, simvastatin, triazolam, vardenafil
CYP3A4 substrates with a narrow therapeutic range	alfentanil, astemizole(a), cisapride(a), cyclosporine, diergotamine, ergotamine, fentanyl, pimozide, quinidine, sirolimus, tacrolimus, terfenadine(a)
Sensitive CYP1A2 substrates	Alosetron, duloxetine
CYP1A2 substrates with a narrow therapeutic range	theophylline, tizanidine
Sensitive CYP2C8 substrates	repaglinide
CYP2C8 substrates with a narrow therapeutic range	paclitaxel
CYP2C9 substrates with a narrow therapeutic range	phenytoin , warfarin
Sensitive CYP2C19 substrates	omeprazole
CYP2C19 substrates with a narrow therapeutic range	s-mephenytoin
Sensitive CYP2D6 substrates	desipramine
CYP2D6 substrates with a narrow therapeutic range	thioridazine

8. EFFICACY ANALYSES

The primary analysis of efficacy in the Phase 2 IMO-2125 + ipilimumab arm, including the hypothesis test of the ORR, will be performed on the first 21 patients in the PIIEE Population as defined in Section 6. An analysis of those in the SIIEE Population will also be performed; efficacy analysis in the combined PIIEE and SIIEE Population may also be summarized. The primary analysis of efficacy in the Phase 2 IMO-2125 + pembrolizumab arm will be performed on the PPIEE Population as defined in Section 6.

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

8.1 Best Overall Response

The best overall response is the best response across all disease assessment visits after baseline taking into account requirements for confirmation. For any response criteria, the best overall response for each subject will be determined by examining investigator-assessed visit-level responses and determining the best confirmed response using the assignment rules in Section 8.1.1 or Section 8.1.2, as appropriate (Paules et al, 2010). Only visit-level disease assessments prior to the start of new anti-cancer therapy or response per the appropriate criteria will be considered.

8.1.1 Confirmed Response using RECIST v1.1

Table 6 shows how the investigator-assessed Best Overall Confirmed Response is assigned for each subject. The table is based on the Best Overall Response confirmation table in the RECIST v1.1 guidelines (Appendix C).

Table 6: Confirmed Response using RECIST V1.1

Visit-Level Response	Next Visit Level Response	Confirmed Response
CR	CR	**CR** (if visit-level disease assessments are ≥ 28 days apart), otherwise **SD**
CR	PR	**PR** (if visit-level disease assessments are ≥ 28 days apart); otherwise **SD**
CR	SD	**SD**
CR, PR, SD	PD	**SD**
CR, PR	NE	**SD**
PR	CR, PR	**PR (**if visit-level disease assessments are ≥ 28 days apart); otherwise, **SD**
PR	SD	**SD**
SD	SD, CR, PR, PD, NE	**SD**
PD	PD	**PD**
NE	NE	**NE**
CR, PR, SD	No 2nd visit	**SD**
PD	No 2nd visit	**PD**
NE	No 2nd visit	**NE**

CR = complete response, PR = partial response, SD = stable disease, PD = progressive disease, NE = not evaluable.

The minimum interval for confirmation of CR and PR is 28 days. Subjects must have at least one post-baseline disease assessment to be assigned SD as the best overall response; otherwise, there is no minimum interval for assignment of SD as the best overall response. Because scans of target and non-target lesions can be done on different dates, time between disease assessments is determined using the following algorithm: (1) calculate the time in days between initial and confirmatory scans for all target and non-target lesions separately (confirmatory assessment date - initial assessment date +1); (2) select the minimum time; and (3) compare to 28 days to determine if the confirmation criterion were met. Date of confirmed best overall response is determined using scan dates as follows: if BOR is CR or PR response date is the latest date of target or non-target lesion scan date or else use the assessment date.

8.1.2 Best Response at an Interim Analysis using RECIST v1.1

Responses of CR and PR may not have had the opportunity to be confirmed at an interim analysis. Therefore, if a subject has an unconfirmed response (i.e., one visit assessment of CR or PR) as the last disease assessment before an interim analysis, the best response in the interim analysis will be reported as an unconfirmed CR (uCR) or unconfirmed PR (uPR).

8.1.3 Confirmed Response using irRC and irRECIST

Table 7 incorporates the response confirmation rules indicated in the irRC and irRECIST guidelines (see Appendix B and Appendix D).

Table 7 Confirmed Response using irRC or irRECIST

Visit-Level Response	Next Visit-Level Response	Confirmed Response
CR	CR	**CR** (if visit-level disease assessments are $\geq$ 28 days apart), otherwise **SD**
CR	PR	**PR** (if visit-level disease assessments are $\geq$ 28 days apart), otherwise **SD**
CR	SD	**SD**
CR, PR, SD	PD	**SD**
CR, PR	NE	**SD**
PR	CR, PR	**PR** (if visit-level disease assessments are $\geq$ 28 days apart); otherwise, **SD**
PR	SD	**SD**
SD	SD, CR, PR, PD, NE	**SD**
PD	PD	**PD** (if visit-level disease assessments are $\geq$ 28 days apart), otherwise, **NE.**
CR, PR, SD	No 2nd visit	**SD**
PD	No 2nd visit	**NE**
NE	No 2nd visit	**NE**

The minimum interval for confirmation of CR, PR and PD is 28 days. Subjects must have at least one post-baseline disease assessment to be assigned SD as the best overall response; otherwise, there is no minimum interval for assignment of SD as the best overall response. The same algorithm as for RECIST v1.1 criteria will be used to determine time between disease assessments for confirmation of CR, PR, and PD.

In some situations, it may be necessary to check across more than two sequential time points in order to determine whether or not a minimum duration criteria has been met. The same logic as used for the pairs of time points should be applied. For example, note the following examples.

- For the triplet CR NE CR, if the minimum criteria for CR duration is met for the interval between the two CR assessments, then **Confirmed Response = CR**. Otherwise **Confirmed Response = SD**.
- For the triplet CR CR CR, if the minimum criteria for CR duration is met for the interval between the first and third CR assessments, then **Confirmed Response = CR**. Otherwise **Confirmed Response = SD**.
- For the triplet PR NE PR, if the minimum interval criteria for PR is met for the interval between the two PR assessments, then **Confirmed Response = PR**. Otherwise **Confirmed Response = SD**.
- For the triplet PR PR PR, if the minimum interval criteria for PR is met for the interval between the first and third PR assessments, then **Confirmed Response = PR**. Otherwise **Confirmed Response = SD**.

For confirmed progression using irRC and irRECIST.

- For the triplet PD NE PD, if the minimum interval criteria for PD is met for the interval between the two PD assessments, then **Confirmed Response = PD**. Otherwise **Confirmed Response = NE**.
- For the triplet PD PD PD, if the minimum interval criteria for PD is met for the interval between the first and third PD assessments but is not met between the first and second PD assessments or between the second and third PD assessments, then **Confirmed Response = PD**. Otherwise **Confirmed Response = NE**.

8.1.4 Derivation of irRECIST Confirmed Response for Phase 1 Subjects Treated at the RP2D

For both combinations, subjects enrolled in the Phase 1 portion of the trial will also be analyzed with the Phase 2 subjects. Therefore, the irRECIST response at each visit, as well as the overall confirmed best response, will be derived. These derived responses will be summarized as described in Section 8.1.3.

Visit 1-Screening:- Derived baseline tumor burden will be the sum of the longest diameters of the lesions that have “Yes” for Baseline Target Lesion. Derived non-target lesions will be all lesions identified on the Non-Measurable Disease Assessment page.

Subsequent disease assessments:- Derived tumor burden will be the sum of the longest diameters of all Baseline Target Lesions and lesions identified as new lesions by “Yes” for “Is this a new lesion?” in the Measurable Disease Assessment page of the eCRF. Derived nadir

tumor burden will be the smallest tumor burden across all previous disease assessments, including baseline. Derived non-target lesions will be all lesions identified on the Non-Measurable Disease Assessment page.

Derived Visit Measurable Response:- Using the derived baseline tumor burden, the percentage change from baseline will be calculated as:

Derived percentage change from baseline:

$$\left[\frac{(Derived\ visit\ tumor\ burden - Derived\ baseline\ tumor\ burden)}{Derived\ baseline\ tumor\ burden}\right] * 100\%$$

Using the derived nadir tumor burdens, the percentage change from nadir will be calculated for subjects with non-zero derived nadir:

Derived percentage change from nadir:

$$\left[\frac{(Derived\ visit\ tumor\ burden - Derived\ nadir\ tumor\ burden)}{Derived\ nadir\ tumor\ burden}\right] * 100\%$$

Subjects who have a value of 0 mm for their derived nadir and a derived tumor burden of at least 5 mm will have a missing derived percentage change from nadir and the derived visit measurable response will be PD. Subjects who have a value of 0 mm for their derived nadir and a derived tumor burden between 0 mm and 5 mm will have a missing derived percentage change from nadir and the derived visit measurable response will be SD. Subjects with a derived nadir of 0 and a derived tumor burden of 0 will have a derived visit measurable response of CR.

Table 8: Measureable Lesion Evaluation

Response	Description of response
irCR	• Complete disappearance of all non-lymph node lesions and no new measurable or non-measurable lesions. • All measurable lymph nodes have diameter <10 mm in short axis.
irPR	• ≥30% decrease in tumor burden from *baseline*.
irSD	• Not meeting criteria for irCR, irPR, or irPD.
irPD	• ≥20% increase in tumor burden from *nadir* and tumor burden≥ 5 mm.

NE	• Assigned if "Unable to evaluate longest diameter" is marked for at least one target lesion in the CRF page RECIST v1.1 measurable disease.

Derived Visit Non-Measurable Response: If there are no new non-measurable lesions, the derived visit non-measurable response is the Status of Non-Target Lesions from the Assessment of RECIST Response page of the eCRF.

Lymph nodes will be identified from "Location" in the Measurable Disease Assessment page of the eCRF.

Table 9: Non-measureable Lesion Evaluation

Response	Status of Non-measurable Lesion (eCRF)
irCR	• Absent
Non-irCR/Non-irPD	• Stable
irPD	• Unequivocal Progression
Not Done/Not Evauable	• Assigned if the RECIST v1.1 non-target lesions response is Not Done or Not Evaluable.

If there have been new non-measurable lesions identified, the derived visit non-measurable response will be irPD if any are assessed with "Unequivocal Progression".

The derived irRECIST response will be determined based on the following:

Table 10: Overall irRECIST Response

Target Lesion (Tumor burden)	Non-Target Lesions	New Lesions: Non-Target	Overall (Time point) Response
irCR	irCR	No	irCR
irCR	Non-irCR/non-irPD	No or Non-Unequivocal Progression	irPR
irCR	NE	No or Non-Unequivocal Progression	irPR

Target Lesion (Tumor burden)	Non-Target Lesions	New Lesions: Non-Target	Overall (Time point) Response
irPR	Non-irPD or not all evaluated	No or Non-Unequivocal Progression	irPR
irSD	Non-irPD or not all evaluated	No or Non-Unequivocal Progression	irSD
Not evaluated	Non-PD	No or Non-Unequivocal Progression	NE
irPD	Any	Yes or No	irPD
Any	irPD	Yes or No	irPD
Any	Any	Unequivocal Progression	irPD

8.1.5 Best Response at an Interim Analysis using irRECIST

Similar to assigning best response by RECIST v1.1 at an interim analysis, if a subject has an unconfirmed response (i.e., one visit assessment of CR or PR) by irRC or irRECIST as the last disease assessment before an interim analysis, the best response in the interim analysis will be reported as an unconfirmed CR (uCR or uirCR) or unconfirmed PR (uPR or uirPR).

8.2 Exploratory Endpoints

Exploratory endpoint analyses, except for analysis of patient reported outcome (PRO) quality of life using the EORTC QLQ-C30 results, are outside the scope of this Statistical Analysis Plan.

8.3 Baseline, Worst, and Best-case Post-Baseline Values

Unless otherwise noted, baseline is defined as the last non-missing value recorded before the first dose of study drug. Unscheduled visits will be used in the determination of baseline values, when applicable.

Worst-case post-baseline values will be identified from all scheduled and unscheduled visits. For measures with degradation from both increases and decreases, Worst-cases will be identified and summarized for both.

Best-case post-baseline values will be identified from all scheduled and unscheduled visits. For measurable tumor assessment Best-case will be identified as the largest decrease, or, for subjects who have no decrease, the smallest increase in post-baseline assessment.

8.4 Missing Data

Subjects who discontinue from the study before completing an on-study radiographic tumor evaluation will be counted as non-responders in the evaluation of ORR.

Subjects who discontinue from the study or who are lost to follow-up without objective tumor progression while on treatment will be censored on the date of the last assessment documenting absence of disease progression in the evaluation of PFS and DoR. Subjects who discontinue from the study or who are lost to follow-up before death will be censored at the date they were last known to be alive in the evaluation of OS.

The following algorithms will be applied to missing and incomplete start and stop dates **(**i.e., AEs and concomitant medications**)**:

Start Dates

- If the day portion of the start date is missing, then the start date will be estimated to be equal to the date of first dose of study drug, provided the start month and year are the same as the first dose of study drug and the stop date is either after the first dose of study drug or completely missing. Otherwise, the missing day portion will be estimated as '01'.
- If both the day and month portions of the start date are missing, then the start date will be estimated to be equal to the date of first dose of study drug, provided the start year is the same as the first dose of study drug and the stop date is either after the first dose of study drug or completely missing. Otherwise, the event will be assumed to start on the first day of the given year (e.g., ??-???-2013 is estimated as 01-JAN-2013).
- If the start date is completely missing and the stop date is either after the dose of study drug or completely missing, the start date will be estimated to be the date of first dosing of the study drug. Otherwise, the start date will be estimated to be the first day of the same year as the stop date. All other non-AE and non-concomitant medication day calculations where only partial dates are available will be handled as follows: the first day of the month will be used in the calculations if the day part of a start date is missing and January 1 will be employed if both the month and day parts of a start date are missing.

Stop Dates

- If only the end day is unknown, the day will be assumed to the last day of the month (e.g., ??-JAN-2013 will be treated as 31-JAN-2013).
- If both the end day and month are unknown, the event will be assumed to have ceased on the last day of the year (e.g., ??-???-2013 will be treated as 31-DEC-2013).
- If the stop date is completely missing or the event is continuing, the event will be assumed to be after first dose of study drug and will be imputed using the last known date on the study.

No imputations will be made for missing values other than those described in this section. Summaries will be based on observed data only.

8.5 Efficacy Endpoints

ORR is defined as the proportion subjects with a best confirmed overall response of complete response (CR) or partial response (PR), with assessment of response to be determined by the investigator using irRECIST and RECIST v1.1.

OS is defined as the number of months from initiation of treatment to death from any cause. Subjects who have not died at their last contact will be censored on the date of last contact. The specifications for the time to death calculation are:

- If death is reported either on AE or Death CRF pages, OS will be calculated as *Date of Documentation of (Death – First Dose Date + 1)/ 30.4375*.
- Subjects will be censored at their last contact date if death is not reported at the data cut-off date for study closure, and their survival time will be calculated as (*[Last Contact Date - First Dose Date + 1] / 30.4375*). Last contact date is defined as the last date reported among, Adverse Event (AE start date), the Study Exit Status, Hematology, Chemistry, Assessment of RECIST v1.1 Response, Assessment of irRECIST Response, Long Term Follow Up, Study Drug Administration (IMO-2125), ipilimumab Infusion and pembrolizumab Infusion pages of the eCRF.
- Subjects lacking data after the date of first dose who do not die will have their survival time censored on the date of first dose with duration of 1 day.

PFS, defined as number of months from the initiation of treatment to disease progression using RECIST v1.1 or irRECIST or death from any cause, will be calculated as ([Date of Documentation of Death or Disease Progression – First Dose Date + 1]/30.43750. Subjects without reported progression at their last contact date will be censored on the date of their last valid disease assessment. A valid disease assessment is any disease assessment with overall visit-level response of irCR irPR, irSD, or irPD (without subsequent confirmation) when using irRECIST and CR, PR, or SD when using RECIST v1.1. Subjects who start new anti-cancer therapy before a PFS event will be censored on the date of initiation of new anti-cancer therapy (Subsequent Anti Cancer Therapy eCRF page).

Duration of response, defined as the length of time from the first occurrence of confirmed response (CR or PR) until confirmed (if necessary) disease progression with assessment of response to be determined by the Investigator using the irRECIST, and RECIST v1.1. DoR will be calculated as *[Date of Documentation of Death or Disease Progression – Date of First Objective Response]/30.4375.* The censoring rules for PFS will be used for DoR. Subjects who

fail to achieve a CR/irCR or PR/irPR during the study will be excluded from the analysis of DoR.

8.6 Interim Analysis

There are 3 interim and 1 final analyses planned:

- A planned analysis of phase 1 results at the completion of dose escalation for both combinations will be conducted.
- An analysis of the safety and efficacy results in each phase 2 arm will be conducted separately after 21 subjects in the primary efficacy population (used in the two-stage design) have had at least 2 post-baseline disease assessments.
- The final analysis by efficacy populations of all subjects in the IMO-2125 + ipilimumab arm will be done when all subjects have had at least 2 post-baseline disease assessments.

8.7 Examination of Subgroups

Subjects will be categorized into subgroups based on whether they had previously been treated with talimogene or another oncolytic viral vector prior to enrollment in this study (yes or no). Another subgroup of interest is subjects with prior anti-PD-(L)1 as monotherapy or in combination therapy (e.g., prior treatment with nivolumab + ipilimumab) or subjects with prior CTLA-4; subjects will be categorized into subgroups based on such prior combination therapy (yes or no). ORR and DRR using RECIST v1.1 and irRECIST will be analyzed by these subgroups if the data support such analyses.

Subjects will be categorized into subgroups based on whether or not they received CYP substrate concomitant medications.

Subjects will be categorized into subgroups based on whether they had previously been treated with Oncolytic Virus, CTLA-4 Inhibitor monotherapy in metastatic setting, CTLA-4 Inhibitor monotherapy, PD-(L)1 Inhibitor monotherapy, CTLA-4 + PD-(L)1 Inhibitor combination or, Other PD-(L)1 combination in the Previous Melanoma Treatment eCRF page; subjects can be in more than one subgroup. ORR, DRR, DCR, and BOR using RECIST and irRECIST will be analyzed by these subgroups if the data support such analyses.

Other subgroups of interest are baseline LDH (elevated or not); disease stage (IV or earlier stage, Stage M1c); BRAF mutation positive with prior targeted therapy, BRAF mutation positive with no prior targeted therapy, BRAF wild type; 8 mg IMO-2125 and ipilimumab combination dose group; subjects without any major protocol deviations; subjects who received at least 1 dose of IMO-2125 and 2 doses of ipilimumab in combination in any phase; and duration of prior anti-PD-1 therapy (≥12 weeks and <12 weeks). Subjects with unknown baseline LDH status will not be included in the subgroup analysis. Targeted therapy is either a BRAF or MEK inhibitor,

or both. Prior anti-PD-1 therapy is PD(L)-1 Inhibitor. ORR, DRR,DCR, and BOR using RECIST and irRECIST will be analyzed by these subgroups if the data support such analyses.

8.8 Multiple Comparison/Multiplicity

The study Type I error rate is split between the phase 2 hypothesis tests for each treatment arm, so that the ORR is tested at the 0.025 significance level for each.

9 METHODS OF EFFICACY ANALYSIS

9.1 Phase 1

Efficacy reporting will consist of listings of the best overall response by irRC and RECIST v1.1 and change in tumor burden (sum of the longest diameters).

9.2 Primary Efficacy Analyses

The primary efficacy endpoint, investigator-assessed ORR using RECIST v1.1, will be analyzed for all subjects in the PPIEE population and the first 21 patients in the PIIEE, as well as the PIIEE population and SIIEE population combined using a one-sided, one sample exact binomial test with $\alpha = 0.025$ in each test. The proportion of subjects achieving a best confirmed response of CR or PR will be tested against the null rates of 0.11 and 0.05 for ipilimumab and pembrolizumab, respectively (Hodi et al, 2010).

The primary efficacy analyses will test the following hypotheses:

H_0: The ORR assessed using the RECIST v1.1, for subjects in the IMO 2125 + ipilimumab treatment arm, is no larger than 0.11;
H_1: The ORR assessed using the RECIST v1.1, for subjects in the IMO 2125 +ipilimumab treatment arm, is at least 0.35.

H_0: The ORR assessed using the RECIST v1.1, for subjects in the IMO 2125 +pembrolizumab treatment arm, is no larger than 0.05;
H_1: The ORR assessed using the RECIST v1.1, for subjects in the IMO 2125 +pembrolizumab treatment arm, is at least 0.35.

9.3 Secondary Efficacy Analyses

9.3.1 Evaluation of Response

Investigator assessments as reported on electric case report forms (eCRFs) will be used to identify confirmed response as described in Section 8.1. The overall irRC/ irRECIST response categories are: Complete Response (irCR), Partial Response (irPR), Stable Disease (irSD), Progressive Disease (irPD), and Not Evaluable (irNE). The overall RECIST v1.1 response categories are: Complete Response (CR), Partial Response (PR), Stable Disease (SD), Progressive Disease (PD), and Not Evaluable (NE). If any post-baseline scheduled tumor assessment is missed, that visit-level response for that visit will be 'Not Done'.

The ORR, DRR, and DCR will be estimated by the MLE for secondary response endpoints. The MLE is $\hat{p} = s_1/n_1$ if the arm stops after Stage 1 and $\hat{p} = (s_1+s_2)/(n_1+n_2)$ otherwise, where s_i=the number of subjects with a response in Stage i and n_i=number of subjects in stage i, i=1,2. All secondary response rate endpoints will be summarized descriptively by treatment arm for phase 2 subjects with the number of subjects with a response, percentage, and exact two-sided 95% CIs.

The number and percent of subjects in each of the best overall tumor response categories, using irRECIST and RECIST v1.1, will be summarized for phase 2 subjects. Exact two-sided 95% confidence intervals will be provided for each best overall tumor response category by treatment arm.

Durable response rate (DRR) is defined as the proportion of subjects experiencing CR or PR by RECIST v1.1 (irCR or irPR by irRECIST) lasting approximately 6 months continuously and beginning within 12 months of the first dose of study treatment. The length of durable response is calculated as ((Date of Documentation of Death or Disease Progression – Date of First Objective Response + 1)/ 30.4375).

The DRR using irRECIST and RECIST v1.1 will be summarized descriptively by treatment arm for phase 2 subjects with the number of subjects, percentage, and exact two-sided 95% CIs.

Disease control rate (DCR) using irRECIST and RECIST v1.1 will be summarized descriptively by treatment arm for phase 2 subjects with the number of subjects, percentage, and exact two-sided 95% CIs.

Swimmers' lane plots will also be produced showing time to response (RECIST v 1.1), duration of response, type of response, and duration of treatment for the phase 2 results.

9.3.2 Evaluation of Time to Event Endpoints

The OS and PFS proportions will be estimated at 6 and 12 months; OS and PFS will also be analyzed overall with Kaplan-Meier estimate including median. For time-to-event endpoints (OS, PFS, and DoR), the Kaplan-Meier method will be used to estimate the probability of event-free survival. The analyses of OS, PFS, and DoR will only be done for the subjects treated at the RP2D for each treatment arm.

Kaplan-Meier plots will be produced for OS and PFS by treatment arm.
Subgroup analysis of overall survival at 6 and 12 months, as well as progression-free survival, may be performed for the 8 mg IMO-2125 and ipilimumab combination dose group if data supports it.

9.3.3 Measurable Disease Assessment

The absolute and percent change from baseline for the sum of longest diameters of the baseline target lesions from measurable tumor assessment CRF page will be listed by dose group for phase 1 subjects and summarized and listed by treatment arm for phase 2 subjects at the Best-case post baseline. The summary may be repeated for injected and non-injected lesions separately.

Waterfall plots of the maximum percentage change from baseline in measurable tumor burden (the sum of the longest diameter) will be produced for the phase 2 results. The bars will not be coded for any factor but the treatment combinations will be distinct colors in the separate figures.

Measurable disease assessment, non-measurable disease assessment, assessment of RECIST v1.1 response, assessment of irRECIST response and assessment of irRC response data will be listed by subject.**Exploratory Analyses**

9.4.1 Pharmacodynamic Markers

Analysis of pharmacodynamic result is not in the scope of this analysis plan and will be addressed separately.

9.4.2 Immunogenicity Analyses

Immunogenicity results will be included in data listings only.

10 SAFETY ANALYSES

All safety analyses will be performed on the Safety Population.

10.1 Extent of Exposure

Exposure will be calculated separately for IMO-2125, ipilimumab and pembrolizumab. Total number of doses (injections or infusions) per subject, total volume administered (mL) per subject, total dose administered (mg) for ipilimumab and pembrolizumab only, and the duration of treatment (months) will be summarized by each dose group. Duration of treatment is defined as the (last dose date minus the first dose date plus 1)/30.4375.

Dose modifications will be reported separately for IMO-2125, ipilimumab and pembrolizumab.

Dose modifications for IMO-2125 will be described by summarizing:

- the number of subjects who had an injection delayed. The "injection delayed" determination will be based on the answer to the question of "Was Intratumoral Injection delayed?" on the "Study Drug Administration (IMO-2125)" CRF pages. The summary will be presented by dose group and overall as well as by cycle (phase 1) and by treatment arm (phase 2), with each injection given representing a new cycle.
- the number of subjects who had dose decreased. The "dose decreased" determination will be based on the answer to the question of "Was planned dose decreased? on the "Study Drug Administration (IMO-2125)" CRF pages. The summary will be presented by dose group and overall as well as by cycle (phase 1) and by treatment arm (phase 2), with each injection given representing a new cycle.

Dose modifications for ipilimumab and pembrolizumab will be described by summarizing:

- the number of subjects who had infusion rate decreased. The "infusion rate decreased" determination will be based on the answer to the question of "Was Infusion Rate decreased?" on the ipilimumab and pembrolizumab infusion CRF pages. The summary will be presented by dose group and overall as well as by cycle, with each infusion given representing a new cycle.
- the number of subjects who had infusion discontinued. The "infusion discontinued" determination will be based on the answer to the question of "Was Infusion Discontinued? on the ipilimumab and pembrolizumab infusion CRF pages. The summary will be presented by dose group and overall as well as by cycle, with each injection given representing a new cycle.
- the number of subjects who had infusion interrupted. The "infusion interrupted?" determination will be based on the answer to the question of "Was infusioninterrupted? on the ipilimumab and pembrolizumab infusion pages. The summary will be presented by dose group and overall as well as by cycle (phase 1) and by treatment arm (phase 2), with each infusion given representing a new cycle.

Data listings for study drug administered will be provided.

10.2 Adverse Events

Adverse event summaries will be restricted to Treatment Emergent Adverse Events (TEAE), which are defined as those AEs that started on or after the date of first dose of study treatment and those existing AEs that worsened during the study. If it cannot be determined whether the AE is treatment emergent due to a partial onset date, then it will be counted as treatment emergent. Verbatim terms on electric case report forms will be mapped to preferred terms and system organ classes using the Medical Dictionary for Regulatory Activities (MedDRA) (version 16.1).

Summaries displayed by system organ class and preferred terms will be ordered by descending order of incidence of system organ class and preferred term within each system organ class, with TEAEs of the same incidence displayed alphabetically. Summaries displayed by preferred term will be ordered by descending order of incidence, with TEAEs of the same incidence displayed alphabetically.

Summaries of the following types will be presented:

- Overall summary of TEAEs which contain an overview of number of subjects with at least one TEAE, at least one IMO-2125-related TEAE, at least one ipilimumab-related TEAE, at least one pembrolizumab-related TEAE, at least one serious TEAE, at least one grade 3 or higher TEAE, at least one TEAE leading to discontinuation, at least one TEAE of action taken with IMO-2125 as drug withdrawn, at least one TEAE of action taken with ipilimumab as drug withdrawn, at least one TEAE of action taken with pembrolizumab as drug withdrawn, at least one immune-related TEAE, and at least one TEAE with fatal outcome. The maximum severity by the CTCAE will also be included.
- Subject incidence of TEAEs by MedDRA SOC and preferred term.
- Subject incidence of TEAEs by preferred term.
- Subject incidence of TEAEs by preferred term, and highest Common Terminology Criteria for Adverse Events (CTCAE) toxicity grade. At each level of subject summarization, a subject is classified according to the highest CTCAE toxicity grade if the subject reported more than one event.
- Subject incidence of IMO-2125-related TEAEs by preferred term. Only those AEs reported as “Related”, “Possibly”, or “Probably”, or which have a missing relationship to IMO-2125 will be included in this summary.
- Subject incidence of ipilimumab-related TEAEs by preferred term. Only those AEs reported as “Related”, “Possibly”, or “Probably”, or which have a missing relationship to ipilimumab will be included in this summary.

- Subject incidence of pembrolizumab-related TEAEs by preferred term. Only those AEs reported as "Related", "Possibly", or "Probably", or which have a missing relationship to pembrolizumab will be included in this summary.
- Subject incidence of serious TEAEs by preferred term.
- Subject incidence of IMO-2125-related serious TEAEs by preferred term. Only those AEs marked as "Related", "Possibly", or "Probably", or which have a missing relationship to IMO-2125 will be included in this summary.
- Subject incidence of ipilimumab -related serious TEAEs by preferred term. Only those AEs reported as "Related", "Possibly", or "Probably", or which have a missing relationship to ipilimumab are considered for this summary.
- Subject incidence of study pembrolizumab serious by preferred term. Only those AEs reported as "Related", "Possibly", or "Probably", or which have a missing relationship to pembrolizumab are considered for this summary.
- Subject incidence of TEAEs that have CTCAE grade 3 or higher by preferred term.
- Subject incidence of TEAEs leading to study discontinuation by preferred term.
- Subject incidence of TEAEs of action taken with IMO-2125 as drug withdrawn by preferred term.
- Subject incidence of TEAEs of action taken with ipilimumab as drug withdrawn by preferred term.
- Subject incidence of TEAEs of action taken with pembrolizumab as drug withdrawn by preferred term.
- Subject incidence of immune-related TEAEs by preferred term.
- Subject incidence of TEAEs with fatal outcome by preferred term.
- Subjects with non-serious TEAEs by SOC and preferred term.

irAEs will be determined from a list of pertinent MedDRA codes provided by the study sponsor.

10.3 Clinical Laboratory Evaluation

Laboratory parameters for serum chemistry, hematology, complement, and coagulation will be summarized by dose group in phase 1 and treatment arm in phase 2 using descriptive statistics at baseline and at worst-case post-baseline.

Select laboratory parameters for serum chemistry, hematology, and coagulation will be assigned grades according to NCI Common Terminology Criteria for Adverse Events (CTCAE) v4.03. The complement parameters will be considered being worse if the post-baseline value is lower than baseline value. The worse case post-baseline value will be the lowest value after baseline. Complement parameter results with 50% decrease from baseline may be summarized separately. Shift tables assessing changes from baseline to assigned worst-case post-baseline in assigned CTCAE grade will be summarized. Shift tables will use results from all visits (scheduled and

unscheduled). For laboratory parameters that are not graded by the CTCAE v4.03, shift tables relative to the normal range will be produced and will also use results from all visits (scheduled and unscheduled). The laboratory parameter will be summarized in applicable shift tables (by CTCAE v4.03 grade and/or relative to the normal range). Laboratory parameters that have bidirectional Worst-cases (that is, laboratory parameters which have both CTCAE or normal range shift for low values and for high values) will have the results for both directions reported.

Shift tables will report the counts and percentages of subjects shifting for each dose group for phase 1 and by treatment arm for phase 2.

Plots for each dose level showing the mean complement with standard error bars by visit will be produced for the phase 1 results. For the phase 1 and 2 results combined, these plots will be by treatment arm.

Table 11: CTCAE Toxicity Grades: Hematology

Analyte	Standard Unit	Directional Change	Toxicity Grades (CTCAE v4.03)
Hemoglobin[1]	g/dL	Decrease	Grade 1: < LLN – 10 g/dL Grade 2: < 10 – 8 g/dL Grade 3: < 8 g/dL Grade 4: Not defined
		Increase	Grade 1: > ULN – (2+ULN) g/dL Grade 2: > (2+ULN) – (4+ULN) g/dL Grade 3: > 4+ULN g/dL Grade 4: Not defined
Lymphocytes	x 10^3/uL	Decrease	Grade 1: < LLN – 0.8 x 10^3/uL Grade 2: < 0.8 – 0.5 x 10^3/uL Grade 3: < 0.5 – 0.2 x 10^3/uL Grade 4: < 0.2 x 10^3/uL
Lymphocytes	x10^9/L	Increase	Grade 1: Not defined Grade 2: >4.0 – 20.0 x 10^3/uL Grade 3: >20.0 x 10^3/uL Grade 4: Not defined
Neutrophils	x10^9/L	Decrease	Grade 1: < LLN – 1.5 x 10^3/uL Grade 2: < 1.5 – 1.0 x 10^3/uL Grade 3: < 1.0 – 0.5 x 10^3/uL Grade 4: < 0.5 x 10^3/uL
Platelets	x 10^3/uL	Decrease	Grade 1: < LLN – 75.0 x 10^3/uL Grade 2: < 75.0 – 50.0 x 10^3/uL

			Grade 3: < 50.0 – 25.0 x 10^3/uL Grade 4: < 25.0 x 10^3/uL
WBC	x 10^6/uL	Decrease	Grade 1: < LLN – 3.0 x 10^3/uL Grade 2: < 3.0 – 2.0 x 10^3/uL Grade 3: < 2.0 – 1.0 x 10^3/uL Grade 4: < 1.0 x 10^3/uL
		Increase	Grade 1: Not defined Grade 2: Not defined Grade 3: >100 x 10^3/uL Grade 4: Not defined

LLN=lower limit of normal. ULN=upper limit of normal. The LLN and ULN for each analyte will be determined from the normal range of each local laboratory.
[1] For increased hemoglobin results, if the baseline value is above the ULN, the baseline value will be used instead of the ULN to assess grades 1, 2, and 3.

Table 12: CTCAE Toxicity Grades: Coagulation

Analyte	Standard Unit	Directional Change	Toxicity Grades (CTCAE v4.03)
aPTT	sec	Increase	Grade 1: >ULN – 1.5 x ULN Grade 2: >1.5 – 2.5 x ULN Grade 3: >2.5 x ULN Grade 4: Not defined
INR	No units	Increase	Grade 1: >ULN – 1.5 x ULN Grade 2: >1.5 – 2.5 x ULN Grade 3: >2.5 x ULN Grade 4: Not defined

LLN=lower limit of normal. ULN=upper limit of normal. The LLN and ULN for each analyte will be determined from the normal range of each local laboratory.

Table 13: CTCAE Toxicity Grades: Chemistry

Analyte	Standard Unit	Directional Change	Toxicity Grades (CTCAE v4.03)
ALT (SGPT)	U/L	Increase	Grade 1: > ULN – 3.0 x ULN Grade 2: > 3.0 – 5.0 x ULN Grade 3: > 5.0 – 20.0 x ULN Grade 4: > 20.0 x ULN
AST (SGOT)	U/L	Increase	Grade 1: > ULN – 3.0 x ULN Grade 2: > 3.0 – 5.0 x ULN Grade 3: > 5.0 – 20.0 x ULN Grade 4: > 20.0 x ULN
Alkaline Phosphatase	U/L	Increase	Grade 1: > ULN – 2.5 x ULN Grade 2: > 2.5 – 5.0 x ULN Grade 3: > 5.0 – 20.0 x ULN Grade 4: > 20.0 x ULN
Albumin	g/dL	Decrease	Grade 1: < LLN – 3 g/dL Grade 2: < 3 – 2 g/dL Grade 3: < 2 g/dL Grade 4: Not defined
Calcium	mg/dL	Decrease	Grade 1: < LLN – 8.0 mg/dL Grade 2: < 8 – 7.0 mg/dL Grade 3: <7 – 6 mg/dL Grade 4: < 6 mg/dL
Calcium	mg/dL	Increase	Grade 1: ULN - 11.5 mg/dL Grade 2: > - 11.5 – 12.5 mg/dL

			Grade 3: > 12.5 - 13.5 mg/dL Grade 4: > 13.5 mg/dL
Cholesterol	mg/dL	Increase	Grade 1: >ULN - 300 mg/dL Grade 2: >300 – 400 mg/dL Grade 3: >400 - 500 mg/dL Grade 4: >500 mg/dL
Creatinine	mg/dL	Increase	Grade 1: > ULN – 1.5 x ULN Grade 2: > 1.5 – 3.0 x ULN Grade 3: > 3.0 – 6.0 x ULN Grade 4: > 6.0 x ULN
GGT		Increase	Grade 1 >ULN - 2.5 x ULN Grade 2: >2.5 - 5.0 x ULN Grade 3: >5.0 - 20.0 x ULN Grade 4: >20.0 x ULN
Glucose	mg/dL	Decrease	Grade 1 <LLN - 55 mg/dL Grade 2: <55 – 40 mg/dL Grade 3: <40 - 30 mg/dL Grade 4: <30 mg/dL
Glucose	mg/dL	Increase	Grade 1: <ULN – 160 mg/dL Grade 2: 160- 250 mg/dL Grade 3: <250 - 500 mg/dL Grade 4: <500 mg/dL
Phosphate	mg/dL	Decrease	Grade 1: <LLN – 2.5 mg/dL Grade 2: <2.5 - 2 mg/dL Grade 3: <2 - 1 mg/dL

			Grade 4: <1 mg/dL
Potassium*	mEq/L	Decrease	Grade 1: <LLN - 3.0 mEq/L
			Grade 2: <LLN - 3.0 mEq/L
			Grade 3: <3 – 2.5. mEq/L
			Grade 4: <2.5 mEq/L
		Increase	Grade 1 >ULN – 5.5 mEq/L
			Grade 2: 5.5>- 6 mEq/L
			Grade 3: >6 - 7 mEq/L
			Grade 4: >7 mEq/L
Sodium	mEq/L	Decrease	Grade 1: < LLN – 130 mEq/L
			Grade 2: Not defined
			Grade 3: < 130 – 120 mEq/L
			Grade 4: < 120 mEq/L
	mEq/L	Increase	Grade 1: > ULN – 150 mEq/L
			Grade 2: > 150 – 155 mEq/L
			Grade 3: > 155 – 160 mEq/L
			Grade 4: > 160 mEq/L
Total Bilirubin	mg/dL	Increase	Grade 1: > ULN – 1.5 x ULN
			Grade 2: >1.5 – 3.0 x ULN
			Grade 3: >3.0 – 10.0 x ULN
			Grade 4: >10.0 x ULN
Uric Acid*	mg/dL	Increase	Grade 1 < ULN - 10 mg/dL
			Not Defined
			Grade 3 < ULN - 10 mg/dL
			Grade 4: <10 mg/dL

LLN=lower limit of normal. ULN=upper limit of normal. The LLN and ULN for each analyte will be determined from the normal range of each local laboratory.

* Indicates laboratory values for which CTCAE grade is not based on the laboratory value; clinical symptoms are also involved.

Urinalysis results will not be summarized but will be listed.

Data listings of laboratory results will be provided for each subject. Laboratory values that are out of the normal range will be flagged in listings, and those that are graded by the CTCAE v4.03 will have the assigned grade included in the listing.

10.4 Vital Signs

Vital signs (weight, blood pressure, heart rate, respiratory rate, and body temperature) will be summarized by dose group and treatment arm using descriptive statistics at baseline and at worst-case post-baseline. Changes from baseline at worst-case post-baseline relative to the normal range will also be summarized. The wost case post-baseline for weight, blood pressure, hear rate, and respiratory rate will be derived in two direcdtions by their highest increase and decrease respectively.

Diastolic BP and Systolic BP will be assigned grades according to NCI Common Terminology Criteria for Adverse Events (CTCAE) v4.03. Shift tables assessing changes from baseline to Worst-case assigned post- baseline in CTCAE grade will be presented.

Table 14: CTCAE Toxicity Grades: Vital Signs

Vital	Standard Unit	Directional Change	Toxicity Grades (CTCAE v4.03)
Diastolic BP	mm Hg	Increase	Grade 1: 80 - 89
			Grade 2: 90 - 99
			Grade 3: >=100
Systolic BP	mm Hg	Increase	Grade 1: 120 - 139
			Grade 2: 140 - 159
			Grade 3: >=160

In addition, shift table assessing changes from baseline to worst decrease post-baseline, in normal range will be summarized for temperature.

Table 15: Normal Range Vital Signs

Vital	Standard Unit	Range
Temperature	F	Low : < 60
		Normal: 60 -100
		High: > 100

Data listings of vital signs will be provided for each subject.

10.5 Physical Examination

Physical examination results will be included in data listings only.

10.6 Electrocardiogram

QTcF in msec will be calculated using the following formula for all subjects:

$$QTcF = QT/(RR)^{0.33}.$$

Overall interpretation results for ECG will be summarized using shift tables (Normal, Abnormal NCS, Abnormal CS) comparing baseline to follow-up. Descriptive statistics at baseline and at Worst-case post-baseline as well as changes from baseline will be summarized QTcF.

In addition, a categorical summary of abnormal QTcF values will be presented.

- At each visit, the number of subjects with QTcF values of > 450 ms, > 480 ms, and > 500 ms will be presented.
- At each post-baseline visit, the number of subjects with change from baseline values in QTcF of > 30 ms and > 60 ms will be presented.

Frequency counts and percentages of subjects shifting from baseline status at worst decrease post-baseline subjects will be summarized; subjects with missing baseline or missing post-baseline result will also be summarized. The shift will be based on QTcF range (≤450, > 450 to ≤ 480, > 480 to ≤ 500, > 500 msec).

A scatterplot of the baseline and worst-case on-treatment QTcF measures will be produced. Reference lines at equivalence (i.e., 45^{o}), an increase of 30 ms, and an increase of 60 ms, as well as absolute references lines at 450 and 500 ms for both axes, will be included.

10.7 ECOG

The frequency counts and percentages of subjects for each ECOG performance status scale will be presented for baseline and worst-case post-baseline. A shift table from baseline to the worst-case post-baseline will be generated as well.

ECOG performance status data will be listed for each subject.

10.8 Subsequent Anti-Cancer Therapy

Subsequent Anti-Cancer Therapy data status data will be listed for each subject

11 PRO FROM THE EORTC QLQ-C30 ANALYSES

Analyses of EORTC QLQ-C30 data will use the Safety Population and be by treatment arm. No missing items or forms will be imputed.

11.1 Missing Data

Patterns of missing EORTC QLQ-C30 data will be summarized descriptively using the following categories: no missing measurements, no baseline measurement, no post-baseline measurement, 1 missing post-baseline measurement, 2 missing post-baseline measurements, 3 missing post-baseline measurements, and 4+ missing post-baseline measurements. These categories are mutually exclusive and collectively exhaustive; that is, every subjects will be in one and only one category for this summary. Subjects will be assigned to a category using the order given; that is, a subject with 1 possible QoL measurement that is missing will be in the no post-baseline category, not the 1 missing post-baseline measurement category. For each category, the number and percentage of subjects in each category will be calculated. The denominator to use for percentages is the number of subjects in the safety population for each treatment arm.

11.2 Scoring the EORTC QLQ-C30 Results

Scoring of all scales will use the EORTC QLQ-C30 Scoring Manual instructions for version 3.0 of the QLQ-C30 instrument.

Let I_i be the score for the ith item on the QLQ-C3 instrument, i=1, 2, 3,…, 30, ranges be the difference between the possible maximum and the minimum response to individual items for scale s, and n_s be the number of items on the scale s.

For all scales, the *RawScore*, *RS*, is the mean of the component items:

$$RawScore_s = RS_s = (I_1 + I_2 + ... + I_{ns}) \div n_s$$

Then for **Functional scales**:

$$Score_s = \{1 - (RS_s - 1) \div range_s\} \times 100$$

and for **Symptom scales/items** and the **Global health status /QoL:** $Score_s = \{(RS_s - 1) \div range_s\} \times 100$.

Global health status / QoL	Scale	Number of Items	Range	Version 3.0 Item Numbers
Global health status/QoL	QL2	2	6	29, 30
Functional scales				
Physical functioning	PF2	5	3	1 to 5
Role functioning	RF2	2	3	6, 7
Emotional functioning	EF	4	3	21 to 24
Cognitive functioning	CF	2	3	20, 25
Social functioning	SF	2	3	26, 27
Symptom scales / items				
Fatigue	FA	3	3	10, 12, 18
Nausea and vomiting	NV	2	3	14, 15
Pain	PA	2	3	9, 19
Dyspnoea	DY	1	3	8
Insomnia	SL	1	3	11
Appetite loss	AP	1	3	13
Constipation	CO	1	3	16
Diarrhoea	DI	1	3	17
Financial difficulties	FI	1	3	28

* *Item range* is the difference between the possible maximum and the minimum response to individual items; most items take values from 1 to 4, giving *range* = 3.

11.3 Summary of EORTC QLQ-C30 Results

EORTC QLQ-C30 scores for each scale and single-item measure will be summarized by baseline and all scheduled visits using the total number of subjects with a measurement on that

scale at that visit, the mean, standard error, median, minimum, and maximum. These summaries will also report change from baseline using the same descriptive statistics. Box and whisker plots of change from baseline for each scale by visit will also be produced.

11.4 Analysis of Change from Baseline

For each of the EORTC QLQ-C30 multi-item scales and single-item measures, a mixed model for repeated measures will be run.

For one analysis, the best overall response for a subject will be dichotomized into 2 levels: response of CR or PR, and response of SD, PD, or NE. Another analysis will use a different dichotomization: response of CR, PR, or SD, and response of PD or NE.

The SAS procedure call is

```
Proc mixed data=<SAS dataset name>;
  class visit response subject;
  model <scale name> = visit response visit*response /  htype= 1,3;
  repeated subject;
  lsmeans visit*response / diff;
run;
```

Only differences in least square means between each post-baseline visit and the baseline visit will be reported. The dataset structure will have a separate record for each subject, visit, scale or single-item measure, and score.

12 CHANGES TO PROTOCOL-SPECIFIED ANALYSES

The efficacy analysis in the combined PIIEE and SIIEE Population are added.

13 REFERENCES

Common Terminology Criteria for Adverse Events (CTCAE). Version 4.0, 28 May 2009. U.S. Department of Health and Human Services, National Institutes of Health, National Cancer Institute. NIH Publication No. 03-5410.

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

Paules M, Casey M, Williams G, Swann SR, Murphy PS, Salazar VM, et al. Recommendations for capture, validation and summarisation of data from studies using RECIST. Eur J Cancer. 2011; 47:697-701

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

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

14 APPENDICES

Appendix A: Presentation of Data and Programming Specifications

General

- Specialized text styles, such as bold, italics, borders, shading, superscripted and subscripted text will not be used in tables, figures, and data listings unless they add significant value to the table, figure, or data listing.
- Only standard keyboard characters are to be used in tables and data listings.
- Special characters, such as non-printable control characters, printer-specific, or font-specific characters, will not be used on a table, figure, or data listing.
- Hexadecimal character representations are allowed (e.g., μ, a, ß).
- All footnotes will be left justified and at the bottom of a page. Footnotes should be used sparingly and must add value to the table, figure, or data listing.

Tables

- Formal organization of tabulations may be changed during programming if appropriate, e.g., tables for the different variables may be combined into a single table, or tables with more than one variable may be split into several tables.
- Means and medians will be presented to one more decimal place than the raw data. Standard deviations will be presented to two more decimal places than the raw data. Minimums and maximums will be reported with the same number of decimal places as the raw data.
- Percentages will be presented to the tenths place.
- For frequency counts of categorical variables, categories whose counts are zero will be displayed for the sake of completeness. For example, if none of the subjects discontinue due to "lost to follow-up," this reason will be included in the table with a count of 0. Categories with zero counts will not have zero percentages displayed.
- Lower and upper confidence interval values should be presented to one decimal place more than the raw/derived data (i.e., to the same number of decimal places as the mean).
- Percentiles (e.g., 25%, 75%) should be presented to one decimal place more than the raw/derived data.
- For all inferential analyses, p-values will be rounded to four decimal places (or at the highest level of precision) with a leading zero (0.0001). P-values less than 0.0001 will be presented as "<0.0001".
- The first footnote will be "Source: xxx", where xxx indicates the source listing number(s) and/or source datatset(s) (e.g., ADaM).

Figures

- Legends will be used for all figures with more than one variable or item displayed.
- Figures will be in black and white (no color) unless colors add value to the clarity and readability of a figure. Lines should be wide enough to see the line after being copied.
- The first footnote will be "Source: xxx", where xxx indicates the source table(s) or listing number(s), and/or source dataset(s) (e.g., ADaM).

Listings

- Formal organization of the listing may be changed during programming if appropriate, e.g., additional variables may be included, change in the column order, or the listing may be split into multiple parts due to space constraints, etc.
- If not otherwise specified, all data listings will be sorted by sequence/treatment, center, subject number, visit, and date/time as appropriate.
- All date values will be presented in a SAS date (e.g., 29AUG2001) format.
- All observed time values will be presented using a 24-hour clock HH:MM:SS format (e.g., 01:35:45 or 11:26). Seconds will only be reported if they were measured as part of the study.

Appendix B: Immune-Related Response Criteria

Definition of Best Response According to irRC Criteria:

Best response	irRC
New, measureable lesions (i.e., ≥ 5x5 mm)	Incorporated into tumor burden
New, non-measureable lesions (i.e., < 5x5 mm)	Do not define progression (but preclude irRC)
Non-index lesions	Contribute to defining irRC (complete disappearance required)
CR	Disappearance of all lesions in 2 consecutive observations not less than 4 weeks apart
PR	≥ 50% decrease in tumor burden compared with baseline in 2 observations at least 4 weeks apart
SD	50% decrease in tumor burden compared with baseline cannot be established no 25% increase compared with nadir
PD	At least 25% increase in tumor burden compared with nadir (at any single time point) in 2 consecutive observations at least 4 weeks apart

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

Appendix Table 1: Derivation of irRC overall responses

Measurable response	Nonmeasurable response		Overall response
Index and new, measurable lesions (tumor burden),* %	Non-index lesions	New, nonmeasurable lesions	Using irRC
↓100	Absent	Absent	irCR†
↓100	Stable	Any	irPR†
↓100	Unequivocal progression	Any	irPR†
↓≥50	Absent/Stable	Any	irPR†
↓≥50	Unequivocal progression	Any	irPR†
↓<50 to <25↑	Absent/Stable	Any	irSD
↓<50 to <25↑	Unequivocal progression	Any	irSD
≥25?	Any	Any	irPD†

*Decreases assessed relative to baseline, including measurable lesions only (>5 × 5 mm).
†Assuming response (irCR) and progression (irPD) are confirmed by a second, consecutive assessment at least 4 wk apart.

Data source: Wolchok JD, et al. Clin Cancer Res. 2009;15(23):7412-20.

Appendix C: RECIST (Response Evaluation Criteria in Solid Tumors) version 1.1 Guidelines

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

A. Categorizing Lesions at Baseline

1. Measurable Lesions

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

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

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

2. Non-measurable Disease

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

3. Normal Sites

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

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

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

4. Recording Tumor Assessments

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

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

5. Target Lesions

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

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

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

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

6. Non-target Disease

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

B. Objective Response Status at Each Evaluation

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

1. Target Disease

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

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

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

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

- Indeterminate. Progression has not been documented, and

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

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

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

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

2. Non-target Disease

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

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

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

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

3. New Lesions

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

4. Supplemental Investigations

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

5. Attentive Progression

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

Appendix Table 2: Objective Response Status at Each Evaluation

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

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

Appendix Table 3: Objective Response Status at Each Evaluation for 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

Appendix Table 4 Best overall response when confirmation of CR and PR required.

Overall response First time point	Overall response Subsequent time point	BEST overall response
CR	CR	CR
CR	PR	SD, PD or PR[a]
CR	SD	SD provided minimum criteria for SD duration met, otherwise, PD
CR	PD	SD provided minimum criteria for SD duration met, otherwise, PD
CR	NE	SD provided minimum criteria for SD duration met, otherwise NE
PR	CR	PR
PR	PR	PR
PR	SD	SD
PR	PD	SD provided minimum criteria for SD duration met, otherwise, PD
PR	NE	SD provided minimum criteria for SD duration met, otherwise NE
NE	NE	NE

CR = complete response, PR = partial response, SD = stable disease, PD = progressive disease, and NE = inevaluable.
a If a CR is truly met at first time point, then any disease seen at a subsequent time point, even disease meeting PR criteria relative to baseline, makes the disease PD at that point (since disease must have reappeared after CR). Best response would depend on whether minimum duration for SD was met. However, sometimes 'CR' may be claimed when subsequent scans suggest small lesions were likely still present and in fact the patient had PR, not CR at the first time point. Under these circumstances, the original CR should be changed to PR and the best response is PR.

Appendix D: Overall Response Using irRECIST

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

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

Appendix E: List of Tables, Figures, and Listings

The following TLF numbering is completed according to ICH guidelines. The ICH heading number and description are in **bold**. Minor changes from this planned index do not need to be amended in the SAP.

Formal organization of tabulations may be changed during programming if appropriate, e.g., tables for the different variables may be combined into a single table, or tables with more than one variable may be split into several tables.

The same safety analyses will be done for both phases. Separate efficacy analysis TLFs will be done for phase 1 and phase 2.

List of Tables
Phase 1 and Phase 2 Demographic and Safety Tables

ICH Heading	Table Number	Table Description
14.1		**Demographics and Baseline Characteristics**
	14.1.1	Subject Disposition
	14.1.2	Protocol Deviations
	14.1.3	Demographic Characteristics (Safety Population)
	14.1.4	Baseline Characteristics (Safety Population)
	14.1.5	Body Systems with Relevant Diseases or Disorders at Baseline (Safety Population)
	14.1.6	Baseline Melanoma Characteristics (Safety Population)
	14.1.7	Concomitant Medications (Safety Population)
	14.1.8	Selected Previous Melanoma Treatment (Safety Population)
14.3		**Safety Analyses**
14.3.1		**Adverse Events**
	14.3.1.1	Overall Summary of Treatment-Emergent Adverse Event (Safety Population)
	14.3.1.2.1	Treatment-Emergent Adverse Events by System Organ Class and Preferred Term (Safety Population)
	14.3.1.2.2	Non-SeriousTreatment-Emergent Adverse Events by System Organ Class and Preferred Term (Safety Population)
	14.3.1.2.3	Treatment-Emergent Adverse Events by Preferred Term (Safety Population)
	14.3.1.2.4	Treatment-Emergent Adverse Events by Preferred Term and Maximum CTCAE Toxicity Grade (Safety Population)
	14.3.1.3.1	IMO-2125-Related Treatment-Emergent Adverse Events by Preferred Term (Safety Population)
	14.3.1.3.2	Ipilimumab-Related Treatment-Emergent Adverse Events by Preferred Term (Safety Population)
	14.3.1.3.3	Pembrolizumab-Related Treatment-Emergent Adverse Events by Preferred Term (Safety Population)
14.3.2		**Deaths, Other Serious and Significant Adverse Events**
	14.3.2.1.	Serious Treatment-Emergent Adverse Events by Preferred Term (Safety Population)
	14.3.2.2.1	IMO-2125-Related Serious Treatment-Emergent Adverse Events by Preferred Term (Safety Population)

ICH Heading	Table Number	Table Description
	14.3.2.2.2	Ipilimumab-Related Serious Treatment-Emergent Adverse Events by Preferred Term (Safety Population)
	14.3.2.2.3	Pembrolizumab-Related Serious Treatment-Emergent Adverse Events by Preferred Term (Safety Population)
	14.3.2.4	Treatment-Emergent Adverse Events with CTCAE Grade 3 or Higher by Preferred Term (Safety Population)
	14.3.3.5	Treatment-Emergent Adverse Events Leading To Discontinuation by Preferred Term (Safety Population)
	14.3.2.6.1	Treatment-Emergent Adverse Events of Action Taken with IMO-2125 as Drug Withdrawn by Preferred Term (Safety Population)
	14.3.2.6.2	Treatment-Emergent Adverse Events of Action Taken with Ipilimumab as Drug Withdrawn by Preferred Term (Safety Population)
	14.3.2.6.3	Treatment-Emergent Adverse Events of Action Taken with Pembrolizumab as Drug Withdrawn by Preferred Term (Safety Population)
	14.3.3.7	Immune-Related Treatment-Emergent Adverse Events by Preferred Term (Safety Population)
	14.3.3.8	Treatment-Emergent Adverse Events with Fatal Outcome by Preferred Term (Safety Population)
14.3.4		**Laboratory**
	14.3.4.1.1	Hematology (Safety Population)
	14.3.4.1.2.1	Hematology – Shift from Baseline Relative to the Normal Range (Safety Population)
	14.3.4.1.2.2	Hematology – CTCAE Shift from Baseline (Safety Population)
	14.3.4.2.1	Coagulation (Safety Population)
	14.3.4.2.2.1	Coagulation – Shift from Baseline Relative to the Normal Range (Safety Population)
	14.3.4.2.2.2	Coagulation – CTCAE Shift from Baseline (Safety Population)
	14.3.4.3.1	Serum Chemistry (Safety Population)
	14.3.4.3.2.1	Serum Chemistry – Shift from Baseline Relative to the Normal Range (Safety Population)
	14.3.4.3.2.2	Serum Chemistry – CTCAE Shift from Baseline (Safety Population)
	14.3.4.4.1	Complement Testing (Safety Population)

ICH Heading	Table Number	Table Description
	14.3.4.4.2	Complement Testing – Shift from Baseline Relative to the Normal Range (Safety Population)
	14.3.4.4.3	Complement Testing – >=50% Decrease from Baseline (Safety Population)
14.3.5		**Extent of Exposure**
	14.3.5.1.1	Study Drug (IMO-2125) Exposure (Safety Population)
	14.3.5.1.2	Ipilimumab Exposure (Safety Population)
	14.3.5.1.3	Pembrolizumab Exposure (Safety Population)
	14.3.5.2.1	Dose Modifications for Study Drug (IMO-2125) (Safety Population)
	14.3.5.2.2	Dose Modifications for Ipilimumab (Safety Population)
	14.3.5.2.3	Dose Modifications for Pembrolizumab (Safety Population)
14.3.6		**Vital Signs**
	14.3.6.1	Vital Signs (Safety Population)
	14.3.6.2	Vital Signs – Shift from Baseline Relative to the Normal Range (Safety Population)
	14.3.6.3	Vital Signs – CTCAE Shift from Baseline (Safety Population)
14.3.7		**Electrocardiogram**
	14.3.7.1.1	Electrocardiogram – Overall Interpretation (Safety Population)
	14.3.7.1.2	Electrocardiogram – Overall Interpretation Shift from Baseline (Safety Population)
	14.3.7.2.1	Electrocardiogram – Abnormal QTcF Results (Safety Population)
	14.3.7.2.2	Electrocardiogram – QTcF Shift from Baseline (Safety Population)
14.3.8		**ECOG Performance Status**
	14.3.8.1	ECOG –Shift from Baseline (Safety Population)

Efficacy Phase 2

ICH Heading	Table Number	Table Description
14.2		**EFFICACY Analyses**
	14.2.1.1.1a	Best Overall Response, ORR, Durable Response Rate, and Disease Control Rate – RECIST v1.1 (PIIEE and/or PPIEE Populations)
	14.2.1.1.1b	Best Overall Response, ORR, Durable Response Rate, and Disease Control Rate – RECIST v1.1 (PIIEE and SIIEE Populations)
	14.2.1.1.2	Best Overall Response, ORR, Durable Response Rate, and Disease Control Rate – RECIST v1.1 (SIIEE Population)
	14.2.1.2.1a	Best Overall Response, ORR, Durable Response Rate, and Disease Control Rate – irRECIST (PIIEE and/or PPIEE Populations)
	14.2.1.2.1b	Best Overall Response, ORR, Durable Response Rate, and Disease Control Rate – irRECIST (PIIEE and SIIEE Populations)
	14.2.1.2.2	Best Overall Response, ORR, Durable Response Rate, and Disease Control Rate – irRECIST (SIIEE Population)
14.2.2		**Tumor Response – Subgroup Analysis**
	14.2.2.1.1.1a	Best Overall Response, ORR, Durable Response Rate, and Disease Control Rate by Subgroups of Interest – RECIST v1.1 (PIIEE and/or PPIEE Populations)
	14.2.2.1.1.1b	Best Overall Response, ORR, Durable Response Rate, and Disease Control Rate by Subgroups of Interest – RECIST v1.1 (PIIEE and SIIEE Populations)
	14.2.2.1.1.2	Best Overall Response, ORR, Durable Response Rate, and Disease Control Rate by Subgroups of Interest – RECIST v1.1 (SIIEE Population)
	14.2.2.1.2.1a	Best Overall Response, ORR, Durable Response Rate, and Disease Control Rate by Subgroups of Interest – irRECIST (PIIEE and/or PPIEE Populations)
	14.2.2.1.2.1b	Best Overall Response, ORR, Durable Response Rate, and Disease Control Rate by Subgroups of Interest – irRECIST (PIIEE and SIIEE Populations)

ICH Heading	Table Number	Table Description
	14.2.2.1.2.2	Best Overall Response, ORR, Durable Response Rate, and Disease Control Rate by Subgroups of Interest – irRECIST (SIIEE Population)
14.2.3		**Survival, PFS, and Duration of Response**
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	14.2.3.1b	Overall Survival (OS) (PIIEE and SIIEE Populations)
	14.2.3.2.1a	Progression-Free Survival (PFS) – RECIST v1.1 (PIIEE and/or PPIEE Populations)
	14.2.3.2.1b	Progression-Free Survival (PFS) – RECIST v1.1 (PIIEE and SIIEE Populations)
	14.2.3.2.2a	Progression-Free Survival (PFS) – irRECIST (PIIEE and/or PPIEE Populations)
	14.2.3.2.2b	Progression-Free Survival (PFS) – irRECIST (PIIEE and SIIEE Populations)
	14.2.3.3.1a	Duration of Response (DOR) – RECIST v1.1 (PIIEE and/or PPIEE Populations)
	14.2.3.3.1b	Duration of Response (DOR) – RECIST v1.1 (PIIEE and SIIEE Population)
	14.2.3.3.2a	Duration of Response (DOR) – irRECIST (PIIEE and/or PPIEE Populations)
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	14.2.4.1.2	Change from Baseline in the Sum of the Longest Diameters (PIIEE and/or PPIEE Populations)
14.2.5		**Patient Reported Outcomes – Quality of Life**
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Phase 1

ICH Heading	Table Number	Table Description
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Phase 2

ICH Heading	Table Number	Table Description
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	14.2.2	Overall Survival (PIIEE and PPIEE Populations)
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List of Data Listings (Phase 1 and Phase 2)

ICH Heading	Listing Number	Listing Description	CRF page(s)
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16.2.1		**Discontinued Subjects**	
	16.2.1.1	Subject Disposition	Study Exit Status, Derived
16.2.2		**Protocol Deviations**	
	16.2.2.1	Protocol Deviations	Derived
	16.2.2.2	Inclusion/Exclusion Criteria	Inclusion/Exclusion Findings
16.2.4		**Demographic Data**	
	16.2.4.1	Demographics	Demographics
	16.2.4.2.1	Medical History	Medical History
	16.2.4.2.2	Melanoma Characteristics	Melanoma Characteristics
	16.2.4.3	Prior and Concomitant Medications	Concomitant Medications
	16.2.4.3.1	Sensitive and Narrow Therapeutic Range CYP Substrate Concomitant Medications (All Subjects with CYP Substrates)	Concomitant Meds
	16.2.4.4	Previous Melanoma Treatment **	Previous Melanoma Treatment
16.2.5		**Compliance and/or Drug Concentration data**	
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	16.2.5.1.2	Ipilimumab Infusion	Ipilimumab Infusion
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	16.2.6.3	Assessment of RECIST Response	Assessment of RECIST Response

ICH Heading	Listing Number	Listing Description	CRF page(s)
	16.2.6.4	Assessment of irRC Response*	Assessment of irRC Response
	16.2.6.4	Assessment of irRECIST Response **	Assessment of irRC Response
	16.2.6.5	Derived Efficacy Data	Derived
	16.2.6.5.1	Derived irRECIST response for Phase 1 Subjects taking RP2D **	Derived
	16.2.6.7	Tumor Biopsies	Tumor Biopsies
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16.2.8		**Individual Laboratory Measurements by Subject**	
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	16.2.8.7	Immunogenicity Blood Sample with Ipilimumab/ Pembrolizumab Concentration	Immunogenicity Blood Sample
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	16.2.8.9	Vital Signs	Vital Signs
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	16.2.8.11	Electrocardiogram	ECG /ECG - Post-Dose
	16.2.8.12	ECOG	ECOG Performance Status
	16.2.8.13	Long Term Follow Up	Long Term Follow Up

ICH Heading	Listing Number	Listing Description	CRF page(s)
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Appendix F: Table, Listing and Figure Layouts

See separate document for table, listing and figure mock shells