STATISTICAL ANALYSIS PLAN

Statistical Analysis Plan Version: 3.0

Statistical Analysis Plan Version Date: 25 FEB 2021

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

Protocol Number: 2125-MEL-301

Protocol Version: 4.0

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Sponsor:

Idera Pharmaceuticals, Inc.

Signature page

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1 MODIFICATION HISTORY

Version	Effective Date	Author(s) of Modification	Notes on Modification
1.0	15-NOV-2018	Alison Timm, Manager, Biostatistics, PROMETRIKA, LLC	
2.0	21-JUL-2020	Benny Chan, Senior Biostatistican, PROMETRIKA, LLC	Revised description of the IDMC roles and responsibilities per updated Charter and Protocol v3.0. Added Full Analysis Set to include subjects who are treated and have at least one post-baseline record collected. This analysis set will be used in the sensitivity analyses for ORR and OS. "Modified irRECIST" was updated to "irRECIST" per Protocol v3.0. Modified the stratified analysis approach to combine subjects from small strata instead of dropping subjects from the analysis. Removed Modified ITT Population as no subjects will be dropped from the primary analysis. Added Per Protocol Analysis Set as a sensitivity analysis of the primary endpoint family. Added planned sensitivity analyses for OS.

Version	Effective Date	Author(s) of Modification	Notes on Modification
2.0			Removed interim analysis of OS Updated the assumptions of the OS power calculations and changed the planned sample size per Protocol v4.0. Added duration of response and PFS by blinded independent review as a secondary endpoint. Modified analysis for injected and non-injected lesions to analyze at the subject level, create waterfall plots for responders only. Added AE tables for subjects with organ-injected lesions For QoL, it has been noted that some subjects has been using paper PRO instead of ePRO. Updated the corresponding analysis to run for paper PRO, and ePRO separately and combined as well. Removed QoL missing assessment analysis. Remove summaries of irRECIST from all endpoints, and present irRECIST responses in a listing only.

Version	Effective Date	Author(s) of Modification	Notes on Modification
3.0	22-JAN-2021	Benny Chan, Senior Biostatistican, PROMETRIKA, LLC	Change OS analysis: HR will be generated using a Cox proportional hazards model instead of Pike estimator. Clarify ORR definition and DOR censoring rule. Update to include selected laboratory tests for shift analysis. Add additional analyses for disease control rate, AE by injection status Update date imputation rules to be consistent with other studies in the 2125 drug program Add clarifications for the exposure summary

2 LIST OF ABBREVIATIONS

Abbreviation	Definition
ADA	Anti-drug Antibody
ADaM	Analysis Data Model
AE	Adverse Event
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical
BMI	Body Mass Index
CDISC	Clinical Data Interchange Standards Consortium
CI	Confidence Interval
CMH	Cochran-Mantel-Haenszel
CR	Complete Response
CSR	Clinical Study Report
CTCAE	Common Terminology Criteria for Adverse Events
CV	Coefficient of Variation
CYP	Cytochrome P450
DoR	Duration of Response
DRR	Durable Response Rate
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic Case Report Form
EORTC QLQ-C30	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30
ePRO	Electronic Patient-Reported Outcome
FAS	Full Analysis Set
HR	Hazard Ratio
i.v.	Intravenous
IA	Interim Analysis
ICH	International Conference on Harmonisation
IDMC	Independent Data Monitoring Committee
irAE	Immune-related Adverse Event
irRECIST	Immune-related Response Evaluation Criteria in Solid Tumors
IRT	Interactive Response Technology
ITT	Intent to Treat
LDH	Lactate Dehydrogenase

Abbreviation	Definition
LLN	Lower Limit of Normal
LLOQ	Lower Limit of Quantification
LS	Least Squares
MedDRA	Medical Dictionary for Medical Affairs
MMRM	Mixed Effect Model with Repeated Measures
NCI	National Cancer Institute
NE	Not Evaluable
ORR	Objective Response Rate
OS	Overall Survival
PD	Progressive Disease
PD-1	Programmed Cell Death-1
PFS	Progression-free Survival
PK	Pharmacokinetics
PR	Partial Response
PRO	Patient-reported Outcome
PT	Preferred Term
QoL	Quality of Life
QTcF	Fridericia's Corrected QT Interval
RECIST	Response Evaluation Criteria in Solid Tumors
SAP	Statistical Analysis Plan
SAE	Serious Adverse Event
SD	Stable Disease
SI	International System of Units
SLD	Sum of Longest Diameters
SOC	System Organ Class
TEAE	Treatment-emergent Adverse Event
TLF	Tables, Listings and Figures
TTR	Time to Response
ULN	Upper Limit of Normal
WHO	World Health Organization

3 PURPOSE

This statistical analysis plan (SAP) is written to incorporate the revisions from the protocol amendment v4.0 and provides a description of the planned statistical analyses of the study 2125-MEL-301 data to support the Clinical Study Report (CSR). Mock displays for tables, listings, and figures (TLF) are in separate supporting documents.

This SAP complies with the International Conference on Harmonisation (ICH) Harmonised Tripartite Guideline Topic E9, Statistical Principles for Clinical Trials. It is based upon the following study documents:

- Study Protocol v2.0 (dated 5 Feb 2018)
- Study Protocol v3.0 (dated 10 Jul 2019)
- Study Protocol v4.0 (dated 4 Jun 2020)

All decisions regarding the final analysis of the study data, as defined in this SAP, will be made prior to locking of the study data.

4 STUDY DESIGN

This Phase 3 study is being performed to provide definitive evidence for superiority of the IMO-2125/ipilimumab combination over ipilimumab alone.

This is a randomized Phase 3 global, multi-center, open-label comparison of ipilimumab with and without intratumoral IMO-2125 in subjects with advanced melanoma who had confirmed disease progression during or after treatment with a programmed cell death-1 (PD-1) inhibitor, e.g., nivolumab or pembrolizumab. Confirmed progression is defined by irRECIST criteria. Subjects will be randomized 1:1 to ipilimumab alone or ipilimumab plus IMO-2125. Randomization is stratified on the duration of prior anti-PD-1 therapy (≥12 weeks vs <12 weeks), metastasis stage (M1c vs other), and BRAF mutation status and prior targeted therapy (BRAF wild type, BRAF mutation positive with prior targeted therapy, or BRAF mutation positive with no prior targeted therapy) using block randomization. Targeted therapy is the use of an approved BRAF or MEK inhibitor alone or in combination. The primary endpoint family of the study comprises Objective Response Rate (ORR) and Overall Survival (OS) as evaluated by Response Evaluation Criteria in Solid Tumors (RECIST) v1.1.

Blinded independent review of all clinical and imaging results for response assessment will be performed centrally. Periodic safety reviews will be performed by an Independent Data Monitoring Committee (IDMC) as described in the IDMC Charter.

Per protocol amendment v4.0, the planned interim analysis (IA) of OS will no longer be conducted, and the final analysis will occur when 392 randomized subjects have died or approximately 36 months after the last subject is randomized, whichever occurs first.

4.1 OBJECTIVES AND ENDPOINTS

Table 1: Study objectives and endpoints

Objectives	Endpoints
Primary	
To compare the efficacy (measured by ORR and OS) of intratumoral IMO-2125 in combination with ipilimumab versus ipilimumab alone.	The primary endpoint family (see FDA Guidance for Industry, 2017) includes: • ORR by blinded independent review using RECIST v1.1 • OS
Secondary	
• To assess other measures of clinical benefit. • To assess safety. • To assess IMO-2125 pharmacokinetics (PK). • To assess patient-reported outcomes (PROs) on quality of life (QoL).	The secondary endpoints of this study are: • ORR by investigator assessment using RECIST v1.1 • Duration of response (DoR) by blinded independent review and investigator assessment using RECIST v1.1 • Durable response rate (DRR) by blinded independent review and investigator assessment using RECIST v1.1 • Time to response (TTR) by blinded independent review and investigator assessment using RECIST v1.1 • Progression-free survival (PFS), by blinded independent review and investigator assessment using RECIST v1.1 • Landmark PFS at 1 and 2 years, by blinded independent review and investigator assessment using RECIST v1.1 and landmark OS at 1 and 2 years

Objectives	Endpoints
	• Safety, including adverse events (AEs), laboratory and vital sign tests, electrocardiograms (ECGs), Eastern Cooperative Oncology Group (ECOG) Performance Status, and physical examination • Plasma PK of IMO-2125 • PRO from the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 (EORTC QLQ-C30)
Exploratory	
• To investigate potential biomarkers. • To investigate the incidence of anti-IMO-2125 and anti-ipilimumab antibodies.	The exploratory endpoints include: • Immunologic biomarkers (optional tumor biopsies) • Measurement of anti-IMO-2125 and anti-ipilimumab antibodies

4.2 PRIMARY STUDY HYPOTHESIS

ORR and OS comprise a primary endpoint family with a priori hypotheses to be tested. For ORR, the hypotheses are to demonstrate an increase in the ORR from the expected response of 12% for ipilimumab alone to 24% for the IMO-2125 + ipilimumab combination.

For OS, the hypotheses are to demonstrate improvement in the median survival from 11.40 months (the historical control for ipilimumab alone) to 16.85 months with the IMO-2125 + ipilimumab combination (hazard ratio [HR] = 0.677).

The corresponding hypotheses are:

$$\text{Ho: } HR = 1$$

versus

$$\text{Ha: } HR \leq 0.677$$

4.3 STUDY TREATMENTS

Ipilimumab will be administered intravenous (i.v.) using a 90-minute infusion duration at 3 mg/kg on Weeks 1, 4, 7, and 10 (ipilimumab alone or Weeks 2, 5, 8, and 11 (ipilimumab

with IMO-2125). Cross-over therapy will not be allowed for subjects assigned to ipilimumab alone.

IMO-2125 will be given prior to ipilimumab on days when both are to be administered. IMO-2125, 8 mg will be administered intratumorally as a 1 to 4 mL injection to a single designated lesion at Weeks 1, 2, 3, 5, 8, 11, 16, 20, and 24.

4.4 RANDOMIZATION PROCEDURES AND BLINDING

This is an open-label trial. Randomization will use a central Interactive Response Technology (IRT) system. Subjects will be randomized in blocks of a 1:1 ratio to either ipilimumab with IMO-2125 or ipilimumab alone. Randomization is stratified by the duration of prior anti-PD-1 therapy (≥12 weeks vs <12 weeks), metastasis stage (M1c vs other) and BRAF mutation (BRAF wild type vs BRAF mutation positive with prior targeted therapy vs BRAF mutation positive without prior targeted therapy). Despite this being an open label trial, the sponsor will make every effort to maintain the integrity of the trial by avoiding review of aggregated efficacy results by treatment arm during the course of the trial.

4.5 DETERMINATION OF THE SAMPLE SIZE

In this study, ORR and OS comprise a primary endpoint family; both have a priori hypotheses and will be tested for statistical significance. ORR will be tested first followed by OS. The fallback method for the primary endpoint family will be applied to control the study-wise Type I error rate. Under the fallback method, $\alpha 1 = 0.02$ is assigned to the one-sided ORR test and an alpha of 0.005 is saved for the one-sided OS test. If the ORR test is significant at $\alpha 1 = 0.02$, this alpha is unused and will be passed to the OS test as an additional alpha of 0.02, giving a total alpha for the OS test of 0.025.

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

A sample size of 454 subjects also provides 90% power to test the alternative hypothesis of HR ≤ 0.677 at an α of 0.005 (one-sided). The HR of 0.677 corresponds to an improvement in the median survival from 11.4 months (the historical control for ipilimumab alone) to 16.85 months with the IMO-2125 + ipilimumab combination. The number of required deaths to reach the 90% power is 392.

The OS power calculations are based on log-rank test and assume that the trial will have ~20 months of uniform accrual, an overall study duration up to 56 months, and a 10% drop-out rate. If a total alpha of 0.025 is available for the OS significance test under the fallback

method, then this test will have 90% power to test the alternative hypothesis of HR ≤ 0.72 at an α of 0.025 (one-sided). This corresponds to an improvement in the median survival from 11.4 months (the historical control for ipilimumab alone) to 15.8 months with the IMO-2125 + ipilimumab combination.

4.6 PLANNED INTERIM ANALYSIS AND SAFETY REVIEWS

4.6.1 Interim Analysis of Overall Survival

An interim analysis on the primary endpoint family efficacy measure of OS was planned to be performed at 50% of the required number of deaths in the earlier versions of the protocol. Per protocol version 4.0, the sponsor decided that this interim analysis will no longer be performed.

4.6.2 Interim Sample Size Re-estimation

There is no sample size re-estimation planned for this study.

4.6.3 Independent Data Monitoring Committee Reviews

The IDMC composition and duties are described in a separate Charter. The purpose of the IDMC is to provide independent evaluation of potential emerging risks to study participants, through ongoing evaluation of safety and clinical data contributing to an ongoing risk assessment of the study interventions, and make recommendations to the sponsor regarding the conduct of the study. Please reference the IDMC charter for timing of IDMC meetings.

5 CHANGES IN THE CONDUCT OF PLANNED ANALYSES

There are no planned analyses that differ from those specified in the protocol.

6 STUDY ANALYSIS SETS

6.1 SCREENED SET

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

6.2 INTENT TO TREAT ANALYSIS SET

The Intent to Treat (ITT) Analysis Set comprises all subjects in the Screened Set who were randomized. The ITT Analysis Set will be analyzed using the treatment to which the subject was randomized regardless of the treatment actually received and will be the primary analysis

set for efficacy analyses. Any subject who receives a treatment randomization number will be considered to have been randomized.

6.3 FULL ANALYSIS SET

The Full Analysis Set (FAS) comprises all subjects in the ITT Analysis Set who were treated with at least one dose of study drug, and had at least one post-baseline evaluable tumor assessment. The FAS will be analyzed using the treatment to which the subject was randomized regardless of the treatment actually received. Analysis of OS and ORR evaluated by RECIST v1.1 will be performed on the FAS as a sensitivity analysis.

6.4 PER PROTOCOL ANALYSIS SET

The Per Protocol Analysis Set contains all subjects from the FAS without any exclusionary protocol deviations as defined in the Protocol Deviation Plan approved prior to database lock that could adversely affect the evaluation of the primary endpoint. In addition, subjects need to have at least three doses of IMO-2125 and two doses of ipilimumab for the combination arm and two doses of ipilimumab for the ipilimumab alone arm. Subjects will be analyzed according to their randomized treatment assignment. Analysis of OS and ORR evaluated by RECIST v1.1 will be performed on the Per Protocol Analysis Set as a sensitivity analysis.

6.5 SAFETY SET

The Safety Set comprises all subjects in the ITT Analysis Set who received at least one dose of any study treatment. The Safety Set will be analyzed based on the actual treatment received.

6.6 PHARMACOKINETIC ANALYSIS SET

The PK Analysis Set comprises all subjects who received at least one dose of IMO-2125 with at least one measurable concentration of IMO-2125.

7 GENERAL CONSIDERATIONS

Analysis datasets will be created according to Clinical Data Interchange Standards Consortium (CDISC) standards, and data will be displayed according to reporting standards in this SAP and TLF formats.

SAS Version 9.4 or higher will be used to perform all data analyses and to generate tables, listings, and figures (TLFs).

All data collected in the database will be presented in data listings.

For each subject, data up to the time of study completion, lost to follow-up, or withdrawal from study will be included in the appropriate analysis sets defined in Section 6.

Continuous variables will be summarized in terms of the number of observations, mean, standard deviation, median, minimum, and maximum. Other descriptive statistics (e.g., quartiles, coefficient of variation) may be reported when appropriate. Categorical variables will be summarized using frequency counts and percentages. Analyses that use other descriptive statistics will be specified in the applicable SAP section.

Summaries will order displays by ipilimumab with IMO-2125 first, followed by the ipilimumab alone arm. Unless otherwise stated, summaries and figures will be reported by study arm. Summary statistics of central tendency will use one more decimal place than the collected data. Summary statistics of variability will use one more decimal place than the corresponding measure of central tendency. For example, the mean and median for age in years will be presented to one decimal place and the standard deviation of age will be reported to 2 decimal places. Percentages will be displayed to one decimal place, and proportions will be displayed to 4 decimal places. Durations for treatment exposure (weeks), adverse events (weeks), and response (months) will be displayed to 1 decimal place.

Planned visits will be used in all tables and figures that are by visit. Generally, only planned visits will be used in the summaries, statistical analyses, and calculations of any derived parameters; unscheduled visits will be included in the listings. However, both unscheduled and scheduled visits will be included in the determination of the worst-case (highest and/or lowest) post-baseline shifts for laboratory results, vital signs, and ECG.

All listings will include subject number and randomized treatment arm. The laboratory normal reference ranges will be provided and clinical laboratory test results outside the normal reference range will be flagged in the laboratory data listings.

Unless otherwise stated, all listings will be sorted by treatment arm, and subject number if appropriate, and then by visit date and time.

Deviations from the analyses pre-specified in this SAP will be identified in the CSR.

7.1 MULTICENTER STUDIES

Data from all participating sites will be pooled for analysis.

7.2 MULTIPLE COMPARISONS AND MULTIPLICITY

The Type I error rate will be adjusted for tests of both endpoints (ORR and OS) in the primary endpoint family. ORR will be tested first followed by OS. The fallback method for the primary endpoint family will be applied to control the study-wise Type I error rate.

Under the fallback method, $\alpha 1 = 0.02$ is assigned to the one-sided ORR test and an alpha of 0.005 is saved for the one-sided OS test.

- If the ORR test is significant at $\alpha 1 = 0.02$, this alpha is unused and will be passed to the OS test as an additional alpha of 0.02, giving a total alpha for the OS test of 0.025. The OS test will then be performed at the significance level of 0.025.
- If the ORR test is not significant at 0.02 level, then this alpha of 0.02 will not be available to be passed on for the OS test. The OS test will be performed at the originally reserved alpha of 0.005.

No further adjustment of the Type I error rate will occur. All analyses of secondary endpoints will be descriptive.

8 DATA HANDLING CONVENTIONS

8.1 MISSING DATA

8.1.1 Imputation of Non-Date Missing Data

Unless otherwise explicitly specified, missing data will not be imputed, and analyses will be based on non-missing values.

Missing data occur when any requested data is not provided, leading to blank fields on the collection instrument. These data will be indicated by a "blank" in subject listing displays.

All available time to progression or death data will be analyzed using appropriate statistical methods that allow for censoring when no progression or death is reported; therefore, subjects with shorter treatment and follow-up due to the natural history of their disease, or medical necessities of the treatment of their disease, will not be considered to have missing time to progression or death data. Subjects with premature study withdrawal (including loss to follow-up) will be included in all analyses for which they have relevant data and for which they are in the analysis set of interest. Subjects who are randomized but are not treated will be censored on study day 1.

For variables which determine the proportion of responses using RECIST v1.1, all subjects in the ITT Analysis Set will be included in the denominator when calculating the percentages; that is, missing response data will be imputed as "no response".

Subjects with the designation of treatment relationship for AEs and serious adverse events (SAEs) missing will have the worst case assumed to impute the relationship: if relationship to study treatment is missing, it will be assumed to be "Related".

AEs with a completely missing start date will be assumed to be treatment emergent unless the AE end date is before the date of the first dose of study treatment.

Missing laboratory, vital, and other safety assessment values will not be imputed.

Missing QoL PRO data will not be imputed. At the time of development of this SAP, it is noted that some subjects under protocol version 1 collected QoL data on paper and/or a mixture of paper and electronic media. The handling of mixed modality in the analysis is described in Section 13.

There will be no other imputation for missing data other than as described in Section 8.1.2 for partial dates and times.

In the event that the study is terminated, all available data will be listed and some selected analyses may be performed.

8.1.2 Imputation of Partial Dates

Imputed dates will not be used to derive study day, durations (e.g., duration of adverse events), or elapsed time variables. In addition, imputed dates are not used for deriving the last contact date for overall survival.

Partial date imputation will follow Analysis Data Model (ADaM) conventions. The ADaM approach is to populate the numeric date variables with the imputed date and add a flag variable to the dataset that indicates the level of imputation.

The flag variable can contain the values: blank, 'D', 'M', 'Y'.

blank: indicates that no imputation was done

D = 'Day': indicates that the day portion of the date is imputed

M = 'Month': indicates that the month and day portions of the date are imputed

Algorithms for imputing partial dates for AE are as below:

Adverse Event

Imputations in the adverse events dataset are used for slotting events to the appropriate study time periods and for sorting in data listings. The imputed dates will be used in the derivation of the treatment emergence flag. They will not be used to calculate duration of AEs. If an AE start or end date is partially or completely missing, then the duration of the AE will be set to missing.

Date	Missing Element	Rule
Start Date	day, month, and year	• Do not impute completely missing AE start dates
	day, month only	• If AE start year is same as the year of study start, set to the date of the first dose of study treatment; otherwise, • Set to January 1st of the year the AE started
	day only	• If the AE start year and month are the same as the first dosing date, impute the missing day as the first dosing date; otherwise, • Set start date to the 1st of the month the AE started
End Date	any date element	• No imputation for completely or partially missing AE end dates; as applicable, report the AE as ongoing and the AE duration as missing

Concomitant Medication

Partial concomitant medication start and end dates will be used to derive the reference variables for concomitant medication start and end relative to treatment; any imputed dates will be included in the analysis dataset with an identifier as imputed. The reference variables will be used to differentiate before, during, and after treatment for the concomitant medication. The imputed dates will not be used to calculate study day or duration.

Date	Missing Element	Rule
Start Date	day, month, and year	• If the medication start date is completely missing and the end date is either after the first dose date or completely missing, then set the missing start date as the first dose date.
	day, month only	• If the medication start year is same as the year of study start, set to the first dose date; otherwise, • Set to January 1st of the year the concomitant medication started
	day only	• If the medication start year and month are the same as the first dose date, impute the missing day as the first dose date; otherwise, • Set start date to the 1st of the month the concomitant medication started.
End Date	day, month, and year	• If the end date is completely missing or Ongoing is checked, set the missing end date as the last contact date.
	day, month only	• If the partial end date contains year only, set end date to the earliest of December 31st or the last contact date.
	day only	• If the partial end date contains month and year, set the end date to the earliest of the last day of the end month reported or the last contact date.

8.2 DERIVED VARIABLES

The following sections provide a general description of the derived and transformed variables to be used in data analyses. Separate analysis dataset specifications provide full details on all data derivations and transformations.

8.2.1 Reference Dates

There are three reference dates:

- Because age is an eligibility requirement, the reference date for age is the date initial informed consent for study participation was signed.
- The safety reference date is the first treatment start date and will be used to calculate study day for safety measures.
- The efficacy reference date is the date of randomization.

8.2.2 Study Day for Safety

If the date of interest occurs on or after the safety reference date, then the safety study day will be calculated as (date of interest - safety reference date) + 1. If the date of interest occurs before the safety reference date, then the safety study day will be calculated as (date of interest – safety reference date). There is no safety study day 0.

8.2.3 Study Day for Efficacy

If the date of interest occurs on or after the efficacy reference date, then the efficacy study day will be calculated as (date of interest - efficacy reference date) + 1. If the date of interest occurs prior to the efficacy reference date, then efficacy study day will be calculated as (date of interest – efficacy reference date). There is no efficacy study day 0. Subjects randomized and not treated will be censored at study day 1.

8.2.4 Durations

When durations which are initially calculated in days are to be reported in months, divide the number of days by 30.4375; to report in weeks divide the number of days by 7; to report in years divide the number of days by 365.25.

Age will be calculated as the number of complete years between a subject's birth date and the date of informed consent. If the birth date is incomplete, the subject's birth year will be used to calculate age.

8.2.5 Baseline Definition

Baseline is defined as the most recent, non-missing value prior to the first study treatment dose date and time. For enrolled subjects who did not receive study treatment during the study, baseline is defined as the latest, non-missing collected value before the date of randomization.

8.2.6 Change from Baseline

Change from baseline will only be calculated for measures that have post-baseline records. Change from baseline for safety measures is calculated as:

- visit value – baseline value.

Percentage change from baseline is calculated as:

- (change from baseline / baseline value) * 100

If either the baseline or visit value is missing, the change from baseline and percentage change from baseline are set to missing.

8.2.7 Treatment Emergence Flag

A treatment emergence flag will be derived based on the AE start date (and time if available) to determine an AE occurred before or after first dose date of either study drug. If an AE occurred prior to the first dose date, the AE will be designated as not treatment emergent. If an AE occurred after the first dose date, the AE will be designated as treatment emergent. If an AE occurred on the same date or the same date/time of first dose date(time), the AE will be designated as treatment emergent unless 'NOT APPLICABLE' was recorded for the action taken with both study drugs for the combination arm or the AE was considered related to the either study drug. Similar rules will be applied to the ipilimumab alone arm.

8.2.8 Multiple Assessments

8.2.8.1 Disease Assessment Scans

When a subject has disease assessment imaging for a single visit on multiple dates, the date of the disease assessment will be assigned using the following rules: For RECIST v1.1 response, if the visit response is Progressive Disease (PD), the date of progression is the earliest of:

- all dates of target lesion scans when the target lesion response is PD

- all dates of non-target lesion scans at which the non-target lesion status is unequivocal progression
- all scan dates documenting new lesion(s)

For both sets of response criteria, if more than one source of PD is reported, then the date assigned is the earliest across all sources of PD. If none of the above dates is available, the date of the earliest scan (if available) or visit date for the assessment at which PD is reported is assigned. If the visit response is PD by symptomatic deterioration, the date is the date of the disease assessment visit.

If the visit response is Stable Disease (SD), the date of SD is the earliest date of any lesion assessment at the visit.

If the visit response is Complete Response (CR) or Partial Response (PR), the date of CR or PR is the latest date of any lesion assessment at the visit. If all assessment dates are missing or not reported, then a date of response cannot be assigned.

8.2.8.2 Injected and Non-injected Lesions

To explore the treatment effect of IMO-2125 between the measurable injected and non-injected lesions, the sum of the longest diameters will be calculated separately among the injected lesions and the non-injected lesions for each subject at each nominal visit in the combination treatment arm (ipilimumab with IMO-2125). Due to the potentially different numbers of injected and non-injected lesions involved in the calculation for each subject, the percent reduction from baseline in the sum of the longest diameters will be used for the analysis. For each subject, the paired difference in the percent reduction between the injected and non-injected lesions will be calculated. Any measurable new lesions noted post-baseline will be excluded from the calculation.

8.2.9 Other Assessments

All data will be reported according to the nominal visit for which it was reported (that is, no visit windows will be applied during dataset creation). Unscheduled data will only be included in summaries of worst-case (highest and/or lowest) post-baseline assessments.

If multiple safety assessments on different days are reported for the same scheduled assessment, then the latest assessment for that scheduled assessment will be analyzed.

If multiple assessments are reported on the same date for the same scheduled planned time, then the worst-case result will be analyzed.

Data from all assessments (scheduled and unscheduled), including multiple assessments, will be included in listings.

8.2.10 Strata Used for Analysis

As stated in the protocol, the strata may be collapsed as appropriate with the goal of avoiding strata with too few subjects (the threshold for number of subjects per stratum was pre-defined as 5%). At the time of the finalization of the current version of the SAP, the distribution of subjects across randomization strata was known. The distribution was provided to the Sponsor's medical monitor for review. If a stratum had <5% of subjects, the stratification factor level was combined with another based on clinical judgment. Based on this assessment, stratification factor levels were combined as follows:

1. Metastasis stage M1c and BRAF mutation positive
2. Metastasis stage M1c and BRAF mutation wild type
3. Metastasis stage Other and BRAF mutation positive
4. Metastasis stage Other and BRAF mutation wild type

8.2.11 Other Derived Variables

ECG Corrected QT Interval

Fridericia's corrected QT (QTcF): QT interval / $[(\text{RR interval}/1000)^{1/3}]$, where RR interval is in msec. If RR is missing, then the formula to use is: QT interval / $[(60/\text{HR})^{1/3}]$, where HR = heart rate in beats per minute.

Body Mass Index (BMI)

BMI will be calculated using the following formula:

$$\text{BMI (kg/m}^2\text{)} = \text{Weight (kg)} / [\text{Height (cm)}/100]^2$$

using the height measured at Screening and the weight measured at Day 1 (if available). If weight at Day 1 is not available, the assessment at Screening will be used (if available). If neither is available, then BMI is missing.

Age

Age at informed consent will be calculated using the following formula:

$$\text{Age (years)} = \text{floor}((\text{intck('month', BirthDate, InformedConsentDate}) - (\text{day(InformedConsentDate)} < \text{day(Birthdate)})) / 12)$$

In addition, age at informed consent will be categorized as 18-65, >65-75, or >75.

Race

For subgroup analyses, race will be categorized as white and non-white.

Region

For subgroup analyses, region will be categorized as US and non-US.

8.3 SAFETY PARAMETER RANGES

8.3.1 Laboratory Parameters

Reported laboratory values will be categorized using value ranges that reflect the severity grades in the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) v4.03 for the relevant laboratory parameters. See Appendix Section 16.5.

Laboratory values will also be categorized relative to the normal range: a value that is outside the reference range is either high abnormal (value above the upper limit of the normal [ULN] reference range) or low abnormal (value below the lower limit of the normal [LLN] reference range).

Local laboratories were used in this study. Some of the local laboratories did not provide reference ranges for the corresponding results. For these cases, the reference ranges from the American College of Physicians will be used. Below is the link to these reference ranges: https://annualmeeting.acponline.org/sites/default/files/shared/documents/for-meeting-attendees/normal-lab-values.pdf

8.3.2 ECG Parameters

To report QTcF values, categories referencing the grades in the NCI-CTCAE v4.03 will be used (see adverse event 'Electrocardiogram QT corrected interval prolonged'). Additionally, the post-baseline increase in corrected QT values will be summarized using the ranges below.

ECG Parameter	Reporting Range	Unit
Absolute QTcF interval	≥450 to <481 ≥481 to <501 (Grade 2) ≥501	msec
Increase from baseline QTcF	Increase of ≥31 to ≤60 Increase of >60	msec

The following criteria will be used to flag other clinically significant post-baseline ECG values:

ECG Parameter	Out of Normal Ranges	Unit
PR interval	<110 (L) and >220 (H)	msec
QRS interval	<75 (L) and >110 (H)	msec

8.3.3 Vital Signs

The following criteria will be used to summarize heart rate shift tables:

Vital Sign Parameter	Reporting Range	Unit
Heart Rate	< 50 50 to 120 > 120	bpm

To summarize blood pressure, the below categories will be used to produce shift tables.

Vital Sign Parameter	Reporting Range	Unit
Systolic Blood Pressure	< 90 ≥90 to <120 ≥120 to <150 ≥150 to <180 ≥180	mmHg
Diastolic Blood Pressure	< 50 ≥50 to <70 ≥70 to <90 ≥90 to <110 ≥110	mmHg

To summarize temperature, categories below will be used to produce shift tables.

Vital Sign Parameter	Reporting Range	Unit
Temperature	≤35 > 35 to < 38 ≥38	Degrees Celsius

9 DEMOGRAPHICS, BASELINE DISEASE CHARACTERISTICS, AND SUBJECT DISPOSITION

Unless otherwise stated, all tables and listings in this section will be based on the ITT Analysis Set.

9.1 DISPOSITION OF SUBJECTS

The number and percentage of subjects in each analysis set will be summarized, as will subject status at the end of the study, comprising completed (death), ongoing, or withdrawn

from the study, with reasons for study withdrawal; and study treatment status, comprising completed study treatment or prematurely discontinued study treatment, with reasons for premature discontinuation of study treatment. Duration of active follow-up, defined as the duration between the date of randomization and the date of last disease assessment, in months as well as duration of survival follow-up defined as the duration between the date of randomization and the date of last contact or death, in months will be summarized descriptively.

- Analysis Sets
- Subject Status
- Study Treatment Status
- Duration of Active Follow-up
- Duration of Survival Follow-up

Reasons for study withdrawal and study treatment discontinuation will be presented in the order they are displayed in the electronic Case Report Form (eCRF).

The following listings will be provided:

- Subject disposition
- Reasons for study withdrawal
- Reasons for study treatment discontinuation

This analysis will be repeated for FAS and Per Protocol Analysis Set for sensitivity analysis.

9.2 PROTOCOL DEVIATIONS

Protocol deviations will be categorized as major or minor as defined in 2125-MEL-301 Protocol Deviation Plan. A subset of major protocol deviations will be further classified as exclusionary from the Per Protocol Analysis Set if they are considered having significant impact on the primary efficacy data. The following summary will be provided:

- Major protocol deviations by category

The following listings will be provided:

- All inclusion and exclusion criteria violations
- All protocol deviations including major designation and exclusionary classification from the Per Protocol Analysis Set

9.3 DEMOGRAPHIC AND BASELINE DISEASE CHARACTERISTICS

The following summaries will be provided:

- Demographic and baseline characteristics (age at consent, age categories [18-65, >65-75, >75], race, ethnicity, sex, country, region, height, weight, BMI, baseline lactate dehydrogenase [LDH], LDH categories [≤ULN, >ULN], baseline neutrophil/lymphocyte ratio, and ratio categories [<2.5, ≥2.5])
- Baseline disease characteristics (primary histology, stage, tumor PD-L1 immunohistochemistry result, elevated LDH, BRAF mutation status, and ECOG performance status at baseline)
- Prior systemic anticancer treatment history (all settings)
- Prior systemic anticancer treatment history (unresectable/metastatic disease setting only)

The following listings will be provided:

- Demographic characteristics
- Baseline disease characteristics (excluding ECOG performance status)
- Medical history
- Prior systemic anticancer treatment, including best response and reason for discontinuation if available
- Prior cancer-related surgeries
- Prior radiotherapy
- ECOG performance status

The demographic and baseline disease characteristics analyses will be repeated for FAS and Per Protocol Analysis Set for sensitivity analysis.

9.4 STRATIFICATION FACTORS

The number of subjects at each stratification factor level at randomization and from the clinical data will be summarized using frequencies and percentages and listed. The summary will be by marginal levels of duration of prior anti-PD-1 therapy (≥12 weeks vs <12 weeks), metastasis stage (M1c vs other), and BRAF mutation status and prior targeted therapy (BRAF wild type [i.e., negative], BRAF mutation positive with prior targeted therapy, or BRAF mutation positive with no prior targeted therapy) as well as the 12 stratification cells. The listing will show the randomized and clinical data stratification levels for each subject.

The duration of anti-PD-1 therapy in weeks will be calculated using start and end dates reported on the Prior Systemic Anticancer Treatment page of the eCRF as (therapy end date – therapy start date + 1)/7 when a therapy is referred to as "PD-1 inhibitor".

Metastasis stage will be identified from the Baseline Disease Characteristics page of the eCRF as M1c or Other (if not M1c).

BRAF mutation status is reported on the Baseline Disease Characteristics page of the eCRF as negative or positive. Prior targeted therapy for BRAF mutation positive subjects will be identified as the treatment category of prior systemic anticancer therapy of BRAF inhibitor, MEK inhibitor, other targeted therapy, or any combination of these therapies for those subjects with "Positive" BRAF mutation.

Section 8.2.10 describes how the stratification factors are combined. The combined stratification levels will be summarized showing the levels with metastasis stage (M1c or Other) and BRAF mutation status (BRAF wild type or BRAF mutation positive).

The following summaries will be provided:

- Stratification factor levels as randomized
- Stratification factor levels derived from the clinical data
- Stratification factor levels as combined

The following listing will be provided:

- Stratification factor levels

9.5 CONCOMITANT MEDICATIONS

Concomitant medications will be coded using the World Health Organization (WHO) Drug Dictionary Version B3 Sep 2020. A concomitant medication is defined as any drug or substance administered between the time of the first dose of study treatment and 30 days from the date of the last dose of study treatment, or taken to treat SAEs, irAEs, AEs of Grade 3 or above that occurred within 90 days of the last dose of study treatment, or taken to treat Grade 3 or above treatment-related AEs and SAEs that occurred during either the Active or Survival follow-up periods. This includes medications that were started prior to screening if their use continued during dosing. If the start date or end date of concomitant medication is partial, use the imputation rules defined in Section 8.1.2 to impute the date and determine if the medication was concomitant.

In the summary of concomitant medications, each subject is counted once within each unique term. For example, if a subject takes Amoxicillin on two separate occasions, the subject is counted only once under the ingredient "Amoxicillin".

The summary of concomitant medications using the Safety Set will show the number and percentage of subjects taking concomitant medications by therapeutic class and preferred term (PT). Anatomical Therapeutic Chemical (ATC) Level 4 will be used for the listing and summary.

A similar summary will also be generated for concomitant medications that were used to treat immune-related adverse event as recorded on the Concomitant Medication eCRF page.

Another summary will be generated by category of concomitant immune-modulating medications that were used to treat irAEs. These medication categories include thyroid hormone replacement therapies, systemic steroids, and immune-suppressants. Thyroid hormone replacement therapies will be identified by WHO drug ATC prefix H03, systemic steroids by WHO drug ATC prefix H02, and immuno-suppressants by WHO drug ATC prefix L04. Any medications with one of these prefixes that were indicated on the Concomitant Medication eCRF page as being used to treat irAEs will be included in this summary by preferred term under the corresponding category.

Cancer treatments including, but not limited to, radiotherapy, anticancer treatment, and surgery that occurred after the start of study treatment and were received during the study will be summarized separately. If a subject received more than one type of cancer treatment, he/she will be counted under each of them in the summary. The best overall response from these cancer treatments and procedures will be included in the summary. Biopsies and other diagnostic procedures will not be considered as cancer treatment.

IMO-2125 is a cytokine modulator that may indirectly affect cytochrome P450 (CYP) production or activity, and subsequently affect the exposure to CYP substrates. Therefore, increased AEs or decreased efficacy may occur in patients concurrently administered CYP-sensitive substrates or substrates with a narrow therapeutic range. Any concomitant medications identified as CYP-sensitive substrates or substrates with a narrow therapeutic range will be summarized and listed including any AE(s) that started during the duration of the 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	duloxetine, alosetron
CYP1A2 substrates with a narrow therapeutic range	theophylline, tizanidine

Drug Category	Preferred Term
Sensitive CYP2C8 substrates	repaglinide
CYP2C8 substrates with a narrow therapeutic range	paclitaxel
CYP2C9 substrates with a narrow therapeutic range	warfarin, phenytoin
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

The following summaries will be provided:

- Concomitant medications
- Concomitant medications for irAEs by category (thyroid hormone replacement medications, systemic steroids, immune-suppressants)
- Cancer treatments and surgeries after the start of study treatment
- Concomitant sensitive and narrow therapeutic range CYP substrates

The following listings will be provided:

- Prior and concomitant medications
- Cancer treatment after start of study treatment
- Sensitive and narrow therapeutic range CYP substrate - concomitant medications for subjects who used CYP substrates during the study
- Sensitive and narrow therapeutic range CYP substrate - treatment-emergent adverse events started during or after use of CYP substrates

10 EFFICACY

The analysis of ORR will take place after all randomized subjects fall within one of the following categories:

- completed scheduled study treatment and completed at least 28 weeks on the study;

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

The OS study analysis will take place when 392 deaths have occurred or approximately 36 months after the last subject is randomized, whichever occurs first. All tables, figures, and listings will be produced for the final study analysis. All efficacy tables, listings, and figures will use the ITT Analysis Set.

For determination of best overall response by RECIST v1.1, response assessments of CR and PR require confirmation by imaging ≥4 weeks after the initial documentation of CR or PR.

10.1 ANALYSIS OF THE PRIMARY ENDPOINT FAMILY

10.1.1 Independent Reviewer-Assessed ORR by RECIST v1.1

The final and sole analysis of ORR assessed by blinded independent review using RECIST v1.1 will test the response proportions of the two treatment arms using a stratified Cochran-Mantel-Haenszel (CMH) test for two proportions by the randomized strata as defined in Section 9.4. To allow for adequate time for response and confirmation, the analysis of ORR will take place no sooner than when all randomized subjects completed scheduled study treatment and completed at least 28 weeks on the study; prematurely discontinued study treatment and completed at least 28 weeks on the study; or withdrew, were lost to follow-up, or died before completing at least 28 weeks on the study.

The generic SAS procedure call is:

```
proc freq data=<dataset name>;
   tables strata*response*treatment / cmh ;
run;
```

ORR is defined as the percentage of subjects achieving a CR or PR out of the total number of subjects included in the analysis population. The CR or PR must occur prior to PD and the start of any subsequent anticancer therapy. Subjects with not evaluable, unknown, or missing best response will be handled as non-responders; i.e., they will be included in the denominator when calculating the ORR. The independent reviewer-assessed best overall response and ORR by RECIST v1.1 with 95%, two-sided, confidence intervals (CIs) using the Wald's binomial method will be provided for each treatment arm. The percentage difference of ORR between the two treatment arms with a 95%, two-sided CI, and the p-value from the stratified CMH test will be provided. In support of ORR analysis, the

summary statistics for duration of active follow-up times for all subjects will be provided (see the summary under subject disposition).

The following summary and figures will be provided:

- Independent Reviewer-Assessed Response by RECIST v1.1
- Swimmer's Plot of Independent Reviewer-Assessed Response by RECIST v1.1 for ORR Responders
- Waterfall Plot of Maximum Percent Reduction from Baseline in Individual Sum of the Longest Diameters of Target Lesions, Assessed by Independent Reviewer
- Spider Plot of Individual Percent Change from Baseline in Sum of the Longest Diameters of Target Lesions Over Time, Assessed by Independent Reviewer

The following efficacy listings will be provided:

- Independent Reviewer-Assessed Target Lesions
- Independent Reviewer-Assessed Non-Target Lesions
- Independent Reviewer-Assessed New Lesions
- Independent Reviewer-Assessed Response by RECIST v1.1
- Independent Reviewer-Assessed Response by irRECIST
- Independent Reviewer-Assessed RECIST v1.1 Tumor Response Endpoints (Best Overall Response, ORR, DCR, DRR, DoR)

10.1.2 Sensitivity Analysis of ORR

The main analysis of ORR will be repeated for FAS and Per Protocol Analysis Set as sensitivity analysis. In addition, a sensitivity analysis using an unstratified Chi-square test for two proportions will be performed. The "best case scenario" sensitivity analysis will also be performed with the subjects who do not have any tumor response prior to discontinuation imputed as responders, versus the main ORR analysis with these subjects imputed as non-responders.

The following summaries will be provided:

- Objective Response Rate by RECIST v1.1 for FAS and Per Protocol Analysis Set
- Un-stratified and Best Case Scenario Analysis of Objective Response Rate by RECIST v1.1

Note: Un-stratified and "best case scenario" sensitivity analyses are included in the Independent Reviewer-Assessed Response by RECIST v1.1 table.

10.1.3 Analysis of OS

The analysis of OS will be performed after 392 deaths or approximately 36 months after the last subject is randomized, whichever occurs first. If the test for ORR is significant, based on the fallback method description in Section 4.5, overall survival will be tested using a one-sided, stratified log-rank test with a significance level of 0.025. The same strata used in the stratified analysis of ORR will be employed in the analysis of OS. If the p-value is ≤0.025, the null hypothesis will be rejected with the conclusion that OS in the IMO-2125 + ipilimumab combination arm is statistically superior. Otherwise, if the test for ORR is not significant, the overall survival will be tested using a one-sided, stratified log-rank test with a significance level of 0.005. If the p-value is ≤0.005, the null hypothesis will be rejected with the conclusion that OS in the IMO-2125 + ipilimumab combination arm is statistically superior.

OS will be summarized with median, first, and third quartiles of Kaplan-Meier estimates with corresponding 95% CIs calculated by the Brookmeyer-Crowley method [Brookmeyer, 1982] with log-log transformation. Kaplan-Meier estimates and 95% CIs will also be produced at OS landmark time points at 1 and 2 years. The 95% CIs for Kaplan-Meier estimates at each of the OS landmark time points will be calculated using Greenwood's formula with log-log transformation. OS summaries will include the number of subjects at risk, the number of subjects who died, and the number of censored subjects. In addition, the survival follow-up, defined as the duration between the date of randomization and the date of last contact, in months will be analyzed by reverse Kaplan-Meier method, median and its corresponding 95% CI will be summarized. The figure will identify the number of subjects at risk at each scheduled visit and censored times on the curve. The HR and a 95% CI will be estimated using a Cox proportional hazards model, stratified by the same strata used in the analysis of ORR.

The following table and figure will be provided for OS:

- Overall Survival
- Kaplan-Meier Plot of Overall Survival

The following efficacy listing will be provided:

- Overall Survival

10.1.4 Sensitivity Analysis of Overall Survival

The analysis of OS will be repeated for FAS and Per Protocol Analysis Set. In addition, sensitivity analysis of stratification effects will be performed using an HR estimator with a

corresponding 95% CI that uses an un-stratified HR estimator and un-stratified log rank test for the ITT Analysis Set.

The Kaplan-Meier plot of OS will be used to assess the proportionality of hazards and to determine if there is a delayed treatment effect. If a delayed treatment effect is observed, results from a Fleming-Harrington weighted log-rank test with $\rho = 0$ and $\gamma = 0.5$ will be presented to test the equality of the survival curves between the treatement groups. These weights were chosen a priori anticipating the survival curves could be similar for the first 3 months. If appropriate based on the proportional hazards assessment, the restricted mean survival time will be compared between the treatment arms. These two sensitivity analyses will be conducted using the ITT Analysis Set.

The following summaries will be provided for these sensitivity analyses of OS:

- Overall Survival for FAS and Per Protocol Analysis Set
- Un-stratified Overall Survival
- Overall Survival Using Weighted Log-Rank Test
- Overall Survival Using Restricted Mean Survival Times

10.1.5 Sensitivity Analysis of Overall Survival using Imputed Death Dates

As up to 10% of the enrolled subjects are anticipated to withdraw from the study early, a sensitivity analysis of OS will be performed where the missing death dates are imputed as the last known alive date +1 for the early withdrawn subjects. Results will be summarized with median, first, and third quartiles of Kaplan-Meier estimates with corresponding 95% CIs calculated by the Brookmeyer-Crowley method with log-log transformation. The HR and a 95% CI will be estimated using a Cox proportional hazards model, stratified by the same strata used in the analysis of ORR.

The following summary will be provided:

- Overall Survival Using Imputed Death Dates

10.1.6 Subgroup Analyses of the Primary Endpoint Family

To investigate treatment effect in subgroups, independent reviewer-assessed ORR by RECIST v1.1 and OS will be analyzed for each of the following subgroups:

- Metastasis stage (M1c and Other)
- BRAF mutation status (BRAF wild type and BRAF mutation positive)
- Duration of prior anti-PD-1 therapy (≥12 weeks and <12 weeks)
- Region (US and non-US)

- Baseline ECOG (0 and ≥1)
- Baseline LDH (Normal: ≤ ULN and Abnormal: > ULN)
- Baseline LDH (≤ ULN, ULN to ≤ 2x ULN, > 2x ULN)
- Baseline Neutrophil/Lymphocyte Ratio (<2.5 and ≥2.5)
- Subjects who used CYP substrate concomitant medications and subjects who did not use CYP substrate concomitant medications

The subgroup summaries for ORR by RECIST v1.1 with 95%, two-sided CIs using the Wald's binomial method will be provided for each treatment arm within each subgroup. The subgroup summaries of OS will be summarized by treatment arm within each subgroup with median, first, and third quartiles of Kaplan-Meier estimates with corresponding 95% CIs calculated by the Brookmeyer-Crowley method with log-log transformation.

The following tables and figures will be provided for subgroup analyses:

- Subgroup Analyses of Objective Response Rate
- Subgroup Analyses of Overall Survival
- Forest Plot of Proportion Differences for Objective Response Rate by Subgroup
- Forest Plot of Hazard Ratios for Overall Survival by Subgroup

10.2 ANALYSIS OF SECONDARY EFFICACY ENDPOINTS

10.2.1 Investigator-Assessed ORR by RECIST v1.1

The best overall response and the point estimators of investigator-assessed ORR by RECIST v1.1 with corresponding 95%, two-sided CIs, will be provided. The proportion difference for the ORR by RECIST v1.1 with corresponding 95%, two-sided CIs will be provided.

The following table and figures will be provided:

- Investigator-Assessed Response by RECIST v1.1
- Swimmer's Plot of Investigator-Assessed Response by RECIST v1.1 for ORR Responders
- Waterfall Plot of Maximum Percent Reduction from Baseline in Individual Sum of the Longest Diameters of Target Lesions, Assessed by Investigator
- Spider Plot of Individual Percent Change from Baseline in Sum of the Longest Diameters of Target Lesions, Assessed by Investigator

The following efficacy listings will be provided:

- Investigator-Assessed Target Lesions
- Investigator-Assessed Non-Target Lesions

- Investigator-Assessed New Lesions
- Investigator-Assessed Response by RECIST v1.1
- Investigator-Assessed Response by irRECIST
- Investigator-Assessed RECIST v1.1 Tumor Response Endpoints

10.2.2 Comparison of Best Overall Responses between Independent Review and Investigator

A summary of the differences in the best overall responses by RECIST v.1.1 between independent review and the investigator assessment will be presented by treatment arm and overall in a table format with the number and percentage of independent reviewer responses presented side-by-side with those for the investigator responses. Comparison of the ORR responders and non-responders will be performed by treatment arm and overall to evaluate the number and percentage of concordant and discordant pairs of ORR responses (CR/PR versus non-CR/PR) between the independent reviewer and investigator.

The following summary tables will be provided:

- Concordance of Best Overall Response by Independent Reviewer and Investigator
- Concordance of ORR by Independent Reviewer and Investigator

10.2.3 Analysis of Injected and Non-injected Lesions

For each subject, the sum of longest diameters (SLD) will be calculated separately among the injected lesions and the non-injected lesions at each nominal visit only in the combination treatment arm (ipilimumab with IMO-2125). Note that the sum of the shortest distance (SSD) will be calculated for lymph nodes instead and will be summarized together with SLD in the analysis. For each subject, the percent reduction from baseline in the SLD/SSD, and the paired difference in the percent reduction between the injected and non-injected lesions will be calculated and summarized by study visit. Any new lesions noted post-baseline will be excluded from the calculation. Any non-target lesions without measurement at baseline will be excluded from this analysis. The maximum percent reduction in SLD/SSD by injection status will be presented graphically in a waterfall plot for the ORR responders assessed by independent-reviewer using RECIST v.1.1 (i.e., those with best overall response of CR or PR).

The following table and figure will be provided:

- Paired Difference of Percent Reduction from Baseline in Individual Sum of the Longest Diameters Between Injected and Non-injected Lesions

- Waterfall Plot of Maximum Percent Reduction from Baseline in Individual Sum of the Longest Diameters of Measurable Lesions by Injection Status, ORR Responders Assessed by Independent Reviewer (injection status presented side-by-side)
- Spider Plot of Individual Percent Change from Baseline in Sum of the Longest Diameters of Measurable Lesions by Injection Status, Assessed by Investigator (separate page by injection status)

The following efficacy listing will be provided:

- Sum of the Longest Diameters and Percent Change from Baseline in SLD by Injection Status

10.2.4 Durable Response Rate

The durable response rate will be derived separately for the assessments by blinded independent reviewer and the investigator. DRR will be derived using RECIST v1.1, defined as the rate of CR or PR lasting ≥6 months from the date of first instance of confirmed CR or PR response which begin during the first 12 months of treatment. The denominator will be the number of subjects included in the corresponding analysis set (e.g., ITT). The calculation for the number of days in 6 months is 6*(365.25/12); the cutoff date for 6 months is therefore (scan date + 182.625).

Summaries will include DRR by RECIST v1.1 with corresponding 95%, two-sided CIs using the Wald's binomial method for each treatment arm.

Summaries of DRR are included within the following summary outputs:

- DRR based on Independent Reviewer-Assessed ORR by RECIST v1.1
- DRR based on Investigator-Assessed ORR by RECIST v1.1

Note: DRR analyses are included in the Independent Reviewer-Assessed Response and Investigator-Assessed Response by RECIST v1.1 tables.

10.2.5 Disease Control Rate

The disease control rate (DCR) is defined as the percentage of subjects achieving a confirmed CR, PR, or SD out of the total number of subjects included in the analysis population. The CR, PR, or SD must occur prior to PD and the start of any subsequent anticancer therapy. Subjects with not evaluable, unknown, or missing best response will be handled as non-responders; i.e., they will be included in the denominator when calculating the DCR. The independent reviewer-assessed DCR by RECIST v1.1 with 95%, two-sided CIs using the

Wald's binomial method will be provided for each treatment arm. A similar summary will be provided using the investigator-assessed DCR by RECIST v1.1.

The following summaries will be for DCR:

- Independent Reviewer-Assessed DCR by RECIST v1.1
- Investigator-Assessed DCR by RECIST v1.1

10.2.6 Duration of Response

DoR will be derived separately for the assessments by blinded independent reviewer and the investigator. DoR will be derived using RECIST v1.1, defined as the time in months between the date of the first instance of confirmed CR or PR as the best overall response to the day before the first date that recurrent or progressive disease is objectively documented or date of death. For subjects who have attained CR or PR as the best overall response but do not have progressive disease or died, they will be censored at the same time they will be censored for the primary definition of PFS (See Appendix Section 16.4). Subjects who do not respond will not be included in this analysis.

DoR will be described using Kaplan-Meier estimates with 95% CIs. If there are sufficient number of events, median, first and third quartiles, minimum and maximum for DoR with corresponding 95% CIs will be reported. CIs will be estimated using the Brookmeyer-Crowley method [Brookmeyer, 1982] with log-log transformation. Summaries will also include the number of subjects at risk, the number of subjects with events, and the number of subjects censored.

The following summaries and figures for DoR will be provided:

- DoR based on Independent Reviewer-Assessed ORR by RECIST v1.1 for ORR Responder
- DoR based on Investigator-Assessed ORR by RECIST v1.1 for ORR Responder
- Kaplan-Meier Plot of DoR based on Independent Reviewer-Assessed ORR by RECIST v1.1 for ORR Responder
- Kaplan-Meier Plot of DoR based on Investigator-Assessed ORR by RECIST v1.1 for ORR Responder

10.2.7 Time to Response

TTR will be derived as the time in months from the date of randomization to date of the scan for the first instance of confirmed CR or PR (using RECIST v1.1) by investigator and independent reviewer assessments. Subjects who do not respond will not be included in this analysis.

TTR will be summarized descriptively with mean, standard deviation, median, minimum and maximum.

The following summaries will be provided:

- TTR based on Independent Reviewer-Assessed ORR by RECIST v1.1 for ORR Responder
- TTR based on Investigator-Assessed ORR by RECIST v1.1 for ORR Responder

10.2.8 Analysis of Progression-Free Survival

PFS is defined as the time in months from the date of randomization to progression by RECIST v1.1 or death from any cause. The date of disease progression will be the date of the scan for the first objectively documented PD per RECIST v1.1. Subjects who do not progress including those who have started new anticancer therapy, withdrawn from the study, or been lost to follow-up without disease progression will have their PFS time censored at the last valid disease assessment, defined as a scheduled or unscheduled visit with a disease assessment of CR, PR, or SD (for RECIST v1.1). More detailed censoring rules are in Appendix Section 16.4.

PFS assessed by investigator and independent reviewer will be analyzed using Kaplan-Meier method, the median, first and third quartiles with corresponding 95% CIs are calculated by the Brookmeyer-Crowley method with log-log transformation. If there are a sufficient number of events, Kaplan-Meier estimates and 95% CIs will also be produced at PFS landmark time points at 6 months, 1 and 2 years. The 95% CIs for Kaplan-Meier estimates at each of the PFS landmark time points will be calculated using Greenwood's formula with log-log transformation. Summaries will also include the number at risk, the number of subjects with events, and the number of subjects censored along with their corresponding reason for censoring. Figures will use the Kaplan-Meier estimates and identify the number of subjects at risk at each scheduled visit and censored times on the curve.

The following summaries and figures will be provided for PFS:

- Summary of Independent Reviewer-Assessed PFS by RECIST v1.1
- Summary of Investigator-Assessed PFS by RECIST v1.1
- Kaplan-Meier Plot of Independent Reviewer-Assessed PFS by RECIST v1.1
- Kaplan-Meier Plot of Investigator-Assessed PFS by RECIST v1.1

The following efficacy listing will be provided:

- Progression-free Survival by Independent Reviewer-Assessed and Investigator-Assessed RECIST v1.1

11 SAFETY ANALYSES

All safety analyses will be based on the Safety Set as defined in Section 6.5. Summaries of AEs will include only treatment-emergent AEs (TEAEs), defined as AEs with a start date on or after the date of first dose of study treatment or existing AEs which increase in CTCAE grade after the start of study treatment. If it cannot be determined definitively whether the AE is treatment emergent due to missing or partial onset or end dates, then it will be counted as treatment emergent (see Section 8.2.7 for details).

11.1 EXTENT OF EXPOSURE

Overall exposure will be summarized descriptively by treatment arm and separately by study drug. For ipilimumab, summaries will include the number of infusions received, duration of treatment (weeks), cumulative dose received in milligrams per kilogram (mg/kg) and average dose (mg/kg), per infusion. For IMO-2125, summaries will include the number of injections received, type of injected lesions per eCRF category (i.e., Superficial, Other deep soft tissue, Organ, and Other), duration of treatment (weeks), the cumulative dose received in milligrams (mg), and the average dose (mg) per injection.

To summarize type of injected lesions per eCRF category, subjects will be counted under each type of injection if the subjects received more than one type of injection. Furthermore, the type of injected lesions will also be reclassified into 3 categories: Superficial, Deep, or Visceral (Organ). The Sponsor will perform a review of the 'Other' injection type and map them to the 3 specified categories. If a subject had more than one type of injected lesion during the study, the deepest type of injection will be counted in the summary. For example, a subject who had both deep and visceral injections will be counted under visceral.

Treatment duration will be calculated in weeks for each subject and each treatment using the following formula: Treatment duration (weeks) = (last dose date - first dose date + 1) / 7.

For IMO-2125, cumulative dose received is calculated as the sum of doses (mg) across all injections, and average dose is calculated as the cumulative dose divided by the sum of injections. For ipilimumab, the dose (mg) divided by base weight (kg) will be derived for each subject at each dosing visit. Cumulative dose received is calculated as the sum of dose per weight (mg/kg) across all infusions, and average dose is calculated as the cumulative dose divided by the sum of infusions.

Dose reductions were permitted for patients dosed under Protocol Version 2.0 only. Any dose modifications of study treatment due to irAE will be listed.

The following summaries will be provided:

- IMO-2125 Exposure
- Ipilimumab Exposure

The following listings will be provided:

- IMO-2125 Exposure
- Ipilimumab Exposure
- Dose Modifications Due to irAEs

11.2 ADVERSE EVENTS

Grades of AEs will be assigned according to the CTCAE, Version 4.03. AEs will be coded to the system organ class (SOC) and PT level using the Medical Dictionary for Regulatory Affairs (MedDRA) Dictionary Version 23.0. Treatment-emergent AEs (TEAEs) will be summarized. All AEs will be listed regardless of when they were reported.

Summaries of TEAEs will count the number of subjects, not the number of events; that is, subjects with multiple occurrences of the same TEAE will be counted once.

An overview summary of TEAEs, including counts and percentages of subjects with: any TEAEs; TEAEs of CTCAE Grade 3 or above; TEAEs related to any study treatment; TEAEs related to IMO-2125; TEAEs related to ipilimumab; TEAEs related to any study treatment of CTCAE Grade 3 or above; TEAEs related to IMO-2125 of CTCAE Grade 3 or above; TEAEs related to ipilimumab of CTCAE Grade 3 or above; immune-related TEAEs (see Table 2 in Section 11.5 for the list of AEs); immune-related TEAEs of CTCAE Grade 3 or above, immune-related TEAEs related to any study treatment; immune-related TEAEs related to IMO-2125; immune-related TEAEs related to ipilimumab; TEAEs leading to IMO-2125 discontinuation; TEAEs leading to ipilimumab discontinuation; TEAEs leading to dose modifications (i.e., dose interruptions or dose reduction); SAEs; SAEs of CTCAE Grade 3 or above; SAEs related to any study treatment, SAEs related to IMO-2125; SAEs related to ipilimumab; fatal AEs; fatal AEs related to any study treatment, fatal AEs related to IMO-2125; and fatal AEs related to ipilimumab will be produced.

The frequency and percentage of TEAEs (all grades) will be summarized in descending order of total incidence by SOC and PT. In the SOC row, the number of subjects with multiple events under the same SOC will be counted once. In addition, a separate table for the frequency and percentage of TEAEs (all grades) in descending order of total incidence by PT will be generated. Summaries of TEAEs of CTCAE Grade 3 or above will be produced similarly in descending order of total incidence by PT.

A separate summary will be provided for study treatment-related TEAEs for each study treatment in descending order of total incidence by PT. Treatment-related TEAEs are those

deemed as 'possibly related' or 'related' to the study drug by the investigator. In the IMO-2125 + ipilimumab arm, TEAEs related to either study treatment will be reported. Missing relationship to study treatment will be imputed as described in Section 8.1.1. Similar analysis will be repeated for Grade 3 or above treatment-related TEAE by PT.

In addition, a summary of number and percentage of subjects with any TEAE by maximum grade will be produced. TEAEs will be sorted by PT in descending order of total incidence in the IMO-2125 + ipilimumab arm. Each summary will report the number of subjects with at least one TEAE and the PT reported. Subjects are counted once for each unique PT under the maximum grade. A similar analysis will be repeated for treatment-related TEAE by PT and maximum grade. In the IMO-2125 + ipilimumab arm, TEAEs related to either drug will be reported. This analysis will also be repeated for TEAE related to IMO-2125 and for TEAE related to ipilimumab in both the combination arm and ipilimumab alone arm.

Cumulative TEAEs at 3, 6, 9, and 12 months from first dose will include all TEAEs with a start date on or before 3, 6, 9, or 12 months from the first dose date. The calculation for the days in x months is x*(365.25/12); the cutoff date for x months is therefore (first dose date + x*(365.25/12)). Incidence of subjects experiencing TEAEs up to the specified cut point from first dose will be summarized by PT and maximum grade. A similar analysis will be repeated for treatment-related TEAEs up to the specified cut point from first dose.

Incidence of TEAEs will be summarized by MedDRA PT and time of onset relative to the first exposure of the study drug by 3-week interval during the treatment period. The first onset interval will start at the first dose date and end on the 21st day (Weeks 1-3); the second interval will start on the 22nd day and end on the 42nd day (Weeks 4-6); the third interval will start on the 43rd day and end on the 63rd day (Weeks 7-9); the fourth interval will start of the 64th day and end on the 84th day (Weeks 10-12); the fifth interval will start from the 85th day and end on the 105th day (Weeks 13-15); the sixth interval will start from the 106th day and end on the 126th day (Weeks 16-18); the seventh interval will start from the 127th day and end on the 147th day (Weeks 19-21); and the last will start on the 148th day and end on the 168th day (Weeks 22-24). Adverse events will be assigned to onset categories according to the relative study day when the AE started. AEs with incomplete onset dates will be excluded from this analysis. For subjects who experienced the same AE multiple times and within different onset categories, the event will be counted once in each of the categories in which it started. For each onset category, AE incidences will be calculated by dividing the number of subjects who had each AE during that onset category by the number of subjects who have not dropped out or died at the start of the onset interval. For example, for onset category Weeks 4-6, the denominator will be the number of subjects who have not dropped out or died by the start of Weeks 4-6 interval and were therefore in the risk set for that interval.

All AEs will be listed. This listing will include treatment arm, age, sex, start date and study day, end date and study day, grade, serious (yes or no), irAE (yes or no), relationship to treatment (yes or no), action taken, outcome, and preferred and verbatim terms.

The following summaries will be provided:

- Overall Summary of Treatment-Emergent Adverse Events
- Treatment-Emergent Adverse Events by System Organ Class and Preferred Term
- Treatment-Emergent Adverse Events by Preferred Term
- Treatment-Emergent Adverse Events by Preferred Term and Maximum Grade
- Treatment-Related Treatment-Emergent Adverse Events by Preferred Term (including Treatment-Related, IMO-2125-Related, and Ipilimumab-Related)
- Treatment-Related Treatment-Emergent Adverse Events by Preferred Term and Maximum Grade
- Grade 3 or Above Treatment-Emergent Adverse Events by Preferred Term
- Grade 3 or Above Treatment-Related Treatment-Emergent Adverse Events by Preferred Term
- Cumulative TEAEs at Three Months by Preferred Term and Maximum Grade
- Cumulative TEAEs at Six Months by Preferred Term and Maximum Grade
- Cumulative TEAEs at Nine Months by Preferred Term and Maximum Grade
- Cumulative TEAEs at Twelve Months by Preferred Term and Maximum Grade
- Cumulative Treatment-Related TEAEs at Three Months by Preferred Term and Maximum Grade
- Cumulative Treatment-Related TEAEs at Six Months by Preferred Term and Maximum Grade
- Cumulative Treatment-Related TEAEs at Nine Months by Preferred Term and Maximum Grade
- Cumulative Treatment-Related TEAEs at Twelve Months by Preferred Term and Maximum Grade
- TEAE Incidence by Time to Onset in 3-Week Interval During the Treatment Period

The following listings will be provided:

- All Treatment-Emergent Adverse Events
- Adverse Events Between Signing Consent and the Start of Study Treatment

While pregnancy itself is not considered to be an AE or SAE, any pregnancy complication or elective termination of a pregnancy for medical reasons will be recorded as an AE or SAE as described in the protocol. If any subject or subject's partner becomes pregnant while on the

study, the information will be included in the CSR narratives and no separate table will be produced.

11.3 DEATHS AND SERIOUS ADVERSE EVENTS

A summary of deaths will include the number of subjects who died, the primary reason for death, the number of deaths within 30 days of the last dose of study treatment, the number of subjects alive at last contact with follow-up ongoing, the number of subjects alive at last contact with follow-up ended. The frequency and percentage of serious TEAEs (all grades) will be summarized in descending order of total incidence by PT. A similar analysis will be repeated for treatment-related serious TEAE by PT, for serious TEAE related to IMO-2125 by PT, and for serious TEAE related to Ipilimumab by PT. Grade 3 or above serious TEAEs will also be summarized. Summaries of deaths and SAEs will be repeated for subjects who received visceral injection during the study drug administration. Deaths will also be listed. The listing of SAEs will include a flag for those that are treatment-emergent and will display the SAE's relationship to study treatment.

The following summaries will be provided:

- Serious Treatment-Emergent Adverse Events by Preferred Term
- Grade 3 or Above Serious Treatment-Emergent Adverse Events by Preferred Term
- Treatment-Related Serious Treatment-Emergent Adverse Events by Preferred Term (including Treatment-Related, IMO-2125-Related, and Ipilimumab-Related)
- Treatment-Related Serious Treatment-Emergent Adverse Events by Preferred Term and Maximum Grade
- Deaths

The following listings will be provided:

- All SAEs
- TEAEs Leading to Death
- All Deaths

11.4 ADVERSE EVENTS LEADING TO DISCONTINUATION OF STUDY TREATMENT (WITHDRAWAL), DOSE INTERRUPTIONS, OR DOSE REDUCTIONS

Dose reductions are only permitted for subjects enrolled under Protocol Version 2.0. TEAEs leading to dose interruption and dose reduction will be listed. The following category of TEAEs will be summarized by PT:

- TEAEs Leading to Permanent Discontinuation of IMO-2125 by Preferred Term

- IMO-2125-Related TEAEs Leading to Permanent Discontinuation of IMO-2125 by Preferred Term
- TEAEs Leading to Permanent Discontinuation of Ipilimumab by Preferred Term
- Ipilimumab-Related TEAEs Leading to Permanent Discontinuation of Ipilimumab by Preferred Term

The following listings will be provided:

- TEAEs Leading to Dose Interruption or Dose Reduction
- TEAEs Leading to Treatment Discontinuation

11.5 IMMUNE-RELATED ADVERSE EVENTS

Immune-related AEs (irAEs) are side effects associated with the increased activity of the immune system by immunotherapy agents such as checkpoint inhibitors, which can affect multiple organs of the body including the skin, gastrointestinal tract, endocrine system, liver, lungs, nervous system, and musculoskeletal system.

The following list of AEs were provided in the protocol as a guide to the investigators to identify the immune-related AEs. Any AEs which have been associated with the use of immunotherapy agents were marked as immune-related in the CRF.

- Adrenal insufficiency
- Hypophysitis
- Hypopituitarism
- Hypothyroidism
- Hyperthyroidism
- Other endocrinopathies
- Colitis
- Enterocolitis
- Dermatitis
- Autoimmune dermatitis
- Guillain Barre syndrome
- Hepatitis
- Myasthenia gravis
- Pneumonitis
- Stevens Johnson Syndrome
- Toxic epidermal necrolysis
- Uveitis
- Iritis
- Myocarditis
- Any AEs that the Investigator considers to be of autoimmune or immune-related origin

In addition, the Sponsor medical team also reviews all the events coded under 17 selected MedDRA SOCs that have the potential to identify irAEs (see the list of SOCs below). These AEs are reviewed relative to the dosing of either ipilimumab or tilsotolimod. They are also assessed in the context of the usage of concomitant medications and other AEs that occurred around the same time. This process allows for a holistic review of events in the context of other data elements, thereby providing an exhaustive process for potential irAE identification.

Table 2 List of MedDRA SOCs Used by Sponsor in Identification of Additional Potential irAEs

MedDRA SOCs
Cardiac disorders
Endocrine disorders
Eye disorders
Gastrointestinal disorders
General disorders and administration site conditions
Hepatobiliary disorders
Immune system disorders
Injury, poisoning and procedural complications
Investigations
Musculoskeletal and connective tissue disorders
Neoplasms benign, malignant and unspecified (incl cysts and polyps)
Product issues
Renal and urinary disorders
Respiratory, thoracic and mediastinal disorders
Skin and subcutaneous tissue disorders
Surgical and medical procedures
Vascular disorders

The number and percentage of subjects who experienced at least one irAE will be tabulated. The preferred terms will be identified using the search strategy as described above. The frequency and percentage of immune-related TEAEs will be summarized by PT, as well as by PT and maximum grade. Similar analyses will be repeated for Grade 3 or above immune-related TEAEs and for Grade 3 or above treatment-related immune-related TEAEs. The frequency and percentage of treatment-related immune-related TEAEs will be summarized by PT and maximum grade.

Similarly, the frequency and percentage of immune-related serious TEAEs will be summarized by PT and maximum grade. Similar analysis will be repeated for Grade 3 or above immune-related serious TEAEs by PT. The number and percentage subjects who experienced immune-related TEAEs leading to permanent discontinuation of IMO-2125 and

subjects who experienced immune-related TEAEs leading to permanent discontinuation of ipilimumab will be presented by PT.

A listing of immune-modulating medications which include thyroid hormone replacement therapies, systemic steroid and immuno-suppressants used after occurrence of irAE will be presented. Thyroid hormone replacement therapies will be identified by WHO drug ATC prefix H03, systemic steroids by WHO drug ATC prefix H02, and immuno-suppressants by WHO drug ATC prefix L04.

All irAEs will be listed. This listing will include treatment arm, age, sex, verbatim term and the corresponding coded terms, start date and study day, end date and study day, grade, serious (yes or no), relationship to treatment (yes or no), action taken, and outcome. It will also include an indicator for the source of the irAEs (CRF or sponsor-defined).

The following summaries will be provided:

- Immune-Related Treatment-Emergent Adverse Events by Preferred Term
- Immune-Related Treatment-Emergent Adverse Events by Preferred Term and Maximum Grade
- Grade 3 or Above Treatment-Related Immune-Related Treatment-Emergent Adverse Events by Preferred Term
- Treatment-Related Immune-Related Treatment-Emergent Adverse Events by Preferred Term and Maximum Grade
- Grade 3 or Above Treatment-Related Immune-Related Treatment-Emergent Adverse Events by Preferred Term
- Immune-Related Serious Treatment-Emergent Adverse Events by Preferred Term and Maximum Grade
- Grade 3 or Above Immune-Related Serious Treatment-Emergent Adverse Events by Preferred Term
- Immune-Related TEAEs Leading to Permanent Discontinuation of IMO-2125 by Preferred Term
- Immune-Related TEAEs Leading to Permanent Discontinuation of Ipilimumab by Preferred Term

The following listing will be provided:

- Immune-Related Treatment-Emergent Adverse Events

11.6 ADVERSE EVENTS OF SPECIAL INTEREST

Systemic injection and infusion reaction such as cytokine release syndrome (CRS), anaphylactic and anaphylactoid reactions are deemed to be adverse events of special interest

(AESIs). From communication with U.S. Food and Drug Administration (FDA) on 11 September 2020, the agency agreed with the Sponsor regarding the use of the American Society for Transplantation and Cellular Therapy (ASTCT) Consensus (Lee, 2019) for assessment of CRS events, and FDA's guidance for the industry for immunogenicity assessment for evaluation of anaphylactic events. FDA recommended to assess any fever (not attributable to any other cause), hypotension and hypoxia, and to include related organ toxicities associated with CRS with severity graded according to CTCAE 4.03. FDA also recommended to include definitions of CRS, anaphylaxis, and hypersensitivity based on clinical diagnostic criteria and to provide an analysis based on the clinical criteria to distinguish CRS from anaphylaxis and hypersensitivity by presenting data on the nature, onset, frequency and severity, information about dose modifications and any evidence of recurrence with dose reduction or after drug withdrawal.

The Sponsor has used the following nine MedDRA LLTs for the initial database search for AESIs reported within 14 days after any tilso injections: anaphylaxis, cytokine release syndrome, infusion related reaction, injection site allergic reaction, injection related reaction, allergic reaction, anaphylactic reaction, anaphylactoid reaction, or systemic inflammatory response syndrome. A listing of AEs corresponding to these LLTs was generated to be used for evaluation against the ASTCT definition for CRS as well as the FDA guidance document on anaphylactic reaction which are provided below as a reference:

AE Term	Definition
CRS	A supraphysiologic response following any immune therapy that results in the activation or engagement of endogenous or infused T cells and/or other immune effector cells. A qualified CRS event will include fever along with hypotension and/or hypoxia.
Fever	A disorder characterized by elevation of the body's temperature above the upper limit of normal, and a temperature of 38.0 °C is considered grade 1 fever.
Hypotension	A disorder characterized by a blood pressure that is below the normal expected for an individual in a given environment.
Hypoxia	An Oxygen saturation (SaO2) <94% or an individual requiring supplemental oxygen to correct a deficit in oxygenation is considered to have hypoxia. Oxygen provided only as a comfort measure should not be used.
Anaphylactic reaction	Anaphylaxis is a serious, acute allergic reaction without a particular immunologic mechanism and based on the following clinical features: 1. Acute onset of an illness (minutes to several hours) with involvement of the skin, mucosal tissue, or both, and at least one of the following: • Hypoxia • Hypotension 2. Two or more of the following that occur rapidly after exposure to Tilsotolimod (minutes to several hours): • Involvement of the skin-mucosal tissue

AE Term	Definition
	• Hypoxia • Hypotension • Persistent gastrointestinal symptoms 3. Hypotension after exposure to Tilsotolimod when prior systemic reactions with Tilsotolimod has occurred (minutes to several hours)

In order to perform a more comprehensive assessment of the AESIs, a search of all TEAEs which are coded under any of the following MedDRA SOC and started within 14 days after any tilsotolimod injections will also be conducted:

- General disorders and administration site condition
- Respiratory and mediastinal disorders vascular disorders
- Immune system disorders (see Table 2 in Section 11.5)

The AEs identified will be reviewed and classified by the Sponsor as CRS, anaphylactic reaction or hypersensitivity reaction. The classification will be imported into the analysis dataset for summaries.

Significant AESIs will be summarized, that include Grade 3 and above systemic injection and infusion reactions.

Based on the strategy and definitions stated above, these AEs included under each event type will be determined based on a programmatic search of the AE datasets using the specified LLT in conjunction of a medical review of the AEs identified. The incidence of the AESIs under each event type will be summarized by MedDRA preferred term.

Analyses of time to the first onset of the AESIs will be analyzed using the Kaplan-Meier product-limit method to estimate the quartiles and corresponding 95% confidence intervals for time to onset of each event. For this analysis, subjects who completed or prematurely terminated the study with the specified event will have the time to onset censored at the time of their completion or termination.

A listing of subjects who were identified to have experienced AESIs will be presented with onset, frequency and severity, information about dose modifications and any evidence of recurrence with dose reduction or after drug withdrawal.

Subject ID	PT	Sponsor assessed category	Grade	SAE	Time to Onset	Frequency	Recurrence after dose modification	Recurrence after drug withdrawal	Related Organ Toxicities and grades	Outcome

Abbreviation: PT = Preferred Term.

The following summaries will be provided:

- Significant Treatment-Emergent Adverse Events of Interest by Preferred Term

- Time to Onset of Significant Treatment-Emergent Adverse Events of Interest

The following listing will be provided:

- Significant Treatment-Emergent Adverse Events of Interest

11.7 SUBGROUP ANALYSIS FOR ADVERSE EVENTS

Adverse events will be further examined by Injection Type as reclassified by the Sponsor in Section 11.1 [Visceral (Organ), Deep, and Superficial]. Any summaries by injection type will be performed for the combination treatment arm only.

The following tables will be provided for the AE subgroup analysis:

- Treatment-Emergent Adverse Events by Preferred Term and Injection Type
- Grade 3 or Above Treatment-Emergent Adverse Events by Preferred Term and Injection Type
- Serious Treatment-Emergent Adverse Events by Preferred Term and Injection Type
- Deaths by Injection Type

11.8 CLINICAL LABORATORY EVALUATIONS

The laboratory tests in Section 12.2 of the protocol, Laboratory Assessments, will be summarized as described in this section.

Category	Analyte
Hematology	CBC: white blood cell (WBC), red blood cell (RBC), hemoglobin, hematocrit, platelet count, mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), mean corpuscular volume (MCV) Differential WBC count: neutrophils, monocytes, lymphocytes, eosinophils, basophils, atypical lymphocytes
Coagulation	prothrombin time (PT), activated partial thromoboplastin (aPTT), international normalized ratio (INR)
Complement	CH50, C3, C4
Clinical Chemistry Panel	Renal: Serum sodium, potassium, chloride, carbon dioxide (CO2), calcium, phosphate, creatinine, blood urea nitrogen, uric acid
	Endocrine: serum glucose, free thyroxine (free T4), total or free triiodothyronine (total or free T3), thyroid stimulating hormone (TSH)
	Liver: serum alanine aminotransferase (ALT), aspartate aminotransferase (AST), lactate dehydrogenase (LDH), alkaline phosphatase, albumin, total protein, total bilirubin
	Lipids: Serum cholesterol, triglycerides
Urinalysis	Dipstick testing (urinalysis and microscopy will be conducted only if dipstick results are abnormal)

Laboratory data will be presented in International System of Units (SI) and in the order presented in the protocol. Laboratory grades will be reported using the CTCAE v4.03 (see Appendix Section 16.5); ungraded laboratory assessments will be reported using normal ranges.

Laboratory tests that are graded for both low and high abnormal values will have both values summarized separately with directions (hyper- or hypo-) labeled accordingly.

Separate summary tables of the observed and change from baseline values for hematology, chemistry, coagulation, and complement laboratory tests will be produced.

Definition of the baseline assessment is in Section 8.2.5.

The denominator in percentage calculations at each scheduled visit will be based on the number of subjects with a non-missing value at each visit.

Hematology and chemistry laboratory tests will be summarized using shift tables by treatment arm. Subjects must have a baseline and at least one non-missing post-baseline assessment to be included in the shift analysis.

Summaries of shifts from baseline will be provided for hematology and chemistry laboratory tests that are graded by CTCAE v4.03 (Appendix Section 16.5). This shift table will include a worst-case (defined as the highest CTCAE grade) post-baseline summary that includes data from both scheduled and unscheduled visits. Categories based on value ranges for CTCAE grades will be shown for baseline and worst case post-baseline, with the number and percentage of subjects in each.

Summaries of shifts from baseline with respect to the normal range will be provided for the following laboratory parameters: WBC, RBC, hematocrit, platelet count, neutrophils, lymphocytes, total bilirubin, creatinine, LDH, ALT, AST, and TSH. This shift table will include both shift to lowest and shift to highest post-baseline with respect to the normal range. All data from both scheduled and unscheduled visits will be considered for the shifts. Categories of normal range, below the normal range, and above the normal range will be shown for baseline, the highest and the lowest post-baseline, with the number and percentage of subjects in each. A figure showing the mean, median, quartiles, range, and outliers beyond the interquartile range (boxplot) for each treatment arm at each scheduled visit will be produced for hematology and chemistry parameters. It will have the nominal visit assessment week on the horizontal axis and the parameter value on the vertical axis. The number of subjects assessed in each treatment arm will be displayed below each visit.

A paneled scatterplot of the ratio of maximum total liver function tests to ULN versus baseline liver function tests to ULN will be produced by treatment arm. The liver function tests included in the plot are ALT, AST, total bilirubin, and alkaline phosphatase.

Listing of all laboratory values will be provided with the CTCAE v4.03 grade (if applicable) and laboratory values LLN and ULN will be flagged.

Summaries to be produced are:

- Summary of Change from Baseline in Hematology
- Summary of Change from Baseline in Chemistry
- Summary of Change from Baseline in Coagulation
- Summary of Change from Baseline in Complement
- CTCAE Shifts from Baseline Grade in Hematology
- CTCAE Shifts from Baseline Grade in Chemistry
- Shifts from Baseline Relative to the Normal Range in Selected Laboratory Tests

Figures to be produced are:

- Boxplot for Hematology
- Boxplot for Chemistry
- Liver Function Tests Maximum Values to ULN on Study vs Baseline to ULN

Listings to be produced are:

- Hematology
- Chemistry
- Coagulation
- Complement
- Dipstick Test and Urinalysis

11.9 OTHER SAFETY MEASURES

The denominator in percentage calculations at each scheduled visit will be based on the number of subjects with non-missing values at each visit.

11.9.1 Vital Signs and Weight

Blood pressure values will be categorized into the ranges as listed in Section 8.3.3.

Summary of shifts in blood pressure from baseline will be provided. This shift table will include a summary of the highest and the lowest post-baseline that includes data from both scheduled and unscheduled visits. Categories will be shown for baseline, the highest and the lowest post-baseline, with the number and percentage of subjects in each. Subjects must have a baseline and at least one non-missing post-baseline assessment to be included in the shift analysis.

Summary of shifts in heart rate and temperature from baseline to lowest and highest post-baseline value will be provided. The actual values will be categorized into the ranges as listed in Section 8.3.3. Number and percentage of subjects in each of the categories will be presented for the lowest and highest post-baseline.

Summaries to be produced are:

- Shifts in Blood Pressure from Baseline to Lowest and Highest Post-Baseline
- Shifts in Heart Rate and Temperature from Baseline to Lowest and Highest Post-Baseline

The listing to be produced is:

- Vital Signs (including out of range indicator)

11.9.2 ECG

QTcF values based on Fridericia's formula will be calculated as described in Section 8.2.11 and then rounded to integer values. These integer values will be categorized into the following ranges: <450, 450-480, >480-500, and >500 msec. Changes from baseline in QTcF values will be categorized into: 31-60 and >60 msec.

The mean of the triplicate values at each time point will be used for the analyses of continuous ECG parameters. A summary of the ECG data and their corresponding change from baseline will be provided. A shift in QTcF table will include shifts to the highest post-baseline that includes data from both scheduled and unscheduled visits. Categories of each grade as defined above will be shown for baseline and post-baseline, with the number and percentage of subjects in each. In addition, the changes in QTcF categories as defined above will be summarized at each scheduled visit and at the highest post-baseline. Subjects must have a baseline and at least one non-missing post-baseline assessment in order to be included in the shift analysis.

The following summaries will be provided:

- Summary of Change from Baseline in ECG by Visit
- Shifts in QTcF from Baseline to the Highest Post-Baseline
- QTcF Increase from Baseline to the Highest Post-Baseline

The following listing will be provided:

- ECG

12 PHARMACOKINETIC ANALYSES

For subjects in the ipilimumab + IMO-2125 arm, all subjects who received at least one dose of IMO-2125 with at least one measurable concentration of IMO-2125 will be included in the PK Analysis Set. Blood samples will be drawn for determination of IMO-2125 plasma concentrations at pre-dose, and at 1, 2, and 4 hours post-dose at Week 1 and Week 11. Descriptive summary statistics (number of non-missing observations (n), arithmetic mean, standard deviation, % coefficient of variation (CV) (which is 100* standard deviation/mean), median, minimum, maximum , geometric mean and geometric % CV will be reported for concentration values grouped by week and collection time point. For the calculation of mean concentrations, all concentrations below the Lower Limit of Quantification (LLOQ) will be treated as zero.

The following summary table will be provided:

- Summary of Pharmacokinetic Concentrations

Individual IMO-2125 values (by week, nominal and actual sampling time points) will be listed for all subjects. Other PK analyses are outside the scope of this SAP and will be described in a separate analysis plan. The following listing will be provided:

- Pharmacokinetic Concentrations

13 PATIENT-REPORTED QUALITY OF LIFE

All analyses of patient-reported quality of life data will be descriptive. No p-values will be calculated; point and interval estimates will be reported. All QoL tables, listings, and figures will use the ITT Analysis Set.

The five functional scales (physical, role, cognitive, emotional, and social), three symptom scales (fatigue, pain, and nausea and vomiting), global health status / QoL scale, the single items assessing additional symptoms commonly reported by cancer patients (dyspnoea, loss of appetite, insomnia, constipation, and diarrhoea) and perceived financial impact of the disease, will be scored. At the time of this SAP, it is noted that some subjects under protocol version 2 collected QoL data on paper and/or a mixture of paper and electronic media. For that reason, all the analyses described below, unless stated otherwise, will be done for paper PROs and electronic-PROs (ePROs) separately. In addition, the analyses will be repeated with combined paper PRO and ePRO data.

13.1 SCORING THE EORTC QLQ-C30 RESULTS

The five functional scales (physical, role, emotional, cognitive, and social), three symptom scales (fatigue, pain, and nausea and vomiting), global health status / QoL scale, and single items assessing additional symptoms commonly reported by cancer patients (dyspnoea, insomnia, appetite loss, constipation and diarrhoea) and perceived financial impact of the disease will be scored. 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 i^{th} item on the QLQ-C30 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 scales.

For all scales, the Raw Score, RS, is the mean of the component items:

$$\text{Raw Score}_s = RS_s = (I_1 + I_2 + ... + I_{ns}) \div n_s$$

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	V3.0 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.

13.2 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 deviation, 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.

The following summary and figure will be produced:

- Summary of Change from Baseline in EORTC QLQ-C30 Assessment Scores by Visit Using ePRO, Paper PRO and Combined ePRO and Paper PRO Data

- Line Graph of Mean (+/-SE) Change from Baseline in EORTC QLQ-C30 Scores and Sub-Scale by Visit Using ePRO, Paper PRO and Combined ePRO and Paper PRO Data

The listing to be produced is:

- EORTC QLQ-C30 Assessments Scores Using ePRO, Paper PRO and Combined ePRO and Paper PRO Data

13.3 ANALYSIS OF CHANGE FROM BASELINE IN EORTC QLQ-C30 SCORES

The change from baseline in each EORTC QLQ-30 multi-item scale and single-item measures will be analyzed over all post treatment assessment time points using a mixed effect model for repeated measures (MMRM). The combined data from both paper PRO and ePRO will be used for this analysis. The main MMRM model will include treatment, visit, and treatment-by-visit timepoint interaction term as fixed effects, and stratification factors and baseline score as a covariate.

Due to differences in the visit schedules for the treatment arms, Weeks 7 and 8 will be treated as the same visit. The model-based point estimates including least squares (LS) means, treatment difference in the LS means, and 2-sided 95% CI for the difference for each visit will be reported.

For each MMRM model, select the optimal model covariance structure according to the following steps. Note that if the SAS log contains “converge criteria not meet”, “G matrix (or D or Hessian) is not positive definite”, that model is considered not fitted.

1. Use an unstructured covariance structure without a random subject effect.

2. Use a spatial power covariance structure with a random subject effect

If both these models can be fitted, choose the model with smaller AIC. If only one model is fitted, the fitted model will be the model selected.

If neither of these models can be fitted, then try the next three options in order. Stop at the first model to be fitted.

3. Use an autoregressive(1) covariance structure with a random subject effect.

4. Use an autoregressive(1) covariance structure without a random subject effect.

5. Use a compound symmetric covariance structure without a random subject effect.

If no model fits for a given analysis, do not produce any output.

The generic SAS procedure call is

```
proc mixed data=<SAS dataset name>;
   class treatment visit subject;
   model <change in scale name> = strata baseline visit treatment
         visit*treatment;
   random subject;
   repeated visit / subject=usubjid type=UN;
   lsmeans visit*treatment / diff=all cl alpha=0.05;
run;
```

The following summary will be produced:

- MMRM Analysis of Change from Baseline in EORTC QLQ-C30 Assessment Scores by Visit Using Combined ePRO and Paper PRO Data

13.4 ASSOCIATION BETWEEN CHANGE FROM BASELINE AND BEST OVERALL RESPONSE

To assess the association between QoL data and the best overall response for a subject, the change from baseline in EORTC QLQ-C30 scores will be summarized by best overall response categories. The best overall response for a subject will be dichotomized into 2 levels: response of CR or PR (i.e., ORR Responder), and response of SD, PD, or NE (i.e., ORR Non-Responder).

The following summary will be produced:

- Summary of Change from Baseline in EORTC QLQ-C30 Assessment Scores by Visit and RECIST v1.1 ORR Responder Using Combined ePRO and Paper PRO Data

14 PHARMACODYNAMIC AND BIOMARKERS ANALYSES

Anti-drug Antibody (ADA) to IMO-2125 and ipilimumab will be listed.

Analyses to investigate changes in expression levels of immunologic biomarkers over time in response categories will be conducted. Those analyses are outside the scope of this analysis plan and will be described in a separate SAP.

15 REFERENCES

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Lan KKG and Demets DL. Discrete sequential boundaries for clinical trials. Biometrika. 1983:70(3):659-663.

Schadendorf D, Hodi FS, Robert C, et al. Pooled Analysis of Long-Term Survival Data From Phase II and Phase III Trials of Ipilimumab in Unresectable or Metastatic Melanoma. J Clin Onc. 2015;33:1889-94.

16 APPENDICES

16.1 SCHEDULE OF EVENTS

Table 2: Schedule of Evaluations – Ipilimumab Alone (Arm A)

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

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

1. All Screening tests and assessments must be performed within 28 days before the date of randomization, except for ECOG and laboratory tests, which should be performed within 10 days before the first dose of study drug, and pregnancy test should be performed within 72 hours, if pregnancy test is not performed within 72 hours prior to randomization, it should be done on the first day of ipilimumab dosing.
2. All assessments will occur within a ±3-day window. Ipilimumab dosing should follow the product label (e.g., USPI).
3. Subjects who discontinue study treatment due to completion of the planned treatment or for reasons other than disease progression or start of new anticancer treatment will enter the Active Follow-up Period. Assessments during the Active Follow-up Period will follow the schedule of the disease assessments and

will occur at Week 12 (±1 week), then every 8 weeks (±2 weeks) for the first year and every 12 weeks (±2 weeks) during subsequent years.

4. Subjects who discontinue disease assessments due to either disease progression or the start of new anticancer treatment, with or without disease progression, will enter the Survival Follow-up Period (contacted by telephone every 3 months until death or the end of the study). Assessments will occur within a ±14-day window.
5. Subjects must be randomized within 28 days after signing the ICF; the first dose of study drug should be administered within 2 days after randomization.
6. CBC and chemistries do not have to be repeated if Screening tests are completed within 7 days of start of treatment.
7. PT, aPTT, INR.
8. Vital signs will include systolic and diastolic blood pressure, body temperature, pulse rate, body weight, and height (Week 1 only). Vital signs should be completed prior to treatment administration.
9. WOCBP only. Pregnancy test after randomization should be completed as deemed necessary by the Investigator or required by local law.
10. During the Follow-up Periods, for 90 days after the last dose of study treatment, all SAEs, irAEs, AEs Grade ≥3, and associated concomitant medications for their treatment must be reported. For the remainder of the Follow-up Periods, AE reporting should be limited to Treatment-related Grade ≥3 AEs and SAEs, and the associated concomitant medications.
11. Optional (see Laboratory Manual).
12. To inform treatment management decisions, disease assessments are to be completed at Week 12 (±1 week), then every 8 weeks (±2 weeks) for the first year and every 12 weeks (±2 weeks) during subsequent years.
13. To minimize bias in the PRO data, disease and PRO assessments are to be completed prior to study drug administration and AE evaluations at Weeks 1, 7, and 12 (±1 week), then every 8 weeks (±2 weeks) for the first year and every 12 weeks (±2 weeks) during subsequent years.
14. Per institutional practices following the frequency of active follow-up disease assessments.
15. Follow-on anticancer treatment information will be collected during the telephone calls.
16. Serum samples will be collected for analysis of anti- ipilimumab antibodies; details are provided in the Laboratory Manual. Baseline sample to be collected at Week 1 before the first dose of study treatment.

Table 3: Schedule of Evaluations – Ipilimumab with IMO-2125 (Arm B)

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

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

1. All Screening tests and assessments must be performed within 28 days before the date of randomization, except for ECOG and laboratory tests, which should be performed within 10 days before the first dose of study drug, and pregnancy test should be performed within 72 hours, if not performed within 72 hours of randomization, a pregnancy test should be repeated prior to the first dose of IMO-2125.
2. All assessments and IMO-2125 dosing will occur within a ±3-day window. IMO-2125 doses should be at least 5 days apart.
3. Subjects who discontinue study treatment due to completion of the planned treatment or for reasons other than disease progression or start of new anticancer treatment will enter the Active Follow-up Period. Assessments during the Active Follow-up Period will follow the schedule of the disease assessments and

will occur at Week 12 (±1 week), then every 8 weeks (±2 weeks) for the first year and every 12 weeks (±2 weeks) during subsequent years.

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

16.2 LIST OF TABLES, LISTINGS, AND FIGURES

The IDMC TLFs will be generated based on the schedule as defined in the Charter. The analysis of ORR will take place after all the randomized subjects either completed scheduled study treatment and completed at least 28 weeks on the study, prematurely discontinued study treatment and completed at least 28 weeks on the study, or withdrew, were lost to follow-up, or died before completing at least 28 weeks on the study. The final study analysis will take place when 392 deaths or approximately 36 months after the last subjects is randomized, whichever occurs first. All tables, figures, and listings will be produced for the final study analysis.

Tables, figures, and listings that will be produced for the IDMC meetings are identified with IDMC, the additional TLFs requested by IDMC during the course of the study are confidential and will not be included in the list below; and the final analysis of objective response rate with ORR, and the final analysis of OS with Final. The page header will indicate the timing of the analysis.

Table Title	**Timing of Analysis**
14.1.1.1 Subject Disposition, All Subjects *	IDMC, ORR, Final
14.1.1.2 Subject Disposition, Full Analysis Set	ORR, Final
14.1.1.3 Subject Disposition, Per Protocol Analysis Set	ORR, Final
14.1.2 Duration of Active Follow-up Times, Intent to Treat Analysis Set	ORR, Final
14.1.3 Major Protocol Deviations by Category, Intent to Treat Analysis Set	ORR, Final
14.1.4.1 Demographic Characteristics, Intent to Treat Analysis Set *	IDMC, ORR, Final
14.1.4.2 Demographic Characteristics, Full Analysis Set	ORR, Final
14.1.4.3 Demographic Characteristics, Per Protocol Analysis Set	ORR, Final
14.1.5.1 Baseline Disease Characteristics, Intent to Treat Analysis Set	IDMC, ORR, Final
14.1.5.2 Baseline Disease Characteristics, Full Analysis Set	ORR, Final
14.1.5.3 Baseline Disease Characteristics, Per Protocol Analysis Set	ORR, Final
14.1.6.1 Prior Systemic Anticancer Treatment History in All Settings, Intent to Treat Analysis Set	IDMC, ORR, Final

Table Title	Timing of Analysis
14.1.6.2 Prior Systemic Anticancer Treatment History in Unresectable/Metastatic Disease Setting Only, Intent to Treat Analysis Set	ORR, Final
14.1.7.1 Stratification Factor Levels as Randomized, Intent to Treat Analysis Set	ORR, Final
14.1.7.2 Stratification Factor Levels from the Clinical Data, Intent to Treat Analysis Set	ORR, Final
14.1.8.1 Concomitant Medications, Safety Set	ORR, Final
14.1.8.2 Concomitant Medications for irAEs by Category, Safety Set	IDMC, ORR, Final
14.1.8.3 Cancer Treatments and Surgeries after Start of Study Treatment, Safety Set	ORR, Final
14.2.1.1.1 Summary of Independent Reviewer-Assessed Response by RECIST v1.1, Intent to Treat Analysis Set *	ORR, Final
14.2.1.1.2 Sensitivity Analysis: Summary of Objective Response Rate by RECIST v1.1, Full Analysis Set	ORR, Final
14.2.1.1.3 Sensitivity Analysis: Summary of Objective Response Rate by RECIST v1.1, Per Protocol Analysis Set	ORR, Final
14.2.1.1.4 Sensitivity Analysis: Un-Stratified and Best Case Scenario Analysis of Objective Response Rate by RECIST v1.1, Full Analysis Set	ORR, Final
14.2.1.2 Summary of Investigator-Assessed Response by RECIST v1.1, Intent to Treat Analysis Set *	ORR, Final
14.2.1.3.1 Concordance of Best Overall Response by Independent Reviewer and Investigator, Intent to Treat Analysis Set *	ORR, Final
14.2.1.3.2 Concordance of Objective Response Rate by Independent Reviewer and Investigator, Intent to Treat Analysis Set	ORR, Final
14.2.1.4.1 Subgroup Analysis: Summary of Objective Response Rate by RECIST v1.1 by Metastasis Stage, Intent to Treat Analysis Set	ORR, Final
14.2.1.4.2 Subgroup Analysis: Summary of Objective Response Rate by RECIST v1.1 by BRAF Mutation and Prior Targeted Therapy, Intent to Treat Analysis Set	ORR, Final

Table Title	Timing of Analysis
14.2.1.4.3 Subgroup Analysis: Summary of Objective Response Rate by RECIST v1.1 by Duration of Prior Anti-PD-1 Therapy, Intent to Treat Analysis Set	ORR, Final
14.2.1.4.4 Subgroup Analysis: Summary of Objective Response Rate by Country, Intent to Treat Analysis Set	ORR, Final
14.2.1.4.5 Subgroup Analysis: Summary of Objective Response Rate by Baseline ECOG, Intent to Treat Analysis Set	ORR, Final
14.2.1.4.6 Subgroup Analysis: Summary of Objective Response Rate by Baseline LDH, Intent to Treat Analysis Set	ORR, Final
14.2.1.4.7 Subgroup Analysis: Summary of Objective Response Rate by RECIST v1.1 by Baseline Neutrophil/Lymphocyte Ratio, Intent to Treat Analysis Set	ORR, Final
14.2.1.4.8 Subgroup Analysis: Summary of Objective Response Rate by RECIST v1.1 by CYP Substrate Concomitant Medications Use, Intent to Treat Analysis Set	ORR, Final
14.2.1.5.1 Summary of Duration of Response based on Independent Reviewer-Assessed ORR by RECIST v1.1 for ORR Responders, Intent to Treat Analysis Set *	ORR, Final
14.2.1.5.2 Summary of Duration of Response based on Investigator-Assessed ORR by RECIST v1.1 for ORR Responders, Intent to Treat Analysis Set *	ORR, Final
14.2.1.6.1 Summary of Time to Response based on Independent Reviewer-Assessed ORR by RECIST v1.1 for ORR Responders, Intent to Treat Analysis Set	ORR, Final
14.2.1.6.2 Summary of Time to Response based on Investigator-Assessed ORR by RECIST v1.1 for ORR Responders, Intent to Treat Analysis Set	ORR, Final
14.2.2 Paired Difference of Percent Reduction from Baseline in Individual Sum of the Longest Diameters Between Injected and Non-injected Lesions, Intent to Treat Analysis Set	ORR, Final
14.2.3.1.1 Summary of Overall Survival, Intent to Treat Analysis Set	Final
14.2.3.1.2 Sensitivity Analysis: Summary of Overall Survival, Full Analysis Set	Final

Table Title	Timing of Analysis
14.2.3.1.3 Sensitivity Analysis: Summary of Overall Survival, Per Protocol Analysis Set	Final
14.2.3.2 Sensitivity Analysis: Summary of Overall Survival Using Imputed Death Dates, Intent to Treat Analysis Set	Final
14.2.3.3.1 Sensitivity Analysis: Summary of Un-Stratified Overall Survival, Intent to Treat Analysis Set	Final
14.2.3.3.2 Sensitivity Analysis: Summary of Overall Survival Using Weighted Log-Rank Test, Intent to Treat Analysis Set	Final
14.2.3.3.3 Sensitivity Analysis: Summary of Overall Survival Using Restricted Mean Survival Times, Intent to Treat Analysis Set	Final
14.2.3.4.1 Subgroup Analysis: Summary of Overall Survival by Metastasis Stage, Intent to Treat Analysis Set	Final
14.2.3.4.2 Subgroup Analysis: Summary of Overall Survival by BRAF Mutation Status and Prior Targeted Therapy, Intent to Treat Analysis Set	Final
14.2.3.4.3 Subgroup Analysis: Summary of Overall Survival by Duration of Prior Anti-PD-1 Therapy, Intent to Treat Analysis Set	Final
14.2.3.4.4 Subgroup Analysis: Summary of Overall Survival by Country, Intent to Treat Analysis Set	Final
14.2.3.4.5 Subgroup Analysis: Summary of Overall Survival by Baseline ECOG, Intent to Treat Analysis Set	Final
14.2.3.4.6 Subgroup Analysis: Summary of Overall Survival by Baseline LDH, Intent to Treat Analysis Set	Final
14.2.3.4.7 Subgroup Analysis: Summary of Overall Survival by Baseline Neutrophil/Lymphocyte Ratio, Intent to Treat Analysis Set	Final
14.2.3.4.8 Subgroup Analysis: Summary of Overall Survival by CYP Substrate Concomitant Medications Use, Intent to Treat Analysis Set	Final
14.2.4.1 Summary of Independent Reviewer-Assessed Progression Free Survival by RECIST v1.1, Intent to Treat Analysis Set	Final
14.2.4.2 Summary of Investigator-Assessed Progression Free Survival by RECIST v1.1, Intent to Treat Analysis Set	Final

Table Title	Timing of Analysis
14.3.1.1 IMO-2125 Exposure, Safety Set *	IDMC, ORR, Final
14.3.1.2 Ipilimumab Exposure, Safety Set *	IDMC, ORR, Final
14.3.2.1 Overall Summary of Treatment-Emergent Adverse Events, Safety Set *	IDMC, ORR, Final
14.3.2.2.1 Treatment-Emergent Adverse Events by System Organ Class and Preferred Term, Safety Set	IDMC, ORR, Final
14.3.2.2.2 Treatment-Emergent Adverse Events by Preferred Term, Safety Set	ORR, Final
14.3.2.2.3 Treatment-Emergent Adverse Events by Preferred Term and Injection Type, Safety Set	ORR, Final
14.3.2.3 Treatment-Related Treatment-Emergent Adverse Events by Preferred Term, Safety Set	IDMC, ORR, Final
14.3.2.4.1 Treatment-Emergent Adverse Events by Preferred Term and Maximum Grade, Safety Set	IDMC, ORR, Final
14.3.2.4.2 Treatment-Related Treatment-Emergent Adverse Events by Preferred Term and Maximum Grade, Safety Set *	ORR, Final
14.3.2.5.1 Grade 3 or Above Treatment-Emergent Adverse Events by Preferred Term, Safety Set	IDMC, ORR, Final
14.3.2.5.2 Grade 3 or Above Treatment-Related Treatment-Emergent Adverse Events by Preferred Term, Safety Set	ORR, Final
14.3.2.5.3 Subgroup Analysis: Grade 3 or Above Treatment-Emergent Adverse Events by Preferred Term and Injection Type, Safety Set	ORR, Final
14.3.2.6.1 Immune-Related Treatment-Emergent Adverse Events by Preferred Term, Safety Set	IDMC, ORR, Final
14.3.2.6.2 Immune-Related Treatment-Emergent Adverse Events by Preferred Term and Maximum Grade, Safety Set *	IDMC, ORR, Final
14.3.2.6.3 Grade 3 or Above Immune-Related Treatment-Emergent Adverse Events by Preferred Term, Safety Set	IDMC, ORR, Final
14.3.2.7.1 Treatment-Related Immune-Related Treatment-Emergent Adverse Events by Preferred Term and Maximum Grade, Safety Set	IDMC, ORR, Final

Table Title	Timing of Analysis
14.3.2.7.2 Grade 3 or Above Treatment-Related Immune-Related Treatment-Emergent Adverse Events by Preferred Term, Safety Set	IDMC, ORR, Final
14.3.3.1 Cumulative Treatment-Emergent Adverse Events at Three Months by Preferred Term and Maximum Grade, Safety Set	Final
14.3.3.2 Cumulative Treatment-Emergent Adverse Events at Six Months by Preferred Term and Maximum Grade, Safety Set	Final
14.3.3.3 Cumulative Treatment-Emergent Adverse Events at Nine Months by Preferred Term and Maximum Grade, Safety Set	Final
14.3.3.4 Cumulative Treatment-Emergent Adverse Events at Twelve Months by Preferred Term and Maximum Grade, Safety Set	Final
14.3.3.5 Cumulative Treatment-Related Treatment-Emergent Adverse Events at Three Months by Preferred Term and Maximum Grade, Safety Set	IDMC, Final
14.3.3.6 Cumulative Treatment-Related Treatment-Emergent Adverse Events at Six Months by Preferred Term and Maximum Grade, Safety Set	IDMC, Final
14.3.3.7 Cumulative Treatment-Related Treatment-Emergent Adverse Events at Nine Months by Preferred Term and Maximum Grade, Safety Set	IDMC, Final
14.3.3.8 Cumulative Treatment-Related Treatment-Emergent Adverse Events at Twelve Months by Preferred Term and Maximum Grade, Safety Set	IDMC, Final
14.3.4 Treatment-Emergent Adverse Event by Preferred Term and Time to Onset, Safety Set	ORR, Final
14.3.5.1.1 Serious Treatment-Emergent Adverse Events by Preferred Term, Safety Set *	IDMC, ORR, Final
14.3.5.1.2 Subgroup Analysis: Serious Treatment-Emergent Adverse Events by Preferred Term and Injection Type, Safety Set	ORR, Final
14.3.5.2 Treatment-Related Serious Treatment-Emergent Adverse Events by Preferred Term, Safety Set	ORR, Final
14.3.5.3 Grade 3 or Above Serious Treatment-Emergent Adverse Events by Preferred Term, Safety Set	ORR, Final
14.3.5.4 Immune-Related Serious Treatment-Emergent Adverse Events by Preferred Term and Maximum Grade, Safety Set	ORR, Final

Table Title	Timing of Analysis
14.3.5.5 Grade 3 or Above Immune-Related Serious Treatment-Emergent Adverse Events by Preferred Term, Safety Set	ORR, Final
14.3.5.6.1 Summary of Deaths, Safety Set *	ORR, Final
14.3.5.6.2 Subgroup Analysis: Summary of Deaths by Injection Type, Safety Set	ORR, Final
14.3.6.1 Treatment-Emergent Adverse Events Leading to Permanent Discontinuation of IMO-2125 by Preferred Term, Safety Set	IDMC, ORR, Final
14.3.6.2 IMO-2125-Related Treatment-Emergent Adverse Events Leading to Permanent Discontinuation of IMO-2125 by Preferred Term, Safety Set	ORR, Final
14.3.6.3 Treatment-Emergent Adverse Events Leading to Permanent Discontinuation of Ipilimumab by Preferred Term, Safety Set	IDMC, ORR, Final
14.3.6.4 Ipilimumab-Related Treatment-Emergent Adverse Events Leading to Permanent Discontinuation of Ipilimumab by Preferred Term, Safety Set	ORR, Final
14.3.6.5 Immune-Related Treatment-Emergent Adverse Events Leading to Permanent Discontinuation of IMO-2125 by Preferred Term, Safety Set	ORR, Final
14.3.6.6 Immune-Related Treatment-Emergent Adverse Events Leading to Permanent Discontinuation of Ipilimumab by Preferred Term, Safety Set	ORR, Final
14.3.7.1 Significant Treatment-Emergent Adverse Events by Preferred Term, Safety Set	ORR, Final
14.3.7.2 Time to Onset of Significant Treatment-Emergent Adverse Events, Safety Set	ORR, Final
14.3.8.1 Summary of Change from Baseline in Hematology, Safety Set	ORR, Final
14.3.8.2 Summary of Change from Baseline in Chemistry, Safety Set	ORR, Final
14.3.8.3 Summary of Change from Baseline in Coagulation, Safety Set	ORR, Final
14.3.8.4 Summary of Change from Baseline in Complement, Safety Set	ORR, Final
14.3.8.5 Summary of CTCAE Shifts from Baseline Grade in Hematology, Safety Set	IDMC, ORR, Final
14.3.8.6 Summary of CTCAE Shifts from Baseline Grade in Chemistry, Safety Set	IDMC, ORR, Final

Table Title	Timing of Analysis
14.3.8.7 Summary of Shifts from Baseline Relative to the Normal Range in Selected Laboratory Tests, Safety Set	ORR, Final
14.3.9.1 Summary of Shifts in Blood Pressure from Baseline to Worst Case Post-Baseline, Safety Set	IDMC, ORR, Final
14.3.9.2 Summary of Shifts in Heart Rate and Temperature from Baseline to Lowest and Highest Post-Baseline, Safety Set	IDMC, ORR, Final
14.3.9.3 Summary of ECG Values by Visit, Safety Set	ORR, Final
14.3.9.4 Summary of Shifts in QTcF from Baseline from the Highest Post-Baseline, Safety Set	ORR, Final
14.3.9.5 Summary of QTcF Increase from Baseline from the Highest Post-Baseline, Safety Set	IDMC, ORR, Final
14.4.1 Summary of Pharmacokinetic Concentrations, PK Analysis Set	ORR, Final
14.5.1.1 Summary of Change from Baseline in EORTC QLQ-C30 Assessment Scores by Visit Using ePRO Data, Intent to Treat Analysis Set	ORR, Final
14.5.1.2 Summary of Change from Baseline in EORTC QLQ-C30 Assessment Scores by Visit Using Paper PRO Data, Intent to Treat Analysis Set	ORR, Final
14.5.1.3 Summary of Change from Baseline in EORTC QLQ-C30 Assessment Scores by Visit Using Combined ePRO and Paper PRO Data, Intent to Treat Analysis Set	ORR, Final
14.5.1.4 MMRM Analysis of Change from Baseline in EORTC QLQ-C30 Assessment Scores by Visit Using Combined ePRO and Paper PRO Data, Intent to Treat Analysis Set	ORR, Final
14.5.1.5 Summary of Change from Baseline in EORTC QLQ-C30 Assessment Scores by Visit and RECIST v1.1 ORR Responder Using Combined ePRO and Paper PRO Data, Intent to Treat Analysis Set	ORR, Final

* Topline outputs

Listing Title	Timing of Analysis
16.2.1.1.1 Subject Disposition, All Subjects	ORR, Final
16.2.1.1.2 Reasons for Study Withdrawal, Intent to Treat Analysis Set	ORR, Final

Listing Title	Timing of Analysis
16.2.1.1.3 Reasons for Treatment Discontinuation, Safety Set	ORR, Final
16.2.1.1.4 Inclusion and Exclusion Criteria Violations, All Subjects	ORR, Final
16.2.1.1.5 Protocol Deviations, Intent to Treat Analysis Set	ORR, Final
16.2.1.2.1 Demographic Characteristics, Intent to Treat Analysis Set	ORR, Final
16.2.1.2.2 Baseline Disease Characteristics, Intent to Treat Analysis Set	ORR, Final
16.2.1.2.3 Medical History, Intent to Treat Analysis Set	ORR, Final
16.2.1.2.4 Prior Systemic Anticancer Treatment, Intent to Treat Analysis Set	IDMC, ORR, Final
16.2.1.2.5 Prior Cancer-Related Surgeries, Intent to Treat Analysis Set	ORR, Final
16.2.1.2.6 Prior Radiotherapy, Intent to Treat Analysis Set	ORR, Final
16.2.1.2.7 ECOG Performance Status, Intent to Treat Analysis Set	ORR, Final
16.2.1.3.1 Stratification Factor Levels, Intent to Treat Analysis Set	ORR, Final
16.2.1.3.2 Prior and Concomitant Medications, Intent to Treat Analysis Set	ORR, Final
16.2.1.3.3 Cancer Treatments and Procedures after Start of Study Treatment, Intent to Treat Analysis Set	ORR, Final
16.2.1.3.4 Sensitive and Narrow Therapeutic Range CYP Substrate - Concomitant Medications, All Subjects Used CYP Substrates During the Study, Intent to Treat Analysis Set	ORR, Final
16.2.1.3.5 Sensitive and Narrow Therapeutic Range CYP Substrate - Treatment-Emergent Adverse Events Started During or After Use of CYP Substrates, Intent to Treat Analysis Set	ORR, Final
16.2.2.1.1 Independent Reviewer-Assessed Target Lesions, Intent to Treat Analysis Set	ORR, Final
16.2.2.1.2 Independent Reviewer-Assessed Non-Target Lesions, Intent to Treat Analysis Set	ORR, Final
16.2.2.1.3 Independent Reviewer-Assessed New Lesions, Intent to Treat Analysis Set	ORR, Final
16.2.2.1.4 Investigator-Assessed Target Lesions, Intent to Treat Analysis Set	ORR, Final

Listing Title	Timing of Analysis
16.2.2.1.5 Investigator-Assessed Non-Target Lesions, Intent to Treat Analysis Set	ORR, Final
16.2.2.1.6 Investigator-Assessed New Lesions, Intent to Treat Analysis Set	ORR, Final
16.2.2.1.7 Sum of the Longest Diameters and Percent Change from Baseline in SLD by Injection Status, Intent to Treat Analysis Set	ORR, Final
16.2.2.2.1 Independent Reviewer-Assessed RECIST v1.1 Response, Intent to Treat Analysis Set	ORR, Final
16.2.2.2.2 Investigator-Assessed RECIST v1.1 Response, Intent to Treat Analysis Set	ORR, Final
16.2.2.2.3 Independent Reviewer-Assessed irRECIST Response, Intent to Treat Analysis Set	ORR, Final
16.2.2.2.4 Investigator-Assessed irRECIST Response, Intent to Treat Analysis Set	ORR, Final
16.2.2.2.5 Independent Reviewer-Assessed RECIST v1.1 Tumor Response Endpoints, Intent to Treat Analysis Set	ORR, Final
16.2.2.2.6 Investigator-Assessed RECIST v1.1 Tumor Response Endpoints, Intent to Treat Analysis Set	ORR, Final
16.2.2.2.7 Progression Free Survival by RECIST v1.1 Assessed by Independent Reviewer and Investigator and Overall Survival, Intent to Treat Analysis Set	Final
16.2.3.1.1 IMO-2125 Exposure, Safety Set	IDMC, ORR, Final
16.2.3.1.2 Ipilimumab Exposure, Safety Set	IDMC, ORR, Final
16.2.3.1.3 Dose Modifications Due to irAEs, Safety Set	ORR, Final
16.2.3.2.1 Treatment-Emergent Adverse Events, Safety Set	IDMC, ORR, Final
16.2.3.2.2 Adverse Events Between Signing Consent and the Start of Study Treatment, Safety Set	ORR, Final
16.2.3.2.3 Serious Adverse Events, Safety Set	IDMC, ORR, Final
16.2.3.2.4 Adverse Events Leading to Death, Safety Set	IDMC, ORR, Final

Listing Title	Timing of Analysis
16.2.3.2.5 Treatment Emergent Adverse Events Leading to Dose Interruption or Dose Reduction of Study Treatment, Safety Set	ORR, Final
16.2.3.2.6 Treatment-Emergent Adverse Events Leading to Treatment Discontinuation, Safety Set	IDMC, ORR, Final
16.2.3.2.7 Treatment Related Treatment-Emergent Adverse Events, Safety Set	IDMC, ORR, Final
16.2.3.2.8 Deaths, Safety Set	ORR, Final
16.2.3.2.9 Immune-Related Treatment-Emergent Adverse Events, Safety Set	ORR, Final
16.2.3.2.9 Significant Treatment-Emergent Adverse Events of Interest, Safety Set	ORR, Final
16.2.3.3.1 Chemistry (Local), Safety Set	ORR, Final
16.2.3.3.2 Coagulation (Local), Safety Set	ORR, Final
16.2.3.3.3 Hematology (Local), Safety Set	ORR, Final
16.2.3.3.4 Complement (Central) - CH50/C3/C4, Safety Set	ORR, Final
16.2.3.3.5 Dipstick Test, Urinalysis (Local) and Microscopic Exam (Local), Safety Set	ORR, Final
16.2.3.4 Vital Signs, Safety Set	ORR, Final
16.2.3.5 ECG Assessments, Safety Set	ORR, Final
16.2.3.6 Pharmacokinetics Concentrations, PK Analysis Set	ORR, Final
16.2.3.7.1 EORTC QLQ-C30 Assessment Scores Using ePRO, Paper PRO and Combined ePRO and Paper PRO Data - Single-Item Measures, Intent to Treat Analysis Set	ORR, Final
16.2.3.7.2 EORTC QLQ-C30 Assessment Scores Using ePRO, Paper PRO and Combined ePRO and Paper PRO Data - Global Health Status/QoL and Functional Scale Scores, Intent to Treat Analysis Set	ORR, Final
16.2.3.7.3 EORTC QLQ-C30 Assessment Scores Using ePRO, Paper PRO and Combined ePRO and Paper PRO Data - Symptom Scales/Items Scores, Intent to Treat Analysis Set	ORR, Final

Listing Title	Timing of Analysis
16.2.3.8 Anti-drug Antibodies, Safety Set	IDMC, ORR, Final

Figure Title	Timing of Analysis
14.1.1 Forest Plot of Proportion Differences for Objective Response Rate by Subgroup, Intent to Treat Analysis Set	ORR, Final
14.1.2.1 Swimmer's Plot of Independent Reviewer-Assessed Response by RECIST v1.1 for ORR Responders, Intent to Treat Analysis Set	ORR, Final
14.1.2.2 Waterfall Plot of Maximum Percent Reduction from Baseline in Individual Sum of the Longest Diameters Assessed by Independent Reviewer (Target Lesions Only), Intent to Treat Analysis Set	ORR, Final
14.1.2.3 Spider Plot of Individual Percent Change from Baseline in Sum of the Longest Diameters, Assessed by Independent Reviewer (Target Lesions Only), Intent to Treat Analysis Set	ORR, Final
14.1.2.4 Swimmer's Plot of Investigator-Assessed Response by RECIST v1.1 for ORR Responders, Intent to Treat Analysis Set	ORR, Final
14.1.2.5 Waterfall Plot of Maximum Percent Reduction from Baseline in Individual Sum of the Longest Diameters Assessed by Investigator, Intent to Treat Analysis Set	ORR, Final
14.1.2.6 Spider Plot of Individual Percent Change from Baseline in Sum of the Longest Diameters, Assessed by Investigator, Intent to Treat Analysis Set	ORR, Final
14.1.3 Waterfall Plot of Maximum Percent Reduction from Baseline in Individual Sum of the Longest Diameters Among Measurable Lesions by Injection Status for ORR Responders, Intent to Treat Analysis Set	ORR, Final
14.1.4.1 Kaplan-Meier Plot of Independent Reviewer-Assessed DoR by RECIST v1.1 for ORR Responders, Intent to Treat Analysis Set	ORR, Final
14.1.4.2 Kaplan-Meier Plot of Investigator-Assessed DoR by RECIST v1.1 for ORR Responders, Intent to Treat Analysis Set	ORR, Final
14.1.5 Kaplan-Meier Plot of Overall Survival, Intent to Treat Analysis Set	IDMC, Final
14.1.6 Forest Plot of Hazard Ratios for Overall Survival by Subgroup, Intent to Treat Analysis Set	Final

Figure Title	**Timing of Analysis**
14.1.7.1 Kaplan-Meier Plot of Independent Reviewer-Assessed PFS by RECIST v1.1, Intent to Treat Analysis Set	Final
14.1.7.2 Kaplan-Meier Plot of Investigator-Assessed PFS by RECIST v1.1, Intent to Treat Analysis Set	Final
14.2.1 Boxplot of Hematology by Visit, Safety Set	IDMC, ORR, Final
14.2.2 Boxplot of Chemistry by Visit, Safety Set	IDMC, ORR, Fianl
14.2.3 Liver Function Tests Maximum Values to ULN on Study vs Baseline to ULN, Safety Set	ORR, Final
14.2.4 Mean (+/-SE) Change from Baseline in EORTC QLQ-30 Assessment Scores and Sub-Scale by Visit, Intent to Treat Analysis Set	ORR, Final

16.3 CONFIRMATION RESPONSE IN RECIST V1.1

The following table represents the general algorithm for confirming responses using RECIST v1.1. Confirmation of more complex cases, such as an NE from an unscheduled visit between two CRs, will be programmed appropriately.

Overall Response First Timepoint	Overall Response Subsequent Timepoint	Best Overall Response
CR	CR	CR
CR	PR	SD, PD, or PR
CR	SD	SD provided minimum criteria for SD duration are met at the first timepoint. Otherwise PD
CR	PD	SD provided minimum criteria for SD duration are met at the first timepoint. Otherwise PD
CR	NE	SD provided minimum criteria for SD duration are met at the first timepoint. Otherwise NE
PR	CR	PR
PR	PR	PR
PR	SD	SD
PR	PD	SD provided minimum criteria for SD duration are met at the first timepoint. Otherwise PD
PR	NE	SD provided minimum criteria for SD duration are met at the first timepoint. Otherwise NE
NE	NE	NE

* In the case of SD, measurements must be assessed at least 12 weeks (or 84 days) from the date of randomization.

[Source: https://recist.eortc.org/]

16.4 CENSORING RULE FOR PFS

The following censoring rules will be used for PFS analysis to be consistent with FDA guidance on Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics. [source: https://www.fda.gov/downloads/Drugs/Guidances/ucm071590.pdf]

Situation	Date of Progression or Censoring	Outcome
No baseline tumor assessments	Randomization	Censored
Progression documented between scheduled visits	Earliest of: • Dates of target lesion scans when the target lesion response is PD; or • Dates of non-target scans at which the non-target lesion status is unequivocal progression; or • Dates of scans documenting new lesion (if progression is based on new lesion)	Event
No progression	Date of the last valid disease assessment, defined as a scheduled or unscheduled visit with a disease assessment of CR, PR, or SD	Censored
Treatment discontinuation for undocumented progression	Date of the last valid disease assessment, defined as a scheduled or unscheduled visit with a disease assessment of CR, PR, or SD	Censored
Treatment discontinuation for other reasons	Date of the last valid disease assessment, defined as a scheduled or unscheduled visit with a disease assessment of CR, PR, or SD	Censored
New anticancer treatment started	Date of the last valid disease assessment, defined as a scheduled or unscheduled visit with a disease assessment of CR, PR, or SD, prior to new anticancer treatment started	Censored
Death without documented progression and is not after two or more missed visits	Date of death	Event
Death or progression after two or more missed visits	Date of the last valid disease assessment, defined as a scheduled or unscheduled visit with a disease assessment of CR, PR, or SD	Censored

16.5 CTCAE GRADES FOR LABORATORY TESTS

The following criteria will be used for laboratory shift in CTCAE tables.

CTCAE v4.03 Term	Lab Parameters	Direction	Grade 1	Grade 2	Grade 3	Grade 4
Hypoalbuminemia	ALB	hypo	<LLN - 3 g/dL; <LLN - 30 g/L	<3 - 2 g/dL; <30 - 20 g/L	<2 g/dL; <20 g/L	Life-threatening consequences; urgent intervention indicated
Alkaline phosphatase increased	ALP	hyper	>ULN - 2.5 x ULN	>2.5 - 5.0 x ULN	>5.0 - 20.0 x ULN	>20.0 x ULN
Alanine aminotransferase increased	ALT	hyper	>ULN - 3.0 x ULN	>3.0 - 5.0 x ULN	>5.0 - 20.0 x ULN	>20.0 x ULN
Aspartate aminotransferase increased	AST	hyper	>ULN - 3.0 x ULN	>3.0 - 5.0 x ULN	>5.0 - 20.0 x ULN	>20.0 x ULN
Blood bilirubin increased	BILI	hyper	>ULN - 1.5 x ULN	>1.5 - 3.0 x ULN	>3.0 - 10.0 x ULN	>10.0 x ULN
Cholesterol high	CHOL	hyper	>ULN - 300 mg/dL; >ULN - 7.75 mmol/L	>300 - 400 mg/dL; >7.75 - 10.34 mmol/L	>400 - 500 mg/dL; >10.34 - 12.92 mmol/L	>500 mg/dL; >12.92 mmol/L
Creatinine increased	CREAT	hyper	>1 - 1.5 x baseline; >ULN - 1.5 x ULN	>1.5 - 3.0 x baseline; >1.5 - 3.0 x ULN	>3.0 baseline; >3.0 - 6.0 x ULN	>6.0 x ULN
Hyperglycemia	GLUC	hyper	Fasting glucose value >ULN - 160 mg/dL; Fasting glucose value >ULN - 8.9 mmol/L	Fasting glucose value >160 - 250 mg/dL; Fasting glucose value >8.9 - 13.9 mmol/L	>250 - 500 mg/dL; >13.9 - 27.8 mmol/L; hospitalization indicated	>500 mg/dL; >27.8 mmol/L; life-threatening consequences
Hypoglycemia	GLUC	hypo	<LLN - 55 mg/dL; <LLN - 3.0 mmol/L	<55 - 40 mg/dL; <3.0 - 2.2 mmol/L	<40 - 30 mg/dL; <2.2 - 1.7 mmol/L	<30 mg/dL; <1.7 mmol/L; life-threatening consequences; seizures
Hemoglobin increased	HGB	hyper	Increase in >0 - 2 gm/dL above ULN or above baseline if baseline is above ULN	Increase in >2 - 4 gm/dL above ULN or above baseline if baseline is above ULN	Increase in >4 gm/dL above ULN or above baseline if baseline is above ULN	-
Anemia	HGB	hypo	Hemoglobin (Hgb) <LLN - 10.0 g/dL; <LLN - 6.2 mmol/L; <LLN - 100 g/L	Hgb <10.0 - 8.0 g/dL; <6.2 - 4.9 mmol/L; <100 - 80g/L	Hgb <8.0 g/dL; <4.9 mmol/L; <80 g/L; transfusion indicated	Life-threatening consequences; urgent intervention indicated
Hyperkalemia	K	hyper	>ULN - 5.5 mmol/L	>5.5 - 6.0 mmol/L	>6.0 - 7.0 mmol/L; hospitalization indicated	>7.0 mmol/L; life-threatening consequences

CTCAE v4.03 Term	Lab Parameters	Direction	Grade 1	Grade 2	Grade 3	Grade 4
Hypokalemia	K	hypo	<LLN - 3.0 mmol/L	<LLN - 3.0 mmol/L; symptomatic; intervention indicated	<3.0 - 2.5 mmol/L; hospitalization indicated	<2.5 mmol/L; life-threatening consequences
Lymphocyte count increased	LYM	hyper	-	>4000/mm3 - 20,000/mm3	>20,000/mm3	-
Lymphocyte count decreased	LYM	hypo	<LLN - 800/mm3; <LLN - 0.8 x 10e9/L	<800 - 500/mm3; <0.8 - 0.5 x 10e9 /L	<500 - 200/mm3; <0.5 - 0.2 x 10e9 /L	<200/mm3; <0.2 x 10e9 /L
Neutrophil count decreased	NEUT/ANC	hypo	<LLN - 1500/mm3; <LLN - 1.5 x 10e9 /L	<1500 - 1000/mm3; <1.5 - 1.0 x 10e9 /L	<1000 - 500/mm3; <1.0 - 0.5 x 10e9 /L	<500/mm3; <0.5 x 10e9 /L
Hypophosphatemia	PHOS	hypo	<LLN - 2.5 mg/dL; <LLN - 0.8 mmol/L	<2.5 - 2.0 mg/dL; <0.8 - 0.6 mmol/L	<2.0 - 1.0 mg/dL; <0.6 - 0.3 mmol/L	<1.0 mg/dL; <0.3 mmol/L; life-threatening consequences
Platelet count decreased	PLAT	hypo	<LLN - 75,000/mm3; <LLN - 75.0 x 10e9 /L	<75,000 - 50,000/mm3; <75.0 - 50.0 x 10e9 /L	<50,000 - 25,000/mm3; <50.0 - 25.0 x 10e9 /L	<25,000/mm3; <25.0 x 10e9 /L
Hypernatremia	SODIUM	hyper	>ULN - 150 mmol/L	>150 - 155 mmol/L	>155 - 160 mmol/L; hospitalization indicated	>160 mmol/L; life-threatening consequences
Hyponatremia	SODIUM	hypo	<LLN - 130 mmol/L	-	<130 - 120 mmol/L	<120 mmol/L; life-threatening consequences
Hypertriglyceridemia	TRIG	hyper	150 mg/dL - 300 mg/dL; 1.71 mmol/L - 3.42 mmol/L	>300 mg/dL - 500 mg/dL; >3.42 mmol/L - 5.7 mmol/L	>500 mg/dL - 1000 mg/dL; >5.7 mmol/L - 11.4 mmol/L	>1000 mg/dL; >11.4 mmol/L; life-threatening consequences
White blood cell decreased	WBC	hypo	<LLN - 3000/mm3; <LLN - 3.0 x 10e9 /L	<3000 - 2000/mm3; <3.0 - 2.0 x 10e9 /L	<2000 - 1000/mm3; <2.0 - 1.0 x 10e9 /L	<1000/mm3; <1.0 x 10e9 /L

The table above is extracted from CTCAE v4.03, obtained from NIH website
[Source: https://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm].