Final Statistical Analysis Plan for:

Study IMM-101-015

NCT03711188

A Study of the Safety and Efficacy of IMM-101 in Combination with Checkpoint Inhibitor Therapy in Patients with Advanced Melanoma

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Immodulon Therapeutics Limited Study No: IMM-101-015
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Statistical Analysis Plan

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Version	Change History	Reason	Date
1.0	First Version	N/A	16SEP2020

Contents

LIST OF ABBREVIATIONS

AE	Adverse Event
BMI	Body Mass Index
BOR	Best Overall Response
CI	Confidence Interval
CR	Complete response
CTCAE	Common Terminology Criteria for Adverse Events
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic Case Report Form
irRC	Immune-related Response Criteria
ITT	Intent-to-treat
MedDRA	Medical Dictionary for Regulatory Activities
NE	Non-evaluable
ORR	Overall Response Rate
OS	Overall Survival
PD	Progressive Disease
PFS	Progression-free Survival
PPS	Per Protocol Set
PR	Partial Response
PT	Preferred Term
QTcF	QT corrected for heart rate using Fridericia's formula
RECIST	Response Evaluation Criteria in Solid Tumours
SAE	Serious Adverse Event
SAF	Safety Analysis Set
SAP	Statistical Analysis Plan
SD	Stable Disease
StD	Standard Deviation
SFS	Screening Failure Set
SOC	System Organ Class
TEAE	Treatment Emergent Adverse Event
WHO Drug	World Health Organization Drug Dictionary

1 INTRODUCTION

This document details the statistical analysis of the data that will be performed for the Immodulon Therapeutics Limited study: IMM-101-015 - A study of the Safety and Efficacy of IMM-101 in Combination with Checkpoint Inhibitor in Patients with Advanced Melanoma.

The proposed analysis is based on the contents of Version 2 of the protocol (dated 16 December 2019). In the event of future amendments to the protocol, this statistical analysis plan (SAP) may be modified to account for changes relevant to the statistical analysis.

The table, listing and figure shells are supplied in a separate document which is approved separately.

2 STUDY OBJECTIVES AND DESIGN

2.1 Study Objectives

The primary objectives of this study are to investigate the effectiveness of IMM-101 combined with nivolumab in controlling advanced melanoma and to assess and describe the safety profile of the combination after a maximum of 18 months of treatment with IMM-101 + nivolumab. The safety and efficacy of the combination will be assessed in patients who are either previously untreated (cohort A), or whose disease has progressed during PD-1 blockade (cohort B) and compared with published data on the efficacy and adverse event (AE) profile of nivolumab alone.

2.1.1 Primary Objectives

The primary objectives of the study are:

- To evaluate Overall Response Rate (ORR) after a maximum of 18 months treatment, in patients with advanced melanoma receiving IMM-101 + nivolumab. ORR in both previously untreated patients (cohort A) and in patients whose disease has progressed during PD-1 blockade (cohort B) will be evaluated using Response Evaluation Criteria in Solid Tumours (RECIST) 1.1[1]. ORR will also be assessed for subgroups based on PD-L1 status (positive or negative/undetermined) in cohort A patients.
- To evaluate the safety and tolerability of the combination of IMM 101 + nivolumab in patients with advanced melanoma by examining the profile of AEs experienced.

2.1.2 Secondary Objectives

The secondary objectives of the study are:

- To evaluate Progression-free Survival (PFS) after a maximum of 18 months treatment in patients with advanced melanoma receiving IMM-101 + nivolumab for both cohort A and cohort B, assessed by RECIST 1.1.
- To evaluate Overall Survival (OS) and OS at 1 year in patients with advanced melanoma for both cohort A and cohort B.
- To evaluate changes in laboratory parameters.

- To evaluate local tolerability (injection site reactions).

2.1.3 Exploratory Objectives

The exploratory objectives of the study are:

- To evaluate the ORR in patients with advanced melanoma receiving IMM-101 + nivolumab using immune-related Response Criteria (irRC) for both cohort A and cohort B.
- To evaluate the Duration of Response and Time to Response in patients with advanced melanoma receiving IMM-101 + nivolumab for both cohort A and cohort B, assessed by RECIST 1.1.
- To evaluate Disease Control for patients in cohort B of the study only, defined as those patients with a response of stable disease (SD) based on RECIST 1.1. and assessed at each scan assessment point from Week 14 onwards.
- To evaluate Best Overall Response (BOR) for patients in cohort B to include any responses obtained following a change in therapy from IMM-101 + nivolumab to IMM-101 + ipilimumab, by including all tumour assessments on study.
- To evaluate the safety and tolerability of the combination of IMM 101 + ipilimumab in patients with advanced melanoma by examining the profile of AEs experienced for any patients in cohort B of the study who took IMM-101 + ipilimumab as subsequent treatment.
- Monitoring of selected markers of tumour burden and immunological status in patients receiving IMM-101 (to be reported separately to other endpoints).

2.2 Study Endpoints

2.2.1 Primary Endpoints

The primary efficacy endpoint of the study is the ORR calculated from the BOR of patients as assessed by RECIST 1.1. ORR will be assessed at the end of study or when all patients have withdrawn, if this is sooner. For cohort B, ORR will apply to BOR from tumour assessments during IMM-101 + nivolumab treatment only. ORR and BOR will also be assessed for subgroups based on PD-L1 status (positive or negative/undetermined) in cohort A patients.

The primary safety endpoint of the study is the incidence, frequency and severity of AEs, serious adverse events (SAEs), treatment related AEs, immune-related AEs, Grade 3 and above AEs and AEs leading to IMM-101 discontinuation or study withdrawal experienced during treatment with IMM-101 + nivolumab for both cohorts.

2.2.2 Secondary Endpoints

The secondary efficacy endpoints of the study are:

- PFS assessed by RECIST 1.1 after a maximum of 18 months treatment in patients receiving IMM-101 + nivolumab.
- OS and OS at 1 year, for both cohort A and cohort B. The median OS (if applicable) and OS rate at 12 months will be estimated.

The secondary safety endpoints of the study are:

- Incidence and frequency of laboratory parameter abnormalities.
- Change from baseline values in laboratory parameter values.
- Incidence and frequency of local injection site reactions.

2.2.3 Exploratory Endpoints

The exploratory efficacy endpoints of the study are:

- ORR using irRC in patients in both cohort A and cohort B receiving IMM-101 + nivolumab.
- Duration of Response and Time to Response for both cohort A and cohort B receiving IMM-101 + nivolumab and assessed by RECIST 1.1.
- Disease Control, for patients in cohort B of the study only and defined as those patients with a response of stable disease based on RECIST 1.1, assessed at each scan assessment point from Week 14 onwards.
- BOR for cohort B to include any responses obtained following a change in therapy from IMM-101 + nivolumab to IMM-101 + ipilimumab.
- Immunological markers from blood and biopsy samples (to be reported separately to other endpoints).

The exploratory safety endpoint of the study is for any patients in cohort B of the study who took IMM-101 + ipilimumab as subsequent treatment. The incidence, frequency and severity of AEs, SAEs, treatment related AEs, and immune-related AEs from the start of treatment with ipilimumab will be examined.

2.3 Study Design

This open-label, non-comparative, non-randomised study consists of two cohorts; patients with unresectable, Stage III or Stage IV metastatic melanoma who are either previously untreated (cohort A), or whose disease has progressed during PD-1 blockade (cohort B).

Treatment for patients in both cohorts is continued until disease progression (as assessed by RECIST 1.1) subject to the following qualifications: unacceptable side-effects, the Investigator's decision to discontinue treatment, withdrawal of patient consent, or 18 months of study treatment, whichever is the sooner. Patients with a complete response maintained over 2 scans should continue treatment unless the Investigator considered this not in the patient's best interest.

The study will continue until all patients have had the opportunity of 18 months treatment on study. Patients will be recruited from two sites within the UK.

2.4 Visit Structure

The visit structure and scheduled assessments are detailed in Section 8 and Appendix 1 of the protocol.

3 SAMPLE SIZE

Sufficient patients will be screened for 18 patients to be enrolled into cohort A and 8 into cohort B of this open-label study. Patients withdrawn during the course of the

study will not be replaced. No formal sample size calculation has been performed and the sample size is considered a sufficient and adequate number of patients to investigate the efficacy signals of IMM-101 combined with nivolumab in controlling advanced melanoma and to explore the safety profile of the combination therapy.

4 INTERIM DATA REVIEWS

By-cohort interim data reviews will be conducted for the primary efficacy and primary safety endpoints of ORR (RECIST 1.1) and incidence, frequency and severity of AEs, when all subjects have had the opportunity for 1 year on study (Cohort A) or after 6 months on study (Cohort B). No other endpoints will be presented at the interim analysis time points. All summaries will be presented on the Intent-to-Treat set with the exception of AEs which will be summarised using the Safety Analysis Set. These two analysis sets are expected to be the same as detailed in Section 5.3. The interim data reviews will be performed separately for each cohort and therefore the tables and listings will present only data for the relevant cohort. In tables the alternative cohort and if applicable, the overall column will be present but will not contain results data for the alternative cohort.

Due to the COVID-19 pandemic, recruitment was suspended at both study sites in March 2020. As the majority of Cohort A and B subjects had already been enrolled, the interim data review of background and demographic characteristics and of ORR will include only those subjects recruited to the point of recruitment suspension which will be 11 subjects in Cohort A and 5 subjects in Cohort B. The interim data review of background and demographic characteristics (see Section 4.1) and safety will include all subjects enrolled at the time of the data reviews, which may be more than these subjects if recruitment resumes prior to interim database lock for either interim data review. The listings of background and demographic characteristics will contain a flag to indicate subjects who did not have the opportunity to complete the 12 months and 6 months on study for Cohorts A and B respectively.

The tables and listings to be presented at each of the interim data reviews will be detailed in IMM-101-015 (ICS17002) Interim Analysis Outputs.pdf. The document also indicates the analysis set used to present each interim data review output, as this may differ from the analysis set used at the final analysis detailed in Table 1 of Section 5.3. An asterisk has also been added to the titles of the outputs which will be presented at interim data review in the shells document.

4.1 Background and Demographic Characteristics

Summary tables and listings will be provided for demography, baseline disease status, melanoma diagnosis details and previous systemic treatment for melanoma for the subjects included in the interim data reviews. Further information on each of these presentations can be found in Section 5.7 of this SAP.

4.2 Overall Response Rate

ORR (RECIST 1.1) will be assessed at the interim data review, using scan assessment results up to and including the 12-month assessment for the first 11 enrolled Cohort A subjects and for the first 5 Cohort B subjects up to and including the 6-month assessment. The scan assessments included for each interim data review are derived using dates for each subject. For example, for Cohort B, Week 26 is the 6-month

timepoint, hence scheduled scans up to Week 22 scan and any unscheduled scans up to Week 26 will be used according to date calculations. Week 30 scans will not be included. The 6-month timepoint will be calculated as 6 months from the date of first dosing with IMM-101 (Day 0). Similarly, with respect to the 12 month timepoint for Cohort A.

ORR is defined as the number of subjects with a BOR of CR or PR divided by the number of subjects in the Intent-to-treat analysis set in each cohort of the study. The BOR will be determined once all the data up to and including the 12-month assessments for Cohort A or the 6-month assessment for Cohort B are available. It is defined as the best response designation based on confirmed responses determined by the investigator according to RECIST 1.1, recorded between the date of first post-screening scan and the date of last scan at/prior to the assessment at the 12-month assessment (Cohort A) and 6-month assessment/last assessment prior to change of treatment to IMM-101 + ipilimumab whichever is sooner (Cohort B).

A summary table will be presented for the Objective Response Rate (RECIST 1.1) at last on-study assessment with data cut-off as defined above. Corresponding baseline and follow-up lesions assessments, response assessments and best objective response up to these time points will also be listed.

Further information on the derivation of BOR can be found in Section 5.13.1 of this SAP.

4.3 Adverse Events

Incidence, frequency and severity of AEs will be assessed at the interim data reviews, using all available AE information in the database up to the cut-off dates in each respective Cohort for all subjects.

4.4 Clinical Laboratory Evaluation

Summaries of the clinical significance over time for both haematology and biochemistry will be assessed at the interim data reviews, using all available information in the database up to the cut-off dates in each respective Cohort for all subjects.

5 ANALYSIS PLAN

5.1 General

Summary statistics for continuous variables will consist of the number of non-missing observations (n), mean, standard deviation (StD), minimum, median and maximum, unless specified otherwise.

For categorical variables the number and percentage of subjects in each category will be presented, based on the number of non-missing observations apart from disposition of subjects, protocol deviations, background and demographic characteristics, prior and concomitant medications/procedures and adverse events where the percentage will be based on the number of subjects in the analysis set, or subgroup of the analysis set, with a missing category presented where applicable. Any exceptions to these are detailed within the table, listing and figure shells.

The mean and median will be displayed to 1 more decimal place than the original data values and the StD will be displayed to 2 more decimal places than the original data values. The minimum and maximum will be displayed to the same number of decimal places as the original data. Percentages will be displayed to 0 decimal places; percentages will not be presented when the count is zero.

5.2 General Derivations

This section provides details of general derivations. Derivations specific to the parameter of interest are detailed within the specific SAP section.

5.2.1 Definition of Baseline

Baseline is defined as the last assessment value prior to first administration of IMM-101.

5.2.2 Visit and Study Day

Throughout this SAP any references to “Visit XX” refer to the pre-specified visits defined in the protocol where Day 0 (Visit 1 – Week 0) is the date of first administration of IMM-101.

Data listings by visit will additionally present study day, indicating the duration of time since first administration of IMM-101. Study day will be calculated relative to the first date of administration of IMM-101 (Study Day 1).

5.2.3 Incomplete Dates

For calculation purposes, incomplete dates will be completed using worst case. Further details are detailed in the relevant sections as required.

5.2.4 Scheduled Scan Windows

Each scan, whether scheduled or unscheduled, will be allocated to a scheduled scan time point if it is within the scheduled scan timetable window +/- 7 days (see protocol Appendix 1). If there is more than one scan within a scheduled scan time window, the closest scan prior to the scheduled timepoint, or after it if there are no scans prior, will be considered the scheduled scan for that timepoint. For efficacy assessments, all scans will be included whether they are scheduled or unscheduled. Listings of scan data will include the allocated visit (as defined above) and a flag to indicate if this differs from the original visit recorded at site.

5.2.5 Non-numeric Values

In the case where a variable is recorded as “>x”, “≥x”, “<x” or “≤x”, then for analysis purposes a value of x will be taken. Where a range of values is quoted the midpoint of the range will be taken. If a laboratory safety parameter is reported as being below the limit of quantification or < x, the value of the limit will be used in the calculation of summary statistics. The recorded value will be reported in listings.

5.2.6 Methods for Handling Withdrawals and Missing Data

In general, no imputations will be applied. Where imputation may be deemed appropriate, information is detailed in the analysis descriptions.

5.2.7 Site Pooling

Due to the small number of subjects, sites will be pooled for all summaries and analyses.

5.2.8 Subgroup Presentation

The following subgroups are of interest for presentation:

- PD-L1 status at screening (positive/negative or indeterminate) for Cohort A only.
- IMM-101 + ipilimumab in combination for Cohort B only.
- LDH at baseline (≤ upper limit of normal/> upper limit of normal).
- BRAF status at screening (wild type/mutant).
- M staging at screening (M1c and M1d combined/M0, M1a and M1b combined).

Subgroups will be presented provided the following criteria are met:

- For Cohort A the subgroup size is at least 33% of the enrolled Cohort A subjects and less than the total size of the ITT set in Cohort A.
- For Cohort B the subgroup size is at least 50% of the enrolled Cohort B subjects and less than the total size of the ITT set in Cohort B.

Where subgroups do not meet these criteria, information will be gathered from listings only and no summary tables will be provided for the clinical study report (CSR).

The use of these subgroups will be detailed in the relevant sections.

5.3 Analysis Sets

The **Enrolled Set** includes all subjects with confirmation of eligibility at Screening.

The **Screening Failure Set** (SFS) consists of all subjects who started screening but didn't receive IMM-101 for whatever reason. The SFS will include subjects who were eligible at Screening but no longer eligible at Visit 1.

The **Intent-to-Treat** (ITT) **Set** includes all subjects receiving at least one dose of IMM-101, irrespective of compliance with eligibility and other protocol criteria.

The **Per-Protocol Set** (PPS) is a subset of the ITT Set with no major protocol deviations. Major protocol deviations are described in more detail in Section 5.6. The PPS will include both Cohort A and Cohort B patients, although any outputs presented on the PPS will summarise Cohort A only.

The **Safety Analysis Set** (SAF) includes all subjects receiving at least one dose of IMM-101, irrespective of compliance with eligibility and other protocol criteria.

The list of subjects included in the analysis sets will be agreed prior to database lock, once all study data is available. The membership of the ITT and SAF analysis sets is anticipated to be the same.

5.4 Data Presentations

The data will be summarised in tabular form by Cohort apart from disposition of subjects, protocol deviations, background and demographic data (including baseline disease status, medical history, previous melanoma treatment and surgery,

prior/concomitant medications and concomitant surgeries), exposure, compliance and adverse events which will be summarised by Cohort and overall subjects. Cohorts will be labelled ‘Cohort A’ and ‘Cohort B’.

Listings will be sorted by Cohort, subject number and date/time of assessment. Where listings are presented for all subjects, any screening failure subjects will be presented separately from enrolled subjects.

Data will be summarised and listed using the analysis sets as defined in Table 1 of this SAP.

Table 1: Analysis sets used to present summaries and listings

	All Subjects	Enrolled	ITT	SAF
Tables	• Disposition		• Protocol deviations • Demography • Baseline disease status • Compliance • Efficacy (repeated on PPS for selected outputs for Cohort A only)	• Medical history • Previous melanoma treatment/radiotherapy/surgery • Prior and concomitant medications • Concomitant surgical procedures • Exposure • Adverse events • Injection site reactions • Clinical laboratory parameters • Vital signs
Listings	• Completion/withdrawal • Eligibility • Protocol deviations • Analysis sets • Informed consent • Demography • Melanoma diagnosis • Visit dates	• Time on study and study drug exposure • Medical history • Previous melanoma treatment/radiotherapy/surgery • Prior and concomitant medications • Concomitant surgical procedures • Baseline, follow-up and new lesions • Response assessment • Serology sample • Pregnancy test • PD-L1 biopsy • BRAF testing • Blood and biopsy samples • Vital signs • ECG results • Physical examination • ECOG performance status	• Efficacy	• Post completion anti-melanoma treatment • Administration • Adverse events • Injection site reactions • Clinical laboratory parameters

For safety summaries, only scheduled post-baseline data will be tabulated, post-baseline repeat/unscheduled assessments will be disregarded, although they will be listed and in particular all clinically significant values will be noted.

5.5 Disposition of subjects

The number and percentage of all subjects enrolled, included in the SFS, ITT/SAF sets and PPS, who completed the study and prematurely discontinued the study, will be summarised. The number and percentage of subjects will be summarised by their reasons for withdrawal from the study.

Eligibility for each of the analysis sets along with reasons for exclusion will be listed. Study completion/withdrawal data will be listed.

5.6 Protocol Deviations

Prior to database lock, the Immodulon Medical Monitor will review all individual deviations and classify them as major or minor during a data review meeting. Decisions arising from the data review meeting will be documented in the minutes and will be approved by the Immodulon Medical Monitor (on behalf of Immodulon) and the Project Statistician. Major deviations considered having a serious impact on the efficacy results will lead to the relevant subject being excluded from the PPS.

Major protocol deviations may include but are not limited to:

- Prior treatment for naïve disease (Cohort A only).
- Active brain metastases or leptomeningeal metastases (Cohort A only).
- Subject enrolled under Protocol Version 1.0 did not receive the minimum 4 doses of anti-PD-1 therapy before progression (RECIST 1.1) was documented and/or more than 8 weeks had elapsed between the last dose of anti-PD-1 therapy and the start of Screening (Cohort B only).
- Subject enrolled under Protocol Version 2.0 did not receive the minimum 3 doses of anti-PD-1 given as a monotherapy or the minimum 2 doses of anti-PD-1 given in combination regimes before progression (RECIST 1.1) was documented and/or more than 12 weeks but less than 6 weeks had elapsed between the last dose of anti-PD-1 therapy and the start of IMM-101 administration (Cohort B only).
- Subject has not received at least one dose of both IMM-101 and nivolumab.
- Subject does not have at least 1 measurable lesion by CT/MRI (RECIST 1.1) at baseline assessment and/or at least one post baseline measurable scan (whether or not scheduled).
- Subject has received on-study prohibited medications considered likely to have had an impact on the efficacy of study medication.

Protocol deviations which can be attributed to the COVID-19 pandemic will be entered into the eCRF with a comment indicating that the deviation is due to COVID-19. No specific COVID-19 category has been added to the eCRF as COVID-19 is a reason for a deviation and not a deviation in itself. However, these COVID-19-related deviations may be summarised under a separate category of COVID-19 if sufficient in

number and in addition to being identified in data listings, as determined at the data review meeting.

Protocol deviations other than those specified above may be identified. Details of all protocol deviations (start and end dates, review and decision date, deviation category, specific details and classification of major or minor) and subject eligibility will be listed.

Protocol deviations, both major and minor, will be summarised for each deviation category.

5.7 Background and Demographic Characteristics

5.7.1 Demography

Demographic characteristics (age, sex and race) and body measurements (height, weight and body mass index (BMI)) collected at Screening will be summarised.

Age is calculated in years from the date of informed consent.

BMI is calculated as (weight (kg)/height (m)^2).

All subject demographic data will be listed.

5.7.2 Informed Consent

Informed consent details will be listed including the date of informed consent, the protocol version enrolled under, date and confirmation of consent for biopsy samples and the visit and date of the new protocol version if applicable.

5.7.3 Baseline Disease Status

The following baseline information about melanoma will be summarised.

- The time since diagnosis of melanoma will be calculated in months from the date of diagnosis to the first administration of IMM-101 (date of diagnosis – date of first administration of IMM-101 + 1)/30.4375.
- Number staging (III or IV).
- M staging (M0, M1a, M1b, M1c or M1d).
- Site of melanoma (skin, mucosa or unknown).
- Eastern Cooperative Oncology Group (ECOG) performance status, see Section 5.15.10 for information on ECOG.
- BRAF status (wild type or mutant).
- PD-L1 status for Cohort A only (positive/negative or indeterminate).

All information related to baseline disease status will be listed.

5.7.4 Medical History

Clinically significant medical history events for the five years preceding screening will be coded using the latest Medical Dictionary for Regulatory Activities (MedDRA) dictionary version. The version used will be indicated in the data summaries and listings. The number and percentage of subjects will be presented for ongoing conditions and previous conditions separately by system organ class (SOC), and preferred term (PT), where SOC and PT will be presented in decreasing frequency of the total number of subjects with medical history events. All events will be listed.

5.7.5 Previous Melanoma Treatment, Radiotherapy and Surgery

A summary table will present any previous melanoma treatments, including adjuvant (after surgery), neo-adjuvant (prior to surgery) and advanced disease treatments. Medications will be coded using the latest World Health Organization Drug dictionary (WHO Drug) version. The version used will be indicated in the data summary and listing. All treatments will be listed.

Previous radiotherapy will be categorically summarised including the number and percentage of subjects receiving radiotherapy and the radiotherapy location. All instances of radiotherapy will be listed.

Previous melanoma surgery will be coded using the latest MedDRA dictionary version. The version used will be indicated in the data summaries and listings. The number and percentage of subjects receiving surgery for melanoma will be presented by SOC and PT, where SOC and PT will be presented in decreasing frequency of the total number of subjects receiving surgical procedures. All events will be listed.

5.8 Prior and Concomitant Medications

Medications will be coded using the latest WHO Drug version. The version used will be indicated in the data summaries and listings.

Prior medications are defined as those that started and ended prior to the first administration of IMM-101. Medications that are ongoing at the first administration of IMM-101 or started after time of first administration will be deemed to be concomitant medications. If medication dates are incomplete and it is not clear whether the medication was concomitant, it will be assumed to be concomitant.

The number and percentage of subjects taking prior and separately concomitant medications will be summarised by medication class and standardised medication name, where medication class and standardised medication name will be presented in decreasing frequency of the total number of subjects with medications. In summary tables, subjects taking multiple medications in the same medication class or having the same standardised medication recorded multiple times in the study will be counted only once for that specific medication class and standardised medication name.

Medication data will be listed, where concomitant medications will be flagged.

5.9 Concomitant Surgical Procedures

Concomitant surgical procedures will be coded using the latest MedDRA dictionary version. The version used will be indicated in the data summaries and listings. Procedures that occurred on or after the first administration of IMM-101 will be deemed to be concomitant procedures. If surgical procedure dates are incomplete and it is not clear whether the surgery was concomitant, it will be assumed to be concomitant. All surgeries performed prior to first administration of IMM-101 and not related to melanoma surgery will be included within the medical history summaries and listings. All surgeries performed prior to first administration of IMM-101 and related to melanoma surgery will be included within the previous melanoma related surgery summaries and listings.

The number and percentage of subjects receiving surgery will be presented by SOC and PT, where SOC and PT will be presented in decreasing frequency of the total number of subjects receiving surgical procedures. All events will be listed.

5.10 Post-Completion/Withdrawal Anti-Melanoma Treatment

Any anti-melanoma medications received after completion or withdrawal from IMM-101 will be listed. Medications will be coded using the latest WHO Drug version. The version used will be indicated in the listing.

5.11 Administration of IMM-101, Nivolumab and Ipilimumab

Administration details for each study treatment will be listed in full.

For IMM-101, this will include the date and time of administration, details of any delays, the arm chosen for injection, the dose administered and confirmation of the vital signs monitoring. If the dose was not administered, reasons for the missed dose will also be listed.

Nivolumab infusion information will include the date and time of administration, details of any delays, the regimen chosen and regimen modifications, the planned and actual dose with reasons for any differences between the two. If the dose was not administered, reasons for the missed dose will also be listed.

Ipilimumab infusion details will include the date and time of infusion, infusion number, delay details, the planned and actual dose with reasons for any differences between the two will be listed. The date and reason for treatment with ipilimumab will also be listed.

5.12 Exposure and Compliance

An exposure summary will include the time on study, the overall exposure of each of IMM-101, nivolumab and ipilimumab and the total dose exposure of nivolumab. The number of doses of IMM-101, and whether they were full or half doses will also be summarised.

The time on study will be calculated in months as (date of completion/withdrawal - date of first IMM-101 administration + 1)/30.4375.

Overall exposure to each of IMM-101, nivolumab and ipilimumab will be calculated in months as (date of last administration – date of first administration + 1)/30.4375.

Total nivolumab exposure will be calculated in mg across the duration of the subject's participation as the sum of the total dose administered at each nivolumab dosing visit for each subject.

Compliance will be summarised for IMM-101, nivolumab and ipilimumab separately for each visit.

For IMM-101, the number of subjects receiving treatment and whether these were full or half doses, the number of subjects not dosed, the reason for not dosing, the number of subjects with delayed dosing and the reasons for the delay will be summarised.

For nivolumab, the number of subjects receiving the infusion and the reasons if they did not receive the infusion, the number of subjects with delayed infusion and reasons for delayed infusion, the dosing regimen chosen and whether the regimen was modified will be summarised. The number of subjects who received less than, more than or exactly the planned dose will also be summarised.

For ipilimumab, the number of subjects receiving the infusion and the reasons why they received the infusion will be summarised. For each of the four infusions, the

number of subjects with delayed infusion and reasons for delayed infusion and the number of subjects who received less than, more than or exactly the planned dose will also be summarised.

5.13 EFFICACY EVALUATION

5.13.1 Primary Endpoint

The primary endpoint will be analysed using the ITT set and repeated for the PPS for Cohort A only.

Primary Analysis

The primary efficacy endpoint of the study is the ORR calculated from the BOR of subjects as assessed by RECIST 1.1.

The investigator response will be entered into the Response Assessment (RECIST 1.1) page of the electronic Case Report Form (eCRF) at each scan assessment to be used in the derivation of BOR.

A confirmed response will be used in the derivation of BOR. A confirmed response is defined as a response obtained from a scan repeated at least 4 weeks following a scan with designation of complete response (CR) or partial response (PR), as defined using Table 3 of RECIST 1.1. In addition, the following approaches will be taken:

- Where a confirmatory assessment is non-evaluable (NE) but the subsequent scan maintains the same response/progression, the response/progression will be considered confirmed (e.g. PR-NE-PR).
- Subjects without a confirmed response of CR or PR will have their next best response (stable disease (SD) or otherwise progressive disease (PD)) assigned as their BOR.
- Subjects without a BOR assessment, such as those with no post-baseline responses or only NE responses, will be assumed to have a BOR of PD using a worst-case approach.

For Cohort A, BOR is defined as the best confirmed response designation, recorded from the first post-baseline scan until and including the last scan on study for each subject.

For Cohort B, BOR is defined as the best confirmed response designation, recorded from the first post-baseline scan until and including the last scan on study for each subject for those receiving IMM-101 and nivolumab, or the last scan performed prior to treatment with ipilimumab. No scan performed once ipilimumab treatment commences will be included.

All scans within these periods, whether scheduled or unscheduled, will be evaluated for overall response.

ORR is calculated as the number of subjects with a BOR of confirmed CR or PR divided by the number of subjects in the analysis set. ORR is calculated for each cohort separately.

Summaries of BOR (best confirmed overall response designation)

The BOR will be summarised for each cohort. The ORR and accompanying exact binomial 95% confidence intervals (CI) will also be presented.

Listings of lesions assessments and BOR

Listings of the baseline and follow-up target lesions will be provided. These listings will be presented for both assessment using RECIST 1.1 and repeated for assessment using irRC. The response assessment for both RECIST 1.1 and irRC will also be listed. Listings of non-target lesions at baseline and follow-up will be presented. New lesions found after baseline will be listed and the assessments of these previously reported new lesions will also be listed.

A BOR listing will present the responses derived using RECIST 1.1 including confirmed responses only, unconfirmed responses, all responses (confirmed or unconfirmed) up until progression, confirmed responses at interim assessment, and all responses (confirmed or unconfirmed) including those after a treatment change in Cohort B. The BOR derived using irRC will also be presented.

Sensitivity Analysis

Two sensitivity analyses will be performed for comparability with published data:

1. The summary table will be repeated with BOR assessed using confirmed or unconfirmed responses.
2. The summary table will be repeated with BOR assessed using confirmed or unconfirmed responses up until disease progression (i.e. excluding any PR and CR responses following a PD response).

Unconfirmed responses do not need to follow Table 3 of RECIST 1.1. Instead, the BOR is defined as the best overall response during the defined period and does not need to be confirmed at a subsequent timepoint, hence overall responses whether confirmed or not are assessed in the evaluation of BOR.

Exploratory Analysis

Further summaries by subgroup will be provided where BOR is assessed using unconfirmed responses.

The summary table described above will be repeated for each of the following subgroups:

- PD-L1 status at screening (positive/negative or indeterminate) for Cohort A only.
- M staging at screening (M1c and M1d/M0, M1a and M1b) for Cohort A only.
- BRAF status at screening (wild type/mutant) for Cohort A only.
- LDH at baseline (≤ upper limit of normal/> upper limit of normal) for Cohort A and B.

The criteria for presentation of these outputs are described in Section 5.2.8.

5.13.2 Secondary Endpoints

5.13.2.1 PFS Assessed by RECIST 1.1 for Cohorts A and B

PFS will be analysed using the ITT set and analysis will be repeated for the PPS for Cohort A only.

PFS is defined in months as the time between Visit 1 and the first confirmation of progression using RECIST 1.1, or death from any cause (whichever occurs first) (date

of first progression or death – date of Visit 1 + 1). Progression is determined by the investigator using the CT or MRI scan (scheduled or unscheduled) or death due to any cause. Subjects who die without reported progression will be considered to have progressed on the date of their death.

The following censoring rules will apply:

- Subjects who did not progress or die will be right censored on the date of their last evaluable tumour assessment.
- Subjects who did not have any on-study tumour assessments (scans) and did not die will be right censored on their date of first post-Screening visit. Note that this definition is consistent with that used for Checkmate 067[2].
- Subjects who remain on study following radiotherapy or other prohibited treatment will be censored at their last scan assessment prior to the intervention therapy.
- Subjects in Cohort B who change therapy to IMM-101 + ipilimumab without documented progression by RECIST 1.1 will be censored at the date of their last evaluable tumour assessment prior to this change in therapy.

Summaries of PFS

Descriptive statistics will be presented for PFS. The number and percentage of subjects that are censored will be summarised, along with KM estimates for the 25th, 50th and 75th percentiles of PFS and corresponding 95% CIs. PFS will also be presented graphically using a KM plot. The proportion of subjects who have not progressed or died at three monthly intervals will also be presented.

A time to event listing will present the milestones required for calculation of each time to event efficacy parameter.

5.13.2.2 OS and OS at 1 Year for Cohorts A and B

OS and OS at one year will be analysed using the ITT set and analysis will be repeated for the PPS for Cohort A only.

OS is defined in months as the time between Visit 1 and the date of death from any cause (date of death – date of Visit 1 + 1).

OS will be calculated for the entire study duration where subjects without a death date will be right censored at the date the subject was last known to be alive (during or post study). Post-study survival information is collected until database lock, for subjects completing or withdrawing from the study.

OS will also be calculated for subjects at one year, where subjects without a death date will be right censored on the date of Visit 1 + 365 days.

Summaries of OS

Descriptive statistics will be presented for OS for the whole study period and repeated for OS at one year. The number and percentage of subjects that are censored will be summarised, along with KM estimates for the 25th, 50th and 75th percentiles for both OS and OS at one year and corresponding 95% CIs for each. OS and OS at one year will also be presented graphically using a KM plot. The proportion of subjects alive at 3 monthly intervals will also be presented.

Survival status and death details (during or post study) will be listed for each subject.

5.13.3 Exploratory Endpoints

5.13.3.1 ORR assessed by irRC for Cohorts A and B

The analysis as detailed in Section 5.13.1 for the primary endpoint will be repeated where ORR is calculated from the BOR of subjects as assessed by irRC. Analysis will be performed on the ITT set for both cohorts.

For Cohort A, BOR is defined as the best response designation, recorded from the first post-baseline scan until and including the last scan on study for each subject.

For Cohort B, BOR is defined as the best response, recorded from the first post-baseline scan until and including the last scan on study for each subject for those receiving IMM-101 and nivolumab, or the last scan performed prior to treatment with ipilimumab. No scan performed once ipilimumab treatment commences will be included.

All scans within these defined periods, whether scheduled or unscheduled, will be evaluated for overall response.

Unconfirmed responses will be used in the assessment of BOR where BOR is the best overall response during the defined period and does not need to be confirmed at a subsequent timepoint.

Subjects without a BOR assessment, such as those with no post-baseline responses or only NE responses, will be assumed to have a response of PD using a worst-case approach.

ORR is calculated as the number of subjects with a BOR of CR or PR divided by the number of subjects in the analysis set. ORR is calculated for each cohort separately.

Summaries of BOR (irRC)

The BOR will be summarised for each cohort. The ORR and accompanying exact binomial 95% confidence intervals (CI) will also be presented.

5.13.3.2 Duration of Response Assessed by RECIST 1.1 for Cohorts A and B

Duration of response will be analysed using the ITT set and only subjects who have a documented response of CR or PR will be included.

Duration of response is calculated as the time in months from the date of first documented response of CR or PR per RECIST 1.1 until the date of documented PD per RECIST 1.1 or until the date of death due to any cause (date of death or PD – date of documented response + 1). All scans are considered, whether scheduled or unscheduled, in the determination of response and confirmed responses are not required.

Subjects who neither progress nor die will be right censored on the date of their last tumour assessment. For Cohort B subjects who change treatment to IMM-101 and ipilimumab, only responses evaluated until the point of this change in therapy are included.

Summaries of duration of response

Descriptive statistics will be presented for duration of response. The number and percentage of subjects that are censored will be summarised, along with KM estimates for the 25^{th}, 50^{th} and 75^{th} percentiles for the duration of response and corresponding

95% CIs. The proportion of subjects who have not progressed or died following a complete or partial response at three monthly intervals will also be presented.

5.13.3.3 Time to Response Assessed by RECIST 1.1 for Cohorts A and B

Time to response will be analysed using the ITT set and only subjects who have a documented response of CR or PR will be included.

Time to response is calculated as the time in months from Visit 1 to the first documented response of CR or PR per RECIST 1.1 (date of documented response – date of Visit 1 + 1). All scans are considered, whether scheduled or unscheduled, in the determination of response and confirmed responses are not required.

For Cohort B subjects who change treatment to IMM-101 and ipilimumab, only responses evaluated until the point of this change in therapy are included.

Summaries of time to response

Descriptive statistics will be presented for time to response. KM estimates for the 25th, 50th and 75th percentiles for the time to response and corresponding 95% CIs will be presented. The proportion of subjects who have not achieved complete or partial response at 3 monthly intervals will also be presented.

5.13.3.4 Disease Control Assessed by RECIST 1.1 for Cohort B from Week 14 Onwards

Disease control will be analysed using the ITT set for Cohort B only.

Disease control is defined as a subject with a response of CR, PR or SD as per RECIST 1.1. Confirmed responses are not required.

SD determination requires a minimum scan time of 9 weeks from the first administration of IMM-101. Therefore, the first scan to be considered for this determination is Week 14. If unscheduled scans take place earlier than Week 14 but later than Week 9, they will be used for determination of SD for disease control at Week 14. For further information on the scan windows see Section 5.2.4 of this SAP.

Disease control is assessed at each scheduled scan assessment from Week 14 until the end of the study. For subjects who change treatment to IMM-101 and ipilimumab, only responses evaluated until the point of this change in therapy are included.

Disease control rate is calculated as the number of subjects with disease control divided by the number of subjects in the analysis set.

Summaries of Disease Control

The number of subjects with controlled disease and the number without controlled disease will be summarised together with the disease control rate for each scheduled scan assessment. The binomial 95% CIs will also be presented.

Disease control will be listed for each subject in Cohort B for each Visit.

5.13.3.5 BOR Assessed by RECIST 1.1 for Cohort B Including Responses Obtained Following a Change in Therapy

The analysis as detailed in Section 5.13.1 for the primary endpoint will be repeated on Cohort B where ORR is calculated from the BOR of including assessments performed including scans performed following the change to treatment with IMM-101 and ipilimumab. Analysis will be performed on the ITT.

All scans over the entire study, whether scheduled or unscheduled, will be evaluated for overall response. Unconfirmed responses will be used in the assessment of BOR where BOR is the best overall response during the defined period and does not need to be confirmed at a subsequent timepoint. Subjects without a BOR assessment, such as those with no post-baseline responses or only NE responses, will be assumed to have a response of PD using a worst-case approach.

Summaries of BOR in Cohort B (including assessments post ipilimumab)

The BOR will be summarised and the ORR and accompanying binomial 95% CIs will also be presented.

5.13.3.6 Immunological Markers from Blood and Biopsy Samples

This endpoint will not be evaluated within the scope of this SAP.

Listings will detail information for blood and biopsy samples taken for immunological marker assessment.

5.14 Multiplicity

All endpoints and the supportive analyses will be considered as descriptive evidence of efficacy and will be analysed without any procedures to account for multiple comparisons.

5.15 SAFETY EVALUATION

5.15.1 Adverse Events

AEs will be coded using the latest MedDRA dictionary version. The version used will be indicated in the data summaries and listings.

A treatment-emergent adverse event (TEAE) is defined as an AE that started on or after the start of the administration of IMM-101. If adverse event dates are incomplete and it is not clear whether the adverse event was treatment-emergent, it will be assumed to be treatment-emergent.

The relationship with each study treatment will be entered in to the eCRF for IMM-101, nivolumab and ipilimumab. A treatment-related TEAE is defined as a TEAE that is possibly, probably or definitely related to the study treatment. For each treatment, where the TEAE has a missing relationship it is assumed to be related to the treatment for analysis purposes.

A summary table will present the following:

- TEAEs (events and subjects).
- Serious TEAEs (events and subjects).
- Treatment-related TEAEs (relating to IMM-101 and/or nivolumab and/or ipilimumab) (events and subjects).
- Immune-related TEAEs (events and subjects).
- TEAEs with a Common Terminology Criteria for Adverse Events (CTCAE) Grade of 3 or above (events and subjects).
- TEAEs leading to discontinuation of IMM-101 (subjects only).

- TEAEs leading to withdrawal from study (subjects only).
- TEAEs leading to death (subjects only).
- TEAEs by CTCAE grade (1 to 5) (subjects only).
- TEAEs by severity (mild/moderate/severe/life threatening/death) (subjects only).
- TEAEs by relationship to study treatment and the pooled study treatment related category (subjects only).

In the above summaries, if a subject experienced more than one TEAE, the subject will be counted once using the most related event for the “by relationship to study treatment” and “related to IMM-101/nivolumab/ipilimumab” summaries, at the worst grade for the “by CTCAE grade” summary, and at the worst severity for the “by severity” summary.

A summary table will also be produced for Cohort B subjects only for AEs which occur at or after the start of infusion of ipilimumab. Any nivolumab related TEAEs occurring after the start of ipilimumab administration will be included. The summary will present the following:

- TEAEs (events and subjects).
- Serious TEAEs (events and subjects).
- Treatment-related TEAEs (relating to IMM-101 and/or ipilimumab) (events and subjects).
- Immune-related TEAEs (events and subjects).

The following tables will be presented:

- TEAEs by SOC and PT.
- TEAEs by SOC, PT and relationship to IMM-101/nivolumab/ipilimumab and the pooled related categories (related/unrelated).
- Serious TEAEs by SOC and PT.
- Immune-related TEAEs by SOC and PT.
- TEAEs with a CTCAE grade of 3 or above by SOC and PT.

For all of the above, SOC and PT will be presented in decreasing frequency of the total number of subjects with TEAEs.

Further details of the above five tables are given below:

1. If a subject experienced more than one TEAE, the subject will be counted once for each SOC and once for each PT.
2. If a subject experienced more than one TEAE, the subject will be counted once for each PT.
3. If a subject experienced more than one TEAE, the subject will be counted once for each SOC and once for each PT at the worst severity and/or CTCAE grade.
4. If a subject experienced more than one TEAE, the subject will be counted once for each SOC and once for each PT using the most related event.

Adverse event data will be listed in full and this will also include a treatment emergent flag, the time of onset in relation to each treatment and the action taken for each treatment. Separate listings will be provided for serious AEs, immune-related AEs, AEs with a CTCAE grade of 3 or above, AEs leading to study withdrawal or IMM-101 discontinuation and AEs with a fatal outcome.

5.15.2 Injection Site Reactions

The type of injection site reactions from administration of IMM-101 will be summarised at each administration visit.

A further summary will present the worst reported CTCAE grade for each injection site reaction type which occurred over the entire study period. If a subject experienced more than one reaction within an injection site reaction type, the subject will be counted once at the worst CTCAE grade.

Details of all injection site reactions will be listed.

5.15.3 Clinical Laboratory Evaluation

Observed values and change from baseline in haematology and biochemistry assessments will be summarised over time. If the test results are reported in categorical format, the results will be summarised by subject counts and percentage for each category.

Each haematology and biochemistry parameter will be classed as low, normal, high or missing based on the reference ranges. Shift tables in relation to the reference range from baseline over time will be presented.

Tables summarising clinical significance over time for haematology and biochemistry will also be presented.

Haematology and biochemistry data will be listed separately including change from baseline, reference ranges flagging all out of range values and their clinical significance.

Dipstick urinalysis and serology data will be listed only.

5.15.4 Pregnancy test

Pregnancy test details will be listed.

5.15.5 PD-L1 Assessment

The biopsy for PD-L1 assessment for Cohort A will be listed.

5.15.6 BRAF status

Details of BRAF testing will be listed.

5.15.7 Vital Signs

Vital sign observed values and change from baseline values by parameter will be summarised over time.

All vital sign data will be listed including change from baseline.

5.15.8 Electrocardiography

Electrocardiogram (ECG) results for QT corrected for heart rate using Fridericia's formula (QTcF) will be listed including change from baseline values and overall interpretation.

5.15.9 Physical Examination

Details of timings of physical examinations will be listed.

5.15.10 ECOG Performance Status

ECOG performance status assessments will be listed.

The status categories are defined as follows:

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

5.15.11 Visit Dates

The reported visit number and the date of each visit (including unscheduled visits) for each subject will be listed.

6 CHANGES FROM THE PROTOCOL PLANNED ANALYSIS

1. The Cohort A interim data review will be conducted when the first 11 Cohort A subjects enrolled into the study have had the opportunity for 1 year on study. The Cohort B interim data review will be conducted when the first 5 Cohort B subjects enrolled into the study have had the opportunity for 6 months on study. Any further enrolled Cohort A/B subjects will not be included in the data reviews of efficacy, but their AE data will be included in the data reviews of safety.
2. The data cut-off for the interim data reviews has been clarified. This specifies the scan assessments included for each interim data review are derived using dates for each subject and not the nominal scan assessments.
3. Clarification has been made to the definition of the PPS. The definition requires subjects to have complied with the treatment regimen, but this is naturally implied by the definition given any non-compliance would be a protocol deviation.
4. Tables will be produced for the PP analysis set in addition to the ITT analysis set for Cohort A only. Due to the small size of Cohort B, there will be no separate set of tabulations for the PP set in Cohort B. Analysis set assignment and protocol deviations will still be listed for all subjects.

5. Clarification has been made to the requirement for subgroups to be summarised provided the respective subgroup size is at least 33% but less than the total size of the ITT set for Cohort A, and at least 50% but less than the total size of the ITT set for Cohort B.

7 REFERENCES

1 Eisenhauer E.A., Therasse P., Bogaerts J. et al. *New response evaluation criteria in solid tumours: Revised RECIST guideline (version 1.1).* Eur J Cancer, 2009. 45 (2), 228-247.

2 Wolchok J. D. et. al., *Overall Survival with Combined Nivolumab and Ipilimumab in Advanced Melanoma*. N. Eng. J. Med., 2017. 377 (14), 1345.

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