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STATISTICAL ANALYSIS PLAN

IMCGP100-102

A PHASE 1/2 OPEN-LABEL, MULTI-CENTER STUDY OF THE SAFETY AND EFFICACY OF IMCGP100 USING THE INTRA-PATIENT ESCALATION DOSING REGIMEN IN PATIENTS WITH ADVANCED UVEAL MELANOMA

AUTHOR: [redacted]

VERSION NUMBER AND DATE: V4.0 FINAL, 28MAY2020

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STATISTICAL ANALYSIS PLAN SIGNATURE PAGE

Statistical Analysis Plan V4.0 Final (Dated 28MAY2020) for Protocol IMCgp100-102.

	Name	Signature	Date
Author:	[redacted]		
Position/Company:			

Upon review of this document, the undersigned approves this version of the Statistical Analysis Plan, authorizing that the content is acceptable for the reporting of this study.

	Name	Signature	Date
Approved By:	[redacted]		
Position/Company:			
Approved By:	[redacted]		
Position/Company:			
Approved By:	[redacted]		
Position/Company:			
Approved By:	[redacted]		
Position/Company:			

Note the output templates will be signed of separately to the Statistical Analysis Plan.

[redacted]

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MODIFICATION HISTORY

Unique Identifier for this Version	Date of the Document Version	Author	Significant Changes from Previous Authorized Version
1.0 DRAFT	13MAY2016	[redacted]	Not Applicable – First draft version sent to Immunocore
2.0 DRAFT	13JUL2016	[redacted]	Final updates following Immunocore first draft review.
3.0 DRAFT	09AUG2016	[redacted]	Further updates following Immunocore second draft review.
1.0 FINAL	25AUG2016	[redacted]	Finalization of first version.
2.0 FINAL	01MAY2019	[redacted]	Updates to align with Protocol version 8 (Amendment 7), including major changes to the Efficacy, Safety, and Exploratory sections.

3.0 FINAL	20MAY2020	[redacted]	Updates included but not limited to:
			• Changes to exploratory efficacy,
			• Additional subgroups in Section 7.5.
			• Further details on:
			  ○ Concomitant medications
			  ○ Adverse events of special interest
			  ○ Exposure
			  ○ Vital signs
			  ○ Pharmacokinetics
			  ○ Immunogenicity
			  ○ Patient reported outcomes

4.0 FINAL	28MAY2020	[redacted]	Minor formatting updates.

[redacted]

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[redacted]

[redacted]

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1. INTRODUCTION

This document describes the rules and conventions to be used in the presentation and analysis of efficacy, safety, pharmacokinetics (PK) and exploratory endpoints ([redacted]) data for Protocol IMCgp100-102. It describes the data to be summarized and analyzed, including specifics of the statistical analyses to be performed. Details of analyses relating to other study objectives and endpoints will be described in separate documents.

This statistical analysis plan (SAP) is based on Protocol Amendment 7.0 (version 8.0), dated 26th November 2018 and Administrative Letter dated 22nd April 2020.

2. STUDY OBJECTIVES

2.1. PRIMARY OBJECTIVES

The primary objectives are:

- **Phase 1 Dose Escalation**: The primary objective is to identify the maximum tolerated dose (MTD) and/or the recommended Phase 2 dose (RP2D) of IMCgp100 in the intra-patient dose escalation regimen.

- **Phase 2 Dose Expansion**: The primary objective is to estimate the objective response rate (ORR) by independent central review (ICR) based on Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST v1.1) in patients with metastatic Uveal Melanoma (mUM) who are treated with the recommended Phase 2 dose intra-patient escalation (RP2D-IE) of IMCgp100.

2.2. SECONDARY OBJECTIVES

The secondary objectives are:

- To characterize the safety and tolerability of IMCgp100 in the intra-patient dose escalation regimen
- To characterize the PK profile of single-agent IMCgp100 in the intra-patient dose escalation regimen
- To assess the anti-tumor efficacy of IMCgp100 with the parameters of objective response rate (ORR)

[redacted]

(Phase 1), overall survival (OS), progression free survival (PFS), disease control rate ≥ 24 weeks and the duration of response (DOR)

- To evaluate the incidence of anti-IMCgp100 antibody formation following multiple infusions of IMCgp100 in the intra-patient dose escalation regimen
- To determine the rate and duration of minor responses (MinR) (defined as tumor response with a 10%-29% reduction in the sum of longest diameters (SOLD))

2.3. EXPLORATORY OBJECTIVES

[redacted]

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3. STUDY DESIGN

3.1. GENERAL DESCRIPTION

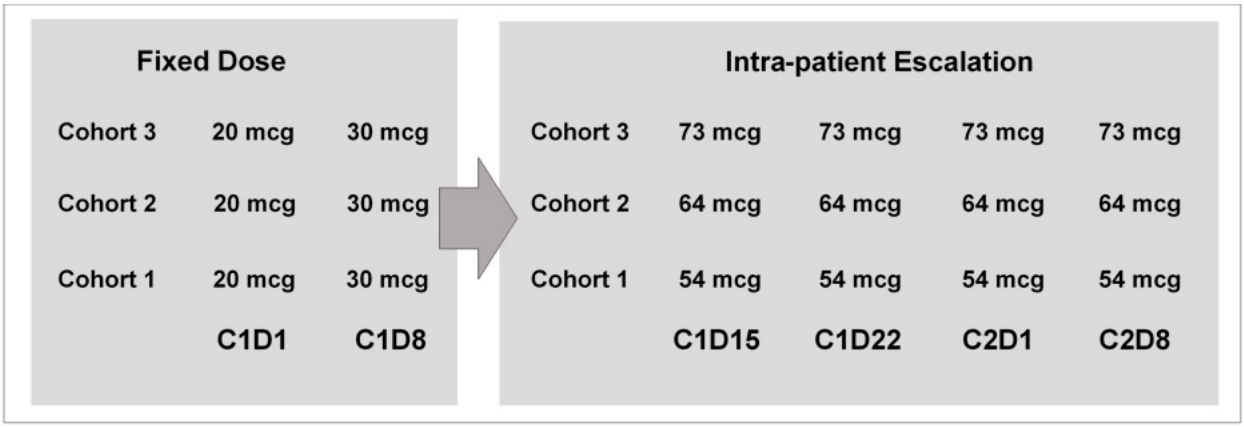
This is a Phase 1/2 study of IMCgp100 administered on a once a week (QW) basis with an intra-patient escalation dosing regimen. The intra-patient escalation occurs at the third weekly dose on Cycle 1 Day 15 (C1D15).

The Phase 1 portion of the study will be a standard 3+3 dose escalation design. Patients in the Phase 1 study will receive 2QW doses of IMCgp100 at a dose level below the identified weekly recommended Phase 2 dose (RP2D-QW, 50mcg flat dose) and then a dose escalation will commence at the third QW dose at C1D15 with the goal to achieve a long-term dosing regimen at a dose higher than that identified for the straight weekly dosing regimen (i.e. RP2D-QW of 50mcg). The dose escalation will identify the RP2D-IE.

Figure 3-1 Figure 3-1 below outlines the dosing schedule for the Phase 1 dose escalation and the Phase 2 expansion. Note: Enrollment into the Phase 1 dose escalation portion has been completed and RP2D-IE was determined to be 68 mcg with 20 mcg given on C1D1, 30 mcg given on C1D8 and then 68 mcg given on C1D15 and the same escalated dose level thereafter. The actual doses assessed in the Phase 1 escalation are provided in Figure 3-1. The Phase 1 dose escalation had an additional Cohort 4 (intra-patient escalation dose of 68 mcg) as an option to evaluate intermediate doses prior to expansion (this is not shown in Figure 3-1).

Figure 3-1 Intra-patient Escalation Regimen

Phase 1 Dose escalation



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Phase 2 expansion

Once the RP2D-IE is determined in the Phase 1 dose escalation then recruitment will begin into the Phase 2 expansion cohorts. These two cohorts will enrol approximately 150 patients combined.

- Cohort A will enrol patients who have experienced disease progression with 1 systemic treatment regimen containing a checkpoint inhibitor, including either a CTLA4 inhibitor (ipilimumab or tremelimumab) and/or a PD-1/PD-L1 inhibitor. Any prior LDT is acceptable in this cohort.
- Cohort B will enrol patients who have experienced disease progression with 1 or 2 prior lines of therapy in the metastatic or advanced setting including chemotherapy, immunotherapy or targeted therapy. Only a single line of local, LDT including chemotherapy, radiotherapy, radiofrequency ablation or embolization is allowed. A line of LDT is defined as one modality of treatment that is administered until completion of treatment or disease progression. For patients who have received prior LDT, this will count as a line of therapy. Prior surgical resection of oligometastatic liver disease is allowed and is not counted as a line of LDT. A patient may have discontinued systemic therapy prior to disease progression if the patient experienced an adverse reaction that required treatment discontinuation, as per Investigator's judgment and applicable labelling. Prior checkpoint inhibitor therapy is acceptable but not required in this cohort.

These expansion cohorts are designed to further characterize the safety, tolerability, and preliminary PK and anti-tumor activity of IMCgp100.

Figure 3-2 outlines the study design. For the purpose of analysis and reporting, patients from cohorts A and B will be combined and referred to as the "Phase 2 Expansion" cohort throughout the SAP due to significant overlap between the two groups and given this cohort assignments were not prospectively implemented during study conduct. Additional details on the Phase 2 Expansion cohorts are provided in Section 3.2 and Section 5.2 of the Protocol.

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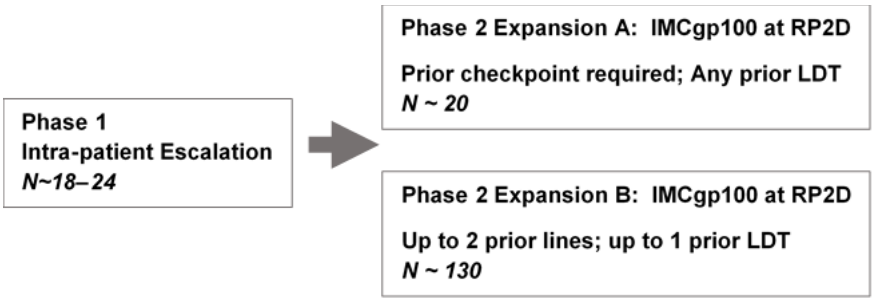
Figure 3-2 Study Design



The study will consist of the following Periods: Pre-screening, Screening, Treatment Period, 90-day Safety Follow-up, Disease Progression Follow-up and Survival Follow-up. Further details of these study periods can be found in Section 3.3 of the Protocol.

Treatment will be administered as described until the patient experiences unacceptable toxicity, or the patient experiences unequivocal, confirmed Progressive Disease (PD) as defined by modified irRECIST (or modified Immune related response criteria (irRC) for patients that discontinued before Protocol version 7). The end of the study will be when a minimum of 80% of the patients have completed the follow-up for disease progression or discontinued the study for any reason, and all patients have completed treatment and the 90-day Follow-up Period, or if the study is terminated early.

3.2. SCHEDULE OF EVENTS

Schedule of events can be found in Section 7.1 of the Protocol in **Table 7-1**.

3.3. CHANGES TO ANALYSIS FROM PROTOCOL

The planned changes to the analysis are the following:

- A Per-Protocol analysis of the Objective Response Rate (ORR) and duration of response in Phase 2 dose expansion only will be produced, which differs from the Protocol.
- Prior therapy subgroups will be defined as i.) combination of systemic therapy and any LDT, ii.) systemic therapy(s) only, and iii.) LDT only. This differs from the Protocol which states only "1 LDT" for subgroup levels i.) and iii.). This is necessary for analysis because any number of prior Liver Directed Therapies may be taken in Phase 2 Expansion Cohort A.
- The denominator in the calculation of the ORR for the Primary Efficacy in Phase 2 will be the total number of patients in the Full Analysis Set (FAS), rather than the subset with measurable disease at baseline, as stated in the Protocol.
- The timing of the interim analysis to assess for benefit risk will be extended to allow the potential of at least 9 months follow up.
- The timing of the primary analysis will be extended to allow to the potential for at least 12 months follow up.
- A further analysis (follow-up) may be conducted after the primary analysis if required, to include further follow-up time for the existing patients.
- Patients in the Phase 1 dose escalation treatment group will not be summarized by dose cohort for most efficacy endpoints as stated in the Protocol, and instead all Phase 1 patients will be summarized as a total pooled group, i.e. 'Phase 1 dose escalation cohorts - Total'. The rationale for this change is due to overlapping PK exposure between the dose levels explored in Phase 1.
- The immune response endpoint (as assessed by area under the tumor response curve) will not be covered in this SAP. The endpoint will not be analyzed as stated in the Protocol under the secondary objectives. The Protocol will not be amended for this, but this was noted in an Administrative Letter to all investigative sites (dated 22APR2020).

4. PLANNED ANALYSES

The following analyses will be performed for this study:

Analysis Number	Analysis Name	Number of patients*	Approximate Minimum follow-up	Purpose
1	Interim Analysis†	Phase 2: 75†	9 months	The interim efficacy analysis will focus on response rate and duration of response (as per ICR) as well as available PFS and OS data. In addition, safety data will also be reviewed to allow an overall assessment of benefit risk. Full details can be found in the IDMC Charter.
2	Primary Analysis	Phase 2: 120 to 150	12 months	The primary analysis will include all patients treated in Phase 2 with a minimum follow up time to adequately analyze the efficacy and safety of IMCgp100. Note: will be considered a secondary analysis if a favourable benefit risk is determined at the interim.

[redacted]

Analysis Number	Analysis Name	Number of patients*	Approximate Minimum follow-up	Purpose
3	Final Analysis	Phase 2: 120 to 150	To be agreed following the primary analysis.	Final analysis of key outputs (mainly overall survival, progression free survival, duration of response and ongoing safety) based on final, locked data.

*The timing of each analysis is determined by the number of patients and their follow-up in Phase 2. Phase 1 data will be reported for the Interim, Primary and Final Analysis. For the interim analysis, the approximate minimum follow-up time of 9 months, is based on 40 weeks (+/- 1 week) and determines the data cut-off date for the interim regardless of whether the 75th patient discontinues early.

†The Independent Data Monitoring Committee (IDMC) will conduct regular safety reviews, in addition to the interim analysis. The interim analysis will become the primary analysis if a favourable benefit-risk is determined at the interim. If that occurs, then the analysis carried out once 120 to 150 patients have completed approximately 12 months of follow-up will be considered secondary.

A data cut-off approach will be applied for the interim and primary analysis. Details of the algorithms applied are described in the document Data Cut-off Approach for SDTM Data V6.0 as referenced in APPENDIX 5.

Following the primary analysis, a decision will be made as to whether further follow up is required or if the study will close. At study closure, arrangements will be made to manage any patients ongoing study treatment, or any follow up required for safety purposes.

All Analyses identified in this SAP will be performed by IQVIA Biostatistics following Sponsor Authorization of this Statistical Analysis Plan, Database Lock (for the final analysis), and Sponsor Authorization of Analysis Sets, based on all patient data up to the follow-up time given in the above table.

4.1. INDEPENDENT DATA MONITORING COMMITTEE

An Independent Data Monitoring Committee (IDMC) will be established to provide oversight of safety and efficacy considerations in the Phase 2 expansion portion of this study. The IDMC will act in an advisory capacity and make recommendations regarding steps to ensure both subject safety and the ethical integrity of the study. The voting members of the committee are external to the sponsor and will not otherwise be involved with the study. The IDMC will include 2-3 clinicians experienced in oncology/melanoma and 1 statistician. Specific details regarding IDMC responsibilities, governance, and documentation will be described in a separate charter that is reviewed and approved by the IDMC members.

The IDMC will perform the regular safety reviews as well as the interim benefit-risk assessment. Following each IDMC meeting, the IDMC will provide recommendations to the Sponsor on any changes that may be needed to the future conduct of the study or if the study should continue as planned.

4.1.1. REGULAR SAFETY REVIEWS

The IDMC will monitor trial safety approximately every 4 months, or at a frequency described in the IDMC charter. Details of the safety data to be reviewed will be agreed between the Sponsor and the IDMC and described in the charter.

4.1.2. INTERIM ANALYSIS TO ASSESS BENEFIT RISK

The interim analysis outputs will be prepared by IQVIA Biostatistics in accordance with the SAP and the IDMC charter. Per the Protocol, the data cut-off (DCO) for the interim analysis is to occur approximately 9 months after the start of treatment for the 75th subject treated in the Phase 2 part of the study.

The interim efficacy analysis will focus on response rate and duration of response (as per ICR) as well as available PFS and OS data. In addition, safety data will also be reviewed to allow an overall assessment of benefit risk.

Depending on the strength of the data, there may be an opportunity to engage with the regulatory authorities with a view to submit this interim data for marketing approval. As a result, the interim analysis data will also be shared with Immunocore's Head of Research and Development. Further details are provided in the IDMC charter.

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5. ANALYSIS SETS

Agreement and authorization of patients included/excluded from each analysis set will be conducted prior to the Interim, Primary and Final analysis of the study.

All patients are considered for each of the below analysis sets, including those in the Phase 1 dose escalation and Phase 2 Expansion cohort parts of the study.

5.1. ALL PATIENTS ENROLLED SET

The All Patients Enrolled (ENR) set will contain all patients who provide the main informed consent for this study. Patients who sign pre-screening informed consent but not the main informed consent will not appear in this analysis set. The All Patients Enrolled Set will be used to summarise patient disposition and the analysis sets.

Any subjects who signed the main informed consent, but never started the study treatment for any reason will be regarded as screen failures. For these patients, the eCRF data collected will not be included in summary analyses but will be reported in the CSR as part of the listings for patient disposition, treatment allocation and inclusion/exclusion criteria.

5.2. FULL ANALYSIS SET

The Full Analysis Set (FAS) comprises all patients assigned to treatment, who received at least one full or partial dose of IMCgp100. The FAS will be used for all demography, baseline characteristics, [redacted] and efficacy data summaries and analyses unless specified otherwise. Patients will be analyzed according to the planned treatment.

5.3. PER-PROTOCOL SET

The Per-Protocol Set (PPS) consists of a subset of FAS patients in the Phase 2 part of the study who meet these 4 criteria: (1) presence of measurable disease at baseline according to Investigator assessment based on RECIST v1.1, (2) $\geq$1 post-baseline tumor assessment or discontinue prior to the first tumor assessment, (3) received at least one full or partial dose of treatment and, (4) no violation of key inclusion or exclusion criteria (as defined below). Patients who are enrolled in violation of these key inclusion or exclusion criteria will be considered as major Protocol violations and will not be included in the PPS.

For the (4) components above, only key inclusion criteria will be considered and will be determined based on values

[redacted]

entered on the *Inclusion/Exclusion Criteria* eCRF page. The key inclusion criteria considered as major protocol violations are #3, #6, and #9 as presented in the table below:

Protocol version number	Inclusion criteria number	Inclusion text
1 - 8	03	Histologically or cytologically confirmed diagnosis of mUM
1 - 4	06	HLA-A2 positive
5 - 8	06	HLA-A*0201 positive by central assay
8	09	Prior therapy requirements as defined in Phase 2 Cohort A or B.

Patients in the PPS will be classified according to planned treatment. The PPS will define the patients used in both the sensitivity analysis of the Primary Efficacy endpoint (i.e. ORR) and one of the Secondary Efficacy endpoints (DOR) for the Phase 2 expansion cohort only. If the PPS and the FAS are identical, then analyses described for the PPS below will not be performed.

5.4. SAFETY SET

The Safety Set (SAF) includes all patients who have received at least one full or partial dose of IMCgp100. Patients will be classified in this set according the actual dose cohort (or the single Expansion cohort in Phase 2) they were assigned to, unless there is evidence from the Protocol Deviations log or the dosing data that an incorrect treatment was received. For example, if a patient received the dose of another cohort (different to their assigned dose cohort) then they will be assigned to the cohort corresponding to the dose they received. Note that a dose reduction is not considered an incorrect treatment.

The safety set will be used for the safety, immunogenicity and pharmacokinetic summary of the study.

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6. GENERAL CONSIDERATIONS

6.1. REFERENCE START DATE AND STUDY DAY

Study Day will be calculated from the reference start date and will be used to show start/stop day of assessments and events.

Reference start date is defined as the day of the first dose of study drug, (Day 1 is the day of the first dose of study drug).

- If the date of the event is on or after the reference date then:

  Study Day = (date of event – reference date) + 1.

- If the date of the event is prior to the reference date then:

  Study Day = (date of event – reference date).

In the situation where the event date is partial or missing, the date will appear partial or missing in the listings, and Study Day and any corresponding durations will appear as missing in the listings.

6.2. BASELINE

Unless otherwise specified, baseline is defined as the last non-missing measurement (including unscheduled assessments) taken prior to the first dose of treatment received (e.g. C1D1 pre-dose). In the case where the last non-missing measurement and the reference start date and time coincide, that measurement will be considered pre-dose and included in the baseline calculation as appropriate. This will be the rule for demography, other baseline characteristics (including disease status), efficacy tumor assessments, laboratory data, ECG data, vital signs data, physical examination data, ADA data, and PK data. The exceptions to this rule are adverse events (AEs) and concomitant medications (CMs) commencing on the reference start date, which will be considered post-baseline. If any ECGs or vital signs are recorded in the “pre-dose panel” on C1D1 but appear with a time after the time of first dose, then they will be queried, but they will be assumed to be ‘post-dose’ (and therefore excluded from the baseline calculation), unless corrected otherwise.

6.3. RETESTS, UNSCHEDULED VISITS AND END OF TREATMENT DATA

In general, for by-visit summaries, data recorded at the nominal or observed visit will be presented. Unscheduled measurements will not be included in by-visit summaries, but will contribute to the baseline value, or best/worst case value where required (e.g. shift tables).

In the case of a retest (same visit number assigned), the earliest available measurement for that visit will be used for by-visit summaries. For best/worst case (e.g. shift tables), all available measurements including retest values will be used.

End of Treatment (EOT) visits will be summarized together in the by-visit summaries.

Listings will include scheduled, unscheduled, retest and early discontinuation data.

6.4. WINDOWING CONVENTIONS

There will be no post-hoc visit windowing for the analyses performed for this study. All data will be organized and analyzed according to the scheduled visit times (allowing for ± 7 days) as outlined in the Protocol and by the visit denoted on the eCRF.

Any unscheduled visits will be organized according to the closest scheduled visit they occurred to, using the previous scheduled visit as part of the unscheduled visit label.

6.5. STATISTICAL TESTS

There will be no formal statistical testing of data. Where appropriate, confidence intervals (CIs) will be presented.

6.6. COMMON CALCULATIONS

For quantitative measurements, change from baseline will be calculated as:

- Test Value at Visit X – Baseline Value

6.7. SOFTWARE VERSION

All analyses will be conducted using SAS version 9.4 in a Windows operating system.

7. STATISTICAL CONSIDERATIONS

Data will be presented by dose cohort and total for Phase 1, with the exception of efficacy data which will be presented for total Phase 1 only as detailed in APPENDIX 1 - Presentation of Treatment Groups. This data can be shared with the full protocol team prior to primary and final analysis since the initial data from these Phase 1 patients have already been published.

All available data from Phase 1 and 2 at the time of the Phase 2 reporting will be included in the Clinical Study Report (CSR). Note this could be based on the interim or the primary analysis depending on which data cut is considered for the main study reporting.

7.1. ADJUSTMENTS FOR COVARIATES AND FACTORS TO BE INCLUDED IN ANALYSES

Not applicable.

7.2. MULTICENTER STUDIES

A summary of the number of patients per country and the number at each site within a country will be produced as a baseline summary. Outcome data by country or site will not be provided unless requested by regulatory or health authorities.

7.3. MISSING DATA

Missing data in general will not be imputed.

Missing efficacy data will be handled as described in Section 14.1.4, 14.2.2 and 14.3.2 of this analysis plan.

7.4. MULTIPLE COMPARISONS/ MULTIPLICITY

Not applicable.

7.5. EXAMINATION OF SUBGROUPS

Subgroup analyses will be conducted as described in the Efficacy analyses – see Section 14.2.3.10.

The following subgroups of interest will be explored:

- Age (<65 vs. ≥65)
- Gender (Male vs. Female)
- Race (White vs. Non-white)
- Region (North America vs. Europe)
- Baseline Eastern Cooperative Oncology Group (ECOG) performance status (0=Fully active vs. 1=Restricted in physically strenuous activity, or greater)
- Baseline Lactate Dehydrogenase (LDH) (≤ ULN vs. > ULN)
- Baseline Absolute Lymphocyte Count (ALC) ("<1.0 x 10^9/L" vs. "≥1.0 x 10^9/L")
- Baseline Alkaline Phosphatase (ALP) (≤ ULN vs. > ULN)
- Largest liver metastasis (liver metastasis diameter < 3 cm vs. liver metastasis diameter ≥ 3 cm vs. no liver metastases)
- Prior immunotherapy (Yes vs. No)
- Prior therapy defined as
    - Combination systemic therapy and any LDT
    - Systemic therapy only
    - LDT only

  In addition, patients with 1 line of checkpoint inhibitor and any LDT may also be explored as a subgroup
- Best response to prior therapy (complete response/partial response vs. stable disease vs. progressive disease/not evaluable/not applicable/missing)

- Best response to prior Immuno-Oncology (IO) (checkpoint inhibitors only), defined as
    - Refractory to prior checkpoint inhibitors (i.e. Best response to any prior checkpoint inhibitor is progressive disease/not evaluable/not applicable/missing)
    - Relapsed following prior checkpoint inhibitors (i.e. Best response to any prior checkpoint inhibitor is stable disease, partial response, or complete response)
    - No prior checkpoint inhibitor
- Onset of Rash within first week of dose, defined as
    - Rash within 7 days of first dose (between study day 1 to 7 inclusive) vs. no rash within 7 days of first dose
    - Note: Rash will be identified using a medically-approved list of preferred terms provided by the Sponsor. See APPENDIX 6 for details

Subgroup categories may be combined if the number of patients within a category is not thought to be sufficient to analyze the efficacy.

8. OUTPUT PRESENTATIONS

APPENDIX 1 shows conventions for presentation of data in outputs.

The template shells provided with this SAP describe the presentations for this study and therefore the format and content of the summary tables, figures, and listings to be provided by IQVIA Biostatistics.

9. DISPOSITION AND WITHDRAWALS

All patients who provide main informed consent will be accounted for in this study.

Patient disposition and discontinuation/withdrawals, and inclusion and exclusion criteria will be presented for the ENR. All Protocol deviations will be reviewed by the medical monitor and other team members as appropriate before the primary and final analysis, and those deviations identified as Important (including those defined in Section 5.3) will be summarized and listed for the FAS.

10. DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

Demographic data and other baseline characteristics will be presented for the FAS.

The following demographic and other baseline characteristics will be summarized and listed for this study:

1. Demography
    - Age (years) – continuous
    - Age groups (years)
        - < 65
        - ≥ 65
    - Sex
    - Is the patient of child bearing potential? (females only) – listed only
    - Race
    - Ethnicity
    - Country
    - ECOG performance status at Baseline
    - Baseline LDH
        - ≤ULN
        - >ULN
    - Baseline ALP
        - ≤ULN
        - >ULN

- Baseline ALC
  - $<1.0 \times 10^9$/L
  - $\geq 1.0 \times 10^9$/L
- Smoking history/status including pack years
- Weight (kg)
- Height (cm)
- BMI (kg/m^2)

2. Disease data
   - Diagnosis and extent of cancer (disease at Baseline).
   - Presence of liver metastases (largest liver metastasis diameter <3 cm vs. largest liver metastasis diameter ≥3 cm vs. no liver metastases).
   - Prior anti-cancer therapy, including (a) the number (%) of patients within the prior therapy categories and prior immunotherapy types in Section 7.5 above and including checkpoint inhibitor class PD-1/PD-L1 and CTLA4 and other immunotherapies, (b) medically-reviewed categories of Therapy Class.
   - Best response on prior anti-cancer therapy for metastatic disease (as identified by medical review) as the number and % of patients with complete response, partial response, stable disease, progressive disease or not evaluable or missing as per Investigator recorded assessment, based on the subset of the FAS who have prior anti-cancer therapy for metastatic disease data recorded. The best response may be repeated on further categories and sub-categories of prior anti-cancer therapies (as identified by medical review).

Pregnancy test results for women of child bearing potential will be collected at Screening and over the course of the study. This information will be presented in a data listing only.

10.1. DERIVATIONS

- Age (years) will be derived using the following SAS code:

  floor ((intck('month',&birth,&date) - (day(&date) < day(&birth))) / 12)

  - &birth = Date of birth
  - &date = Date of informed consent
  - Note: For countries where only the year of birth is provided due to privacy laws, impute birth month and day as June 15. This will only be done as necessary and in analysis derived datasets, not in SDTM (Study Data Tabulation Model) datasets.

- Time since primary diagnosis (years) = (Date of treatment start date – Date of primary diagnosis + 1) / 365.25

- Time since first metastases (years) = (Date of treatment start date – Date of first metastasis + 1) / 365.25

- Time from primary diagnosis to metastatic disease (years) = (Date of metastatic disease – Date of primary diagnosis + 1) / 365.25

  - Note: Partial primary diagnosis dates are imputed using 15th day of month if only month/year present or July 02 if only year present.

- Best response on any prior anti-cancer therapy for metastatic disease = the "best" *best response* as derived from the *Prior Anti-Cancer Therapy (PAT)* eCRF page, considering all medications identified from the medical review. From best to worst, the following order will be used:

  - Complete Response
  - Partial Response
  - Stable Disease
  - Progressive Disease

- Non-Evaluable
- Not Applicable

- BMI (kg/m^2) = weight (kg) / (height (cm) / 100)^2

Note that the date of informed consent will be the main date of informed consent, not the date of pre-screening informed consent and not the date of informed consent for continuing treatment post RECIST-PD.

11. SURGICAL AND MEDICAL HISTORY

Medical History information will be listed only.

- Medical History will be coded using Medical Dictionary for Regulatory Activities (MedDRA) central coding dictionary, using version 22.0 or later (i.e. a later version of MedDRA may be available and used at the time of coding for the reporting period).
- Medical History conditions are defined as those conditions beginning prior to screening which stop prior to/are ongoing at Screening.
- Presented by System Organ Class (SOC) and Preferred Term (PT).

12. CONCOMITANT MEDICATIONS

Concomitant medications and significant non-drug therapies as recorded on the *Prior and Concomitant Medications* eCRF page will be presented and coded using the World Health Organization drug dictionary (WHODD) Anatomical Therapeutic Chemical (ATC) classification system, dated March 2019 or later (i.e. a later version of WHODD may be available and used at the time of coding for the reporting period).

Medications will be listed and summarized with the number and percent of patients receiving concomitant medications by ATC level 2 (coded) and Preferred Name (coded). Concomitant Intravenous (IV) fluids will be summarized by ATC level 3 coded term 'I.V. SOLUTION ADDITIVES' and Preferred Name (coded).

The number and percent of patients receiving concomitant anti-cancer therapy regimens will be also be summarized, as noted in Section 12.1 below. All prior anti-cancer therapies are collected at Screening and are described above in Section 10. Anti-neoplastic therapies since discontinuation of study treatment are described in Section 12.2 below.

See APPENDIX 2 for handling of partial dates for medications from the *Prior and Concomitant Medications* eCRF page. In the case where it is not possible to define a medication as prior, concomitant, or post treatment, the medication will be classified by the worst case; i.e. concomitant.

- 'Prior' medications are medications which started and stopped prior to the first dose of study drug.
- 'Concomitant' medications are medications which:
  - started prior to, on or after the first dose of study drug and no later than the last dose of study drug,
  - AND ended on or after the date of first dose of study drug or were ongoing at the end of the study.
- 'Post' medications are medications which started after the last dose of study drug.

12.1. PROHIBITED CONCOMITANT MEDICATIONS/THERAPIES

During the 'concomitant' period of the study (as above), patients may not receive other additional investigational drugs, agents, devices, chemotherapy, or any other therapies that may be active against cancer. While systemic corticosteroid therapy will interfere with the mechanism of action of the study drugs, its use is recommended in some settings. See Protocol Section 6.5.3 for further details.

Medications/therapies that are prohibited during the study will be flagged in the listing of concomitant medications, as well as summarized in a table by Preferred Name. These will be identified using a medically-approved list of Preferred Names provided by the Sponsor. See APPENDIX 2 for handling of partial dates for concomitant alternative cancer therapies under **Algorithm for Prior / Concomitant Medications**.

12.2. ANTI-NEOPLASTIC THERAPIES POST TREATMENT

Anti-neoplastic therapies since discontinuation of study treatment will be collected during the 90-day Safety follow-up, Disease Progression follow-up and Survival follow-up periods of the study. The information for those patients having these therapies is recorded on the *Antineoplastic therapies since discontinuation* eCRF page, separately from any 'prior' or 'concomitant' anti-cancer therapies.

It will be assumed that data collected on the *Antineoplastic therapies since discontinuation* eCRF page are 'post' medications, unless a Start Date entered is ≤ the date of last dose of study drug. In this case, the Start Date will be

queried, but it will be assumed that the therapy was 'concomitant', unless corrected otherwise. See APPENDIX 2 under **Algorithm for Anti-Neoplastic Therapies Post Treatment Discontinuation** for handling of partial dates for therapies from the *Antineoplastic therapies since discontinuation* eCRF page. If this imputation of a Start Date yields a date after the Stop Date, then impute the Start Date to be equal to the Stop Date instead.

Anti-neoplastic therapies post treatment will be presented in a data listing and summarized as follows:

The number and % of patients receiving subsequent therapy will also be summarized as well as the actual therapy received. Included in the summary will be medically-reviewed categories of Therapy Class.

Further summaries for anti-neoplastic therapies post treatment are described in Section 18.3.

13. STUDY DRUG EXPOSURE

Total actual dose received, duration of treatment in days, dose intensity, and relative dose intensity will be summarized for IMCgp100. Also, number of cycles will be presented in the summary.

Tolerability of study drug will be assessed by summarizing the number and duration of treatment dose interruptions, and the number of treatment dose reductions for IMCgp100. Reasons for dose interruptions and reasons for dose reductions will also be summarized, as well as listed.

The SAF analysis set will be used for presenting all exposure and tolerability variables.

13.1. STUDY DRUG EXPOSURE DERIVATIONS

A cycle is defined as 28 days = 4 weeks, and there is 1 dose administration visit every week.

The following will be derived:

- *Number of cycles started* = total number of cycles of study drug received (including partial cycles and reduced doses).
- *Number of cycles completed* = total number of complete cycles of study drug received without any interruption (but including reduced doses).
- *Total planned dose* = sum of the total dose levels that a patient planned to receive during the study, up to the date of last study drug administration.
- *Duration of treatment* (days) = (date of last study drug administration – date of first study drug administration + 1). Note that this calculation does not include any post dose rest period.
- *Duration of interruption* (days) = (start date of *next* study drug administration following interruption - date

of visit in which interruption started). Note that this is calculated for each interruption a given patient has and is only calculated where study drug administration restarts following interruption.

- "Date of visit in which interruption started" = 'date of visit' from the *Date of Visit* eCRF pages, where the visit may also be a visit classified as "not done". If it is clear that an interruption to dosing has occurred, but no *Date of Visit* eCRF page nor *Administration of Study Drug* eCRF page is entered at least 14 days (i.e. at least 7 days ± 7 day visit window) following the previous dosing visit, where dosing would have been expected, then the date of the *expected* next dose following last administered dose, may be used instead (=previous 'start date of study drug administration' + 14 days). For these cases where 14 days are added, a dose interruption can be counted where there is a gap from a given 'start date of study drug administration' ≥ 15 days from the previous populated 'start date of study drug administration', between two consecutive dosing visits. See the definition of a *dose interruption* below.
- If a patient does not have a "start date of *next* study drug administration following interruption" then a dose interruption is <u>not</u> counted because either:
  - The Date of study drug discontinuation from the *End of Treatment* page of the eCRF is filled out, in which case the study drug was discontinued rather than interrupted, or
  - The outcome (interruption or discontinued) is unknown at the time of data cut-off, where the study drug discontinuation from the *End of Treatment* page is missing and study drug administration remains skipped or omitted. In this case, it is assumed there was no interruption, until there is evidence of the study drug administration restarting.

- *Total actual dose received* = sum of the total dose (in mcg) that a patient received during the study, up to and including date of last study drug administration.
- *Dose intensity* (dose per week) = [*Total actual dose received* / (*Duration of treatment (days) + 6)*] × 7, where adding 6 additional days to the duration accounts for the weekly dose administration.
- *Planned dose intensity* (dose per week) = [*Total planned dose* / (*Duration of treatment (days) + 6)*] × 7, where adding 6 additional days to the duration accounts for the weekly dose administration.
- *Relative dose intensity* (%) = (*Dose intensity* / *Planned dose intensity*) × 100.

<u>Additional Notes on Derivations:</u>

a. The *Administration of Study Drug* eCRF page will be used for these calculations.

b. The *number of cycles started* is counted for all cycles of dosing in which study drug was actually administered. Any administration of study drug received, regardless of the 'Actual dose administered' on the eCRF (any dose > 0 units), that occurs in a given cycle (as indicated by the visit) will be counted as one cycle of that study drug.

i. Note: Multiple doses within a Cycle do not count multiple times towards the *number of cycles started*. For example, four doses (> 0 units) of IMCgp100 during visits in Cycle 1 count as one cycle of study drug since all these dose administrations occurred during a single Cycle (i.e. Cycle 1).

c. The *number of cycles completed* is counted for all cycles of dosing in which study drug was actually administered, and furthermore where no interruption occurs. Therefore, in a 4-week cycle, all doses each week must be administered for the entirety of the cycle, in order to count. Reduced doses are allowed, as per *number of cycles started* above.

d. The *total planned dose* is based on the dose level a patient is originally assigned to, noting that subjects are planned to receive 20 mcg IMCgp100 at C1D1 and 30 mcg IMCgp100 at C1D8. Intra-subject dose escalation occurs at C1D15, with dose level set depending on cohort and all dose administrations from this day are expected to be at that dose level. For Phase 1 and 2 patients enrolled to the study and assigned to treatment under Protocol Amendment 5 and earlier, the **Dose Re-Mapping Table** below applies, in which the Corrected Dose levels are used instead. The planned dose level is used over all visits where a patient planned to receive study drug, even if the dose is missed during the visit, up until the cut-off as described above. This calculation is necessary for the planned dose intensity, which is used to calculate the relative dose intensity.

i. Any scheduled CxDy visits with 'date of visit' from the *Date of Visit* eCRF page ≤ date of last study drug administration are included in the calculation, by adding the appropriate planned dose level for the given visit. If a patient has not yet discontinued treatment on the *End of Treatment* page, then all applicable scheduled CxDy visits through the date of last recorded study drug administration are considered, up until the data cut-off.

ii. Example: In Phase 2, patients are planned to receive 20 mcg at C1D1, 30 mcg at C1D8, and then 68 mcg from C1D15 onwards. Therefore, the total planned dose is calculated as the sum of 20 mcg + 30 mcg + 68 mcg at C1D15 onwards, over all visits where a patient planned to receive study drug.

e. The *total actual dose received* is based on the 'Actual dose administered' entered on the eCRF for each visit administration of study drug. The actual dose administered is summed up over all visits where a patient actually received study drug, up to and including the day of last study drug administration. For Phase 1 and 2 patients enrolled to the study and assigned to treatment under Protocol Amendment 5 and earlier, the **Dose Re-Mapping Table** below applies, in which the Corrected Dose levels are used instead of the values entered on the eCRF.

f. The date of first study drug administration is taken from the earliest 'Dose start date' entered on the eCRF.

g. The date of last study drug administration is taken from the latest 'Dose end date' entered on the eCRF.

[redacted]

Dose Re-Mapping Table:

Protocol Amendment 5 and earlier dose levels (as entered on eCRF)	Corrected Dose, planned and received on or prior to April 7, 2017	Corrected Dose, planned and received after April 10, 2017
20 mcg	No update to dose	No update to dose
30 mcg	No update to dose	No update to dose
50 mcg	No update to dose	No update to dose
60 mcg	54 mcg	54 mcg
70 mcg	67 mcg	64 mcg
80 mcg	76 mcg	73 mcg
75 mcg	68 mcg	68 mcg

Definitions of Dose Interruption/Reduction:

- *Dose interruption* – an entire planned dose dosing visit is skipped or entered as omitted in the eCRF. To clarify, if a dose on a single day is stopped and restarted, but a partial or full dose is still taken *on same visit* (i.e. same Visit label on the eCRF), then this is not a dose interruption. Dose interruptions will be flagged on the *Administration of Study Drug* eCRF page where the response to '*Did the patient receive investigational product at this visit?'* is equal to *'No, reason for dose omission'.* Also, dose interruptions are counted in cases where a patient misses an entire study visit, where dosing is expected, as per the derivation of *total planned dose* above. Therefore, any CxDy visits with 'date of visit' from the *Date of Visit* eCRF page ≤ 'date of discontinuation' from the *End of Treatment* page are considered to be skipped and interrupted, if dose was not administered and study drug administration restarts following interruption. If there is no 'date of discontinuation' date, then all CxDy visits with a populated 'date of visit' are considered in the calculation.
    - Skipped or omitted dosing visits are only counted towards a dose interruption, if study drug administration restarts following interruption. Therefore, as per the *Duration of interruption* definition above, a "start date of *next* study drug administration following interruption" must exist, for a dose interruption to count.
        - Note: skipped or omitted dosing visits leading to discontinuation of study drug, are

counted separately in the Disposition summary under patients who discontinued treatment.

- A single interruption is defined as any length of time a patient misses dosing visits. For example, for IMCgp100 which is administered weekly, a single dose interruption would be defined regardless of whether only 1 week was missed or 2 consecutive weeks dosing were missed.
- An interruption to dosing may occur, in which no *Date of Visit* eCRF page nor *Administration of Study Drug* eCRF page is entered at least 14 days (i.e. at least 7 days ± 7 day visit window) following the previous dosing visit, where dosing would have been expected between two consecutive visits. In this case, a dose interruption may be counted where there is a gap from a given 'start date of study drug administration' ≥ 15 days from the previous populated 'start date of study drug administration', between two consecutive dosing visits. Note: there must be a restart of study drug administration following interruption, for this to count.

- *Dose reduction from protocol dose level* – restarting treatment at a reduced dose of study drug. Dose reductions will be derived from the *Administration of Study Drug* eCRF page where either (i) the 'Actual dose administered' is lower than the protocol specified dose level while patients are escalating from 20 mcg to 30 mcg to the planned/assigned dose level for each cohort, or (ii) the 'Actual dose administered' at a given visit decreases from the 'Actual dose administered' at the previous dose administration visit.
  - (i) It is conceivable that the planned starting doses of 20 or 30 mcg may continue through the C1D15 visit and beyond. The reasons given are highlighted in the eCRF, in the section 'Has the dose reduced from previous visit?'. In these cases, where the planned starting dose of 20 or 30 mcg continue, each repetition of a 'Actual dose administered' = "20 mcg" or each repetition of a 'Actual dose administered' = "30 mcg" will be considered as a **dose reduction from protocol dose level**.
  - (ii) From C1D15 onwards, or from the first post-C1D15 visit that the escalated dose is expected to be received (if the planned starting doses of 20 or 30 mcg continue through C1D15 and beyond), dose reductions are where the 'Actual dose administered' at a given visit decreases from the 'Actual dose administered' at the previous dose administration visit. In this second aspect of the dose reduction criteria, only the *initial* reduction of a 'Actual dose administered' will be considered as a **dose reduction from protocol dose level**.
    - For example, in Phase 2 where patients are planned to receive 68 mcg from C1D15 onwards, a reduction to say 50 mcg at C1D22 from the 68 mcg at C1D15 is counted as a dose reduction. But continuing to be prescribed 50 mcg at C2D1 onwards is <u>not</u> considered further dose reductions. However, if the patient increases their dose level back up to 68 mcg at a visit, and then reduces again back down to 50 mcg,

then the *initial* reduction back down to 50 mcg is again counted as a dose reduction. Similarly, an exposure profile of: 20-30-68-50-50-30 is considered to consist of two dose reductions, the first reduction from 68 to 50 mcg and the second reduction from 50 to 30 mcg.

- Note: Any **dose reduction from protocol dose level** will be both summarized with the corresponding reason (Adverse Event or Other), as well as listed.

- *Dose reduction from prescribed dose* – Any case where the 'Actual dose administered' is lower than the 'Prescribed dose level' at a given dose administration visit. Note: The 'Prescribed dose level' is entered by the Investigator as the *intended/planned* dose to be received at a given visit, even if that is less/reduced from the Protocol-specified dose level.

  - Unlike, the above *dose reduction from protocol dose level* which will be summarized, a **dose reduction from prescribed dose** will only be listed as "Planned dose?" = 'No'. It is expected that the only kind of dose reductions from prescribed dose are caused by infusion extravasation events, also recorded on the *AE*/*SAE* eCRF page. Apart from these types of events, all other cases where 'Actual dose administered' is lower than the 'Prescribed dose level' will be queried with Data Management.

    - Note: Due to an infusion extravasation event, an infusion may stop and restart, and then a partial or full dose may still be taken *on the same visit*. In the case of a full dose being administered after a stop/restart, a **dose reduction from prescribed dose** will <u>not</u> count, and in this case, the record of this occurring will be shown in the exposure and AE data listings. Only when less than the prescribed dose is administered at a visit (i.e. a partial dose) will "Planned dose?" = 'No'. Otherwise, "Planned dose?" as entered on the eCRF should be 'Yes'.

    - Note: Both kinds of dose reductions, (1) a **dose reduction from protocol dose level** and (2) a **dose reduction from prescribed dose**, can both occur at the same visit if an intended reduction was planned by the investigator, and then on top of that the 'Actual dose administered' is lower than the 'Prescribed dose level', due to an infusion extravasation event.

<u>Other definitions:</u>

- *Received intra-patient dose escalation as planned*– defined as receiving the full planned cohort-specified dose level on C1D1 (i.e. 20 mcg IMCgp100), C1D8 (i.e. 30 mcg IMCgp100), and C1D15 (i.e. the planned/ IVRS assigned dose level for a particular cohort).

Further notes on exposure:

- When dose is interrupted, reduced, or discontinued due to an Adverse Event (AE), then the "Action taken with study drug" item on the *AE/SAE* eCRF page should be completed accordingly. However, the Action can only be selected once per AE, so in the case that interruptions/reductions/discontinuation are consecutive on the *Administration of Study Drug* eCRF page, then the *AE/SAE* eCRF page may only have the most extreme and ultimate Action recorded. The order of extremity from least extreme to most extreme is: an interruption, a reduction, and a discontinuation.

13.1.1. Missing Data Methods For Study Exposure Variables

Missing data for elements of certain study exposure variables will be handled as follows:

- The date of first study drug administration is not expected to be missing for any patients.
- If the date of last study drug administration is missing or partial, then the date will be taken instead from the Date of discontinuation on the *End of Treatment* page of the eCRF.
- The handling of missing start/end dates from the *Administration of Study Drug* eCRF page that are not the first/last study drug administrations are to be as follows:
    - If the dose start date is missing and the dose end date is known, then the start date is set to the end date.
    - If the study drug end date is missing and the dose start date is known, then the end date is set to the start date.
    - If both dose start and end date are missing from the *Administration of Study Drug* eCRF page then these are set to a known date from a *Date of Visit* eCRF page.

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14. EFFICACY OUTCOMES

14.1. PRIMARY EFFICACY

14.1.1. PRIMARY EFFICACY VARIABLES & DERIVATIONS

14.1.1.1. Phase 1 dose escalation

Not applicable, the primary endpoint is a safety endpoint.

14.1.1.2. Phase 2 dose expansion

For Phase 2 dose expansion, the primary efficacy variable is the objective response rate, defined as the proportion of patients with a *best* overall response of complete response (CR) or partial response (PR) based on the ICR data, according to RECIST v1.1. The denominator in the calculation of the ORR will be the number of patients in the FAS.

Data summaries and listings will be presented overall for the Phase 2 expansion cohorts.

All guidelines for the implementation of RECIST v1.1 based on ICR are given in the Independent Review Charter.

14.1.2. DERIVATION OF BEST OVERALL RESPONSE USING RECIST V1.1 CRITERIA

To determine whether an *objective* response (i.e. CR or PR) exists for a patient, the best *overall* response (BOR) to a patient's tumor assessments during the study will be derived as follows.

A BOR is calculated based on the overall visit responses from each RECIST assessment. It is the best response a patient has had following the date of first dose of study drug, but on or prior to either (i) disease progression according to RECIST v1.1, (ii) the last evaluable tumor assessment in the absence of disease progression (including death), or (iii) starting any subsequent alternative cancer therapy including another investigational agent, whichever comes first. In other words, for patients who progress and subsequently have a response, the BOR will not include the response after progression. Furthermore, tumour assessments performed after initiating another anti-cancer therapy will not be included in the calculation of BOR. See Sections 12.1 and 12.2 for how alternative cancer therapies are collected while concomitant with study drug treatment and post treatment.

The individual visit overall responses from each RECIST assessment will be provided by ICR as part of an external data transfer. Using these overall responses at each visit, a patient's BOR is derived in the following order, checking for best outcome before worst:

[redacted]

1. **Complete Response (CR)**: At least one confirmed visit response of CR.

2. **Partial Response (PR)**: If not CR, at least one confirmed visit response of PR.

3. **Stable Disease (SD)**: If not CR/PR, at least one visit response of SD recorded at least 8 weeks after date of first dose of study drug. Includes unconfirmed CR or PR recorded at least 8 weeks after date of first dose of study drug.

4. **Progressive Disease (PD)**: If not CR/PR/SD, a disease progression or death in the absence of progression

5. **Not-Evaluable (NE)**: No evidence of CR, PR, SD, or PD. Either by default or the only visit response by ICR is 'NE'.

Further considerations for deriving BOR:

- Stable disease should be recorded at least 8 weeks ± 1 week, i.e. at least 49 days (to allow for the assessment window), after first dose. For determination of a best response of SD, the **earliest** of the dates contributing towards a particular overall visit assessment will be used. The same goes for determining a best response of SD for any unconfirmed CR or PR recorded at least 8 weeks after first dose.
- Patients who have a PD event (progression or death) after 2 or more consecutive missed/non-evaluable tumor assessment visits, will not contribute to the BOR derivation. Specifically:
    - For patients who die with no evaluable follow-up tumor assessments or no evaluable baseline assessment, if the death occurs *after* 2 visits of the first dose of study drug, then the BOR will be NE.
    - For patients who die with no evaluable follow-up tumor assessments or no evaluable baseline assessment, if the death occurs *within* 2 visits of first dose of study drug, then the BOR will be PD (for death in the absence of progression).
        - Note: the definition of 2 visits (allowing for early and late visits) in this case equates to **18 weeks** (126 days) from the first dose of study drug.
    - Note: The scheduled tumor assessment scheme for RECIST is mandated every 8 weeks (±1 week) from Cycle 3 Day 1 until 40 weeks on study (approximately Cycle 11 Day 1). Thereafter, tumor assessments are every 12 weeks (±1 week) until disease progression or patient withdrawal. Therefore, in order to determine if a PD event occurred after 2 missed/non-evaluable tumor assessment visits, the definition of 2 visits (allowing for early and late visits) will be as follows:
        - If the previous evaluable tumor assessment is less than study day 218 (i.e. just prior to

week 31), then 2 visits equates to **18 weeks** (126 days) from the previous evaluable tumor assessment.

- Unless the previous evaluable tumor assessment is at Screening or there are no evaluable tumor assessments, in which case 2 visits equates to **18 weeks** (126 days) from the date of first dose of study drug.

- If the previous evaluable tumor assessment is greater than or equal to study day 218 and less than study day 288 (i.e. from week 31 to just prior to week 41), then 2 visits equates to **22 weeks** (154 days) from the previous evaluable tumor assessment. This is because 2 missed/non-evaluable tumor assessment visits over this specific time period would be when the scheduled frequency of tumor assessments changes from every 8 weeks (±1 week) to every 12 weeks (±1 week).

- If the previous evaluable tumor assessment is greater than or equal to study day 288 (i.e. week 41 onwards), then 2 visits equates to **26 weeks** (182 days) from the previous evaluable tumor assessment.

- The date of progression will be determined based on the **earliest** of the imaging dates of the component that triggered the progression. This could be a mixture of the target, non-target, and/or new lesion imaging dates. To determine which components (as determined by ICR) led to progression, the individual RECIST visit responses recorded by the ICR will be used. If the "Target lesions response" = PD, then the earliest target lesion imaging date will be considered. Likewise, if the "Non-target lesions response" = PD, then the earliest non-target lesion imaging date will be considered. Finally, if "New Lesions" = UNEQUIVOCAL, then the earliest new lesion imaging date will be considered.

14.1.3. CONFIRMATION OF OBJECTIVE RESPONSE USING RECIST V1.1 CRITERIA

Confirmation of response is required for declaring PR or CR in the ORR. A confirmed response is defined as an initial response (CR or PR) followed by a response at least 4 weeks later (for CR this needs to be confirmed by CR and for PR this needs to be confirmed by either PR or CR). The *initial* overall visit assessment which showed a response will use the **latest** of the imaging dates contributing towards a particular overall visit assessment. The same will be done for the *confirmation* overall visit assessment.

In the case where a patient has two non-consecutive visit responses of PR, then, as long as the time between the 2 visits of PR is greater than 4 weeks and there are no PD between the PR visits, the patient will be defined as a responder. For confirmation of response to count, visit responses of NE are allowed between visit responses of CR to confirm a CR, and likewise, visit responses of NE or SD are allowed in between visit responses of PR/CR to confirm a PR. For example, if a patient has visit responses of CR, NE, CR, then, as long as the time between the 2 visits of

CR is greater than 4 weeks, then a best response of CR will be assigned.

See Table 7-2 of the Protocol for the disease assessment collection plan.

PD per RECIST v.1.1 does not require confirmation.

14.1.4. Missing Data Methods for Primary Efficacy Variable

No adjustments for missing data will be made for the RECIST v1.1 criteria that are used for the Phase 2 primary efficacy analyses. However, an underlying assumption will be made such that missing tumor response data is not indicative of a complete or partial (objective) response. Therefore, any missing overall visit responses for RECIST tumor assessments are considered as Not Evaluable in the calculation of the BOR.

14.1.5. Primary Analysis of Primary Efficacy Variables

14.1.5.1. Phase 1 dose escalation

Not applicable, the primary endpoint is a safety endpoint.

14.1.5.2. Phase 2 dose expansion

For Phase 2 dose expansion, ORR will be estimated according to the number and % of patients with an objective response (BOR of CR or PR). The associated 95% two-sided confidence interval for the true ORR using the exact Clopper-Pearson method (Clopper & Pearson, 1934) will also be presented.

BOR and ORR will be summarized based on the patients in the FAS.

14.1.6. Sensitivity Analysis of Primary Efficacy Variable

14.1.6.1. Phase 2 dose expansion – Repeat using Per-Protocol Set

For the primary analysis for Phase 2 dose expansion, the calculation of ORR with 95% confidence intervals as described in Section 14.1.5.2, will also be performed using the PPS to obtain additional information on the robustness of results across analysis sets. If the PPS and the FAS are identical, then these additional summaries will not be reported.

14.2. SECONDARY EFFICACY

For the Phase 1 dose escalation, tumor based secondary efficacy endpoints will be derived and reported based on Investigator assessment data.

For the Phase 2 dose expansion, tumor-based secondary efficacy endpoints will be derived and reported based on the ICR data. In addition, summaries based on Investigator assessment data will be produced as supportive.

Investigator response and ICR will be derived in the same way unless specified otherwise. ICR data will be based on the visit responses provided by ICR and Investigator responses will be derived based on the overall visit responses recorded on the eCRF. Actual imaging dates will be used when deriving time-related variables or assessing confirmation of response.

All secondary efficacy outputs will be based on the FAS unless otherwise stated. Data outputs for Phase 1 and Phase 2 will be presented together. Phase 1 data will be combined and presented as "Phase 1 dose escalation cohorts - Total" unless specified otherwise. Phase 2 data will be presented by overall expansion.

Tumor- based secondary efficacy endpoints will be based on RECIST v1.1. All guidelines for the implementation of RECIST v1.1 criteria are given in Appendix 1 of the Protocol.

See APPENDIX 1 - Presentation of Treatment Groups for details on how the treatment groups will be presented.

14.2.1. SECONDARY EFFICACY VARIABLES & DERIVATIONS

The following secondary efficacy variables will be reported based on RECIST v1.1:

Phase 1 dose escalation:

- BOR, ORR, Disease Control Rate (DCR), time to response, duration of response, best percentage change in tumor size, and PFS based on Investigator assessment data.
- Overall survival.

Phase 2 dose expansion:

- BOR, DCR, time to response, duration of response, best percentage change in tumour size, and PFS based on ICR data. Investigator assessment data will be presented as supportive (including the ORR endpoint).
- Concordance between the ICR and Investigator assessment data for BOR.
- Overall survival.
- Rate and duration of minor responses (MinR) based on ICR and Investigator assessment.

14.2.1.1. BOR and ORR using RECIST v1.1

BOR and ORR will be derived as described above for the primary efficacy in Section 14.1.2 for the following:

- Phase 1 and Phase 2 using Investigator assessment data.
- Phase 1 and Phase 2 using Investigator assessment data excluding patients with non-measurable disease at baseline by Investigator assessment.
- Phase 1 using available ICR data – BOR listed only.
- Phase 2 using ICR data, excluding patients with non-measurable disease at baseline by ICR.

Note: The BOR derivation of Not-Evaluable using Investigator assessment from the eCRF is as follows:

- **Not-Evaluable (NE)**: No evidence of CR, PR, SD, or PD. Either by default or the only overall visit response by the Investigator is 'Not Assessable'.

Note: ORR determined by ICR is the primary efficacy variable for Phase 2.

14.2.1.2. Progression Free Survival

Progression Free Survival is defined as the time from first dose of study drug until the date of disease progression or death (by any cause in the absence of disease progression) regardless of whether the patient withdraws from assigned treatment or receives another anti-cancer therapy prior to progression.

Time for PFS will be calculated in number of months, calculated in two steps as:

i. Time in days = (date of event – reference date) + 1, where reference date is first dose date of IMCgp100.

ii. Therefore, time in months = days / (365.25 / 12). In other words, 1 month = 30.4375 days.

Rules for right-censoring are as follows:

- Patients who have not progressed or died at the time of analysis will be censored at the time of the latest tumor assessment date of their last evaluable scan (Note: evaluable means an overall visit response not equal to NE).
- If a patient progresses or dies after 2 or more missed/non-evaluable tumor assessment visits, the patient will be censored at the date of the latest tumor assessment of their last evaluable scan.
- If a patient has no evaluable follow-up tumor assessments or has no evaluable baseline assessment, then the patient will be censored at the date of first dose of study drug (Day 1).

- Note: An exception to this rule is if the patient (with no evaluable tumor assessment visits or no baseline data) dies within 2 visits of first dose of study drug, then the patient will be counted as an event.

In order to determine whether a death/progression is censored or an event, an exact time period is needed to define 2 visits being missed or consecutively non-evaluable. This is defined as per the derivation of BOR for the key primary Phase 2 efficacy analysis in Section 14.1.2, under "Further considerations for deriving BOR".

Important derivation notes for PFS Time:

- The PFS time will always be derived based on imaging dates, not visit dates.
- Imaging dates contributing towards a particular visit may be performed on different dates. The following rules will be applied:
  - RECIST v1.1 (Investigator assessment data): For the investigational site assessments, date of progression will be determined based on the **earliest** of the imaging dates of the component(s) that triggered the progression. This could be a mixture of the target, non-target, and/or new lesion imaging dates. To determine which components (as determined by the Investigator) led to progression, the individual RECIST visit responses recorded on the *Assessment of disease based on imaging (According to RECIST 1.1)* eCRF page will be used. If the "Target lesions response" = Progressive Disease (PD), then the target lesion imaging dates will be considered. Likewise, if the "Non-target lesions response" = Progressive Disease (PD), then the non-target lesion imaging dates will be considered. Finally, if "New Lesions" = Yes, then the new lesion imaging dates will be considered.

  - RECIST v1.1 (ICR data): The same approach as per the Primary Analysis for Phase 2 will be used for ICR data, for deriving the date of progression, as per Section 14.1.2 under Further considerations for deriving BOR.

  - When censoring a patient for PFS the patient will be censored at the **latest** of the dates contributing to a particular overall visit assessment.

14.2.1.3. Overall Survival

Overall Survival is defined as the time from the date of first dose of study drug until death due to any cause in general. Any patient not known to have died at the time of analysis will be right-censored based on the last recorded date on which the patient was known to be alive, i.e. the latest of (i) the "Date of Last Contact" (for those patients still alive) on the *End of Study* eCRF page and (ii) "Date patient last known to be alive" on the *Survival Follow Up* eCRF page. Also, to make sure that the last date patient was known to be alive is accurate as possible, any date from the eCRF that indicates the patient is still alive will also be considered. The eCRF pages to be included in this check are: *AE/SAE* (including hospitalization dates), *Prior and Concomitant Medication,* any page relating to

patient Disposition*, Administration of Study Drug 1-3, Vital Signs, Electrocardiogram,* all Laboratory pages*, Physical Examination, Punch Skin Biopsy,* all Tumor Scan pages*,* and *ECOG Performance Status*. The eCRF page dates that are not included in this check are: visit dates or signature dates or any other module that is not a true assessment date, e.g., sample processing dates.

Time will be calculated in number of months, calculated in exactly the same way as described for PFS above.

14.2.1.4. Duration of Response

Duration of response is defined as the time from the date of first documented objective response (CR or PR) until the date of documented disease progression or death by any cause in the absence of disease progression; the end of response should coincide with the date of progression or death for the PFS endpoint. The time of the initial response will be defined as the **latest** of the dates contributing towards the first documented OR (i.e. partial or complete response). As for the ORR, an objective response here requires confirmation at least 4 weeks later. The *initial* overall visit assessment which showed a response is used for the initial response (i.e. as date of onset of response), as opposed to the *confirmation* visit assessment.

Time will be calculated in number of months, calculated exactly the same way as described for PFS above. Time to response will not be defined (i.e. set to missing) for those patients who do not have documented OR.

If a patient does not progress following a response, then their duration of response will be right-censored at the PFS censoring time. Duration of response will not be defined (i.e. set to missing) for those patients who do not have a documented OR.

14.2.1.5. Time to Response

Time to response is defined as the time from the date of first dose of study drug until the date of first documented objective response. The time of the initial response will be defined as the **latest** date contributing towards the first documented OR (i.e. partial or complete response). As for the ORR, an objective response here requires confirmation at least 4 weeks later. The *initial* overall visit assessment which showed a response is used for the initial response, as opposed to the *confirmation* visit assessment.

Time will be calculated in number of months, calculated exactly the same way as PFS above. Time to response will not be defined (i.e. set to missing) for those patients who do not have documented OR.

14.2.1.6. Best Percent Change in Baseline of Tumor Size

Tumor size will be defined at each visit, as entered by the investigator on the *Sum of Diameters (According to RECIST1.1/irRC)* eCRF page or as provided by ICR.

The change from baseline in tumor size will be calculated as the difference between the tumor size at each post-

baseline visit and the tumor size at baseline for each patient. The percent change from baseline is then calculated as:

$$\frac{Tumor\ size\ at\ Visit\ X - Tumor\ size\ at\ Baseline}{Tumor\ size\ at\ Baseline} \times 100$$

The *best* percent change for a patient is then defined as the maximum percent reduction from baseline or the minimum percent increase from baseline (in the absence of a reduction) on or prior to either (i) disease progression, (ii) the last evaluable tumor assessment in the absence of disease progression (including death), or (iii) starting any subsequent alternative cancer therapy including another investigational agent, whichever comes first. This means the best percent change in tumor size will align with the BOR definition, as described in Section 14.1.2 above.

14.2.1.7. Disease Control Rate

Disease Control Rate is defined as the proportion of patients with either an objective response (i.e. partial or complete response), or with a BOR of stable disease recorded at least 24 weeks (±1 week) after date of first dose of study drug. The estimated DCR will also be repeated using a definition of BOR of stable disease recorded at least 16 weeks (±1 week) after date of first dose of study drug.

Stable disease should be recorded at least 24 weeks ± 1 week, i.e. at least 161 days (to allow for the assessment window), after first dose. For the repeat analysis including stable disease of at least 16 weeks ± 1 week, the number of days used as a cut-off will be at least 105 days after first dose. The BOR of stable disease includes unconfirmed CR or PR in this timeframe. For determination of a BOR of stable disease, the **earliest** of the dates contributing towards a particular overall visit assessment will be used. As for the ORR, an objective response of partial or complete response here requires confirmation at least 4 weeks later. Stable disease does not require confirmation.

14.2.1.8. Rate and Duration of Minor Response

Minor response is defined as a reduction from baseline in sum of diameters between 10%–29%, where the non-target lesion visit response is not unequivocal progression and no new lesions are present. The sum of diameters is defined as per RECIST v1.1 as the sum of longest diameters or short axis of target lesions (mm). Minor response requires confirmation at least 4 weeks after the initial response as described in Section 14.1.3 for CR and PR.

The rate of minor response (or better) is defined as the proportion of patients with a confirmed CR, PR, or MinR. It will be calculated for both the Investigator assessment and ICR data following RECIST v1.1. The denominator in the calculation of the Minor response rate will be the number of patients in the FAS according to ICR.

Duration of response, including minor response, will be derived as described above in Section 14.2.1.4 based on patients with a BOR of CR, PR, or MinR.

Rate and duration of minor response will be defined for Phase 2 dose expansion only.

14.2.2. Missing Data Methods for Secondary Efficacy Variables

No adjustments for missing data will be made for any response data used for the Secondary efficacy analyses. However, as per the Phase 2 primary efficacy analysis, an underlying assumption will be made such that missing tumor response data is not indicative of a complete or partial (objective) response, nor of stable disease or progressive disease. Therefore, any missing overall visit responses for tumor assessments are either considered as Not Evaluable in the calculation of the BOR or are ignored in any of the other calculations.

14.2.3. Analysis of Secondary Efficacy Variables

14.2.3.1. BOR and ORR using RECIST v1.1

The primary efficacy analysis of the ORR using RECIST v1.1 criteria will be repeated using the Investigator assessment data and ICR for Phase 1, and the Investigator assessment data for Phase 2, as described in Section 14.1.5.2.

The BOR, ORR and corresponding 95% confidence interval for the true ORR (using the exact Clopper-Pearson method (Clopper & Pearson, 1934)) will be presented based on the patients in the FAS. In addition, BOR will also be summarized based on the FAS to include patients only with measurable disease at baseline.

14.2.3.2. Concordance between Investigator assessment and ICR of BOR for RECIST v1.1

The agreement/disagreement between the Investigator assessment and ICR of BOR for RECIST v1.1 will be summarized for Phase 2 dose expansion. A “shift” type summary will be presented for the frequency of BOR values between Investigator and ICR, for all five categories of CR, PR, SD ≥ 8 weeks, PD, and NE. Percentages will be displayed based on the FAS.

14.2.3.3. Progression Free Survival

Progression Free Survival will be presented graphically using Kaplan-Meier plots. The estimated progression free survival rates at 3, 6, 9 and 12 months will be estimated via the Kaplan-Meier method and displayed and repeated for every 3 months after if follow-up goes beyond 12 months. The corresponding 95% confidence interval (using the Greenwood formula method of Kalbfleisch and Prentice, 1980) for each estimated PFS rate will be presented. Also, median PFS time and the corresponding 95% CI (using the method of Brookmeyer and Crowley, 1982 with the log-log transformation) will be summarized. The number and % of patients who have had progression events (disease progression or death) will also be presented.

The median follow-up time for PFS and the corresponding 95% confidence interval (using the method of Brookmeyer and Crowley, 1982 with the log-log transformation) will also be summarized using the reverse Kaplan-

Meier (KM) method. The analysis involves the event and censoring rules specified in Section 14.2.1.2 to be switched (i.e. the patients with documented disease progression or death become 'censored', and the censored patients are treated as the 'event').

14.2.3.4. Overall Survival

Overall Survival will be graphically analyzed and summarized in the same way as PFS (see Section 14.2.3.3).

The median follow-up time for overall survival will also be summarized using the reverse KM method in the same way as PFS (see Section 14.2.3.3). The analysis involves the event and censoring rules specified in Section 14.2.1.3 to be switched (i.e. the patients with documented death become 'censored', and the censored patients are treated as the 'event').

14.2.3.5. Duration of Response

Duration of response will be graphically analyzed and summarized in the same way as PFS (see Section 14.2.3.3). Duration of response will be derived for patients with CR and PR only.

The median follow-up time for duration of response will also be summarized using the reverse KM method in the same way as PFS (see Section 14.2.3.3). The analysis involves the event and censoring rules specified in Section 14.2.1.414.2.1.3 to be switched (i.e. the patients with documented disease progression or death become 'censored', and the censored patients are treated as the 'event').

For the Phase 2 Expansion, duration of response by ICR will be reported based on the FAS. Also, this will be repeated for the PPS. For Phase 1, duration of response will be reported by Investigator assessment in the FAS only.

14.2.3.6. Time to Response

Time to response data will be summarized using descriptive statistics for patients with CR or PR only.

14.2.3.7. Change in Tumor Size

Tumor size will be presented graphically using a waterfall plot, to present each patient's best percent change in tumor size as a separate bar, with the bars ordered from the largest increase to the largest decrease. For each patient's bar, the best overall response will be shown using a different color for each tumor response option.

In addition, a spider plot will be produced to display the percent change in tumor size across time for patients with minor response or better.

For both waterfall and spider plots, any post-baseline visits where the number of assessable target lesions is less than the number of assessable target lesions at baseline, will consequently not contribute to patients' tumor size

calculations to be plotted.

Change in tumor size will be based on the FAS with measurable disease at baseline.

14.2.3.8. Disease Control Rate

The DCR will be summarized as described above for ORR (Section 14.2.3.1) based on the FAS.

14.2.3.9. Rate and Duration of Minor Response

Response rate and duration of response including minor response (i.e. for confirmed CR, PR, or MinR) will be summarized as described above for ORR (Section 14.2.3.1) based on the FAS, and for Phase 2 dose expansion only.

Duration of minor response will be graphically analyzed and summarized in the same way as PFS (see Section 14.2.3.3). Duration of response will be derived for patients with CR, PR and MinR only.

The median follow-up time for duration of minor response will also be summarized using the reverse KM method in the same way as PFS (see Section 14.2.3.3). The analysis involves the event and censoring rules specified in Section 14.2.1.8 to be switched (i.e. the patients with documented disease progression or death become 'censored', and the censored patients are treated as the 'event').

14.2.3.10. Subgroup Analyses of Efficacy Variables

Subgroup analyses will be produced as per the subgroups specified in Section 7.5 for Phase 2. The subgroup analyses will be produced for RECIST v1.1 by ICR for ORR, PFS, OS, and Duration of response.

The point estimates (ORR proportion, PFS median, OS median, Duration of response median) and their corresponding 95% confidence intervals will also be displayed in a forest plot. The reference line on the forest plot will correspond to the point estimate for all patients in the FAS.

14.2.3.11. Swimmer Plot of Tumor Data

Swimmer plots will be produced showing duration of treatment, best overall responses (CR, PR, SD, Minor response, and PD according to RECIST v1.1 by ICR and/or Investigator assessment) and time to progression and/or death, where applicable.

14.3. EXPLORATORY EFFICACY

14.3.1. EXPLORATORY EFFICACY VARIABLES & DERIVATIONS

The following exploratory efficacy variables will be reported:

Phase 1 dose escalation:

- Duration of treatment post RECIST-PD based on irRECIST by ICR and Investigator
- BOR from start of treatment based on irRECIST by ICR or Modified irRECIST/irRC

Phase 2 dose expansion:

- BOR and Duration of treatment post RECIST-PD based on irRECIST by ICR and Investigator
- BOR from start of treatment based on irRECIST by ICR or Modified irRECIST/irRC

14.3.1.1. Tumor assessments using irRECIST by ICR or Modified irRECIST/irRC Criteria

Phase 1 and 2 patients were initially assessed for tumor response by the Investigator using the Modified irRC criteria. However, the Protocol was amended to use Modified irRECIST criteria instead, from Protocol version 7 (dated 15th December 2017) onwards. Patients initially assessed by Modified irRC and still ongoing tumor assessment at the time of implementation of Protocol version 7, were switched to the new Modified irRECIST criteria for all new tumor assessments. For those patients who "switched", tumor response data from prior visits under Modified irRC were reviewed and updated in line with Modified irRECIST where possible.

Note: To capture the Investigator assessed Modified irRECIST data a new *ORRECIST* eCRF page was implemented. This new page captures the total measurable tumor burden (TMTB - the sum of all measurable target lesions plus any new measurable lesions) and also the Modified irRECIST overall visit response. Appendix 2 in the Protocol, version 7 and onwards, give further details on the Modified irRECIST guidelines used by the investigator.

To determine tumor-based endpoints based on Investigator assessed Modified irRECIST the following programming rules will be applied:

1. Patients who completed tumor assessment prior to Protocol version 7 should have Modified irRC data for tumor assessment. These patients will be identified from not having any fields completed on the new *ORRECIST* eCRF page.

2. Patients who "switched" from Modified irRC to Modified irRECIST will be handled as follows:
    a. Where available, Modified irRECIST data from the *ORRECIST* eCRF page will be used to derive tumor based Modified irRECIST endpoints (using TMTB and overall response by Protocol-defined Modified irRECIST criteria)
    b. Prior to RECIST v1.1 progression, if Modified irRECIST data are not available (i.e. TMTB and/or overall visit response are missing on the *ORRECIST* eCRF page) then the RECIST v1.1 SOLD and RECIST v1.1 overall response will be substituted as the Modified irRECIST TMTB and Modified irRECIST overall visit response, respectively, as these will be exactly the same prior to RECIST v1.1 progression.
    c. On or after RECIST v1.1 progression, if no Modified irRECIST data are available then tumor response by Modified irRECIST will be considered missing/not done.
    d. In order to determine which patients could have RECIST v1.1 data substituted for Modified irRECIST prior to RECIST v1.1 progression, they must have at least one visit where the Modified irRECIST overall visit response is not equal to NE. This is to separate patients assessed by Modified irRECIST from the patients mentioned above who were only assessed per Modified irRC criteria.
3. For new patients enrolled from Protocol version 7 onwards, Modified irRECIST data should be collected throughout the study. However, if Modified irRECIST data is missing for any tumor assessments then the above rules outlined above for the patients who "switched" will be used to derive the Modified irRECIST TMTB and the overall visit response.

In addition to the Investigator assessed Modified irRECIST criteria, Phase 2 patients were also assessed centrally by ICR. ICR follows the published irRECIST guideline outlined in the Independent Review Charter which differs from the Protocol-defined Modified irRECIST criteria, where progression is defined differently (see below for further detail).

Phase 2 patients will have their tumor response reported by ICR for irRECIST. Investigator assessments based on the Protocol-defined Modified irRECIST/irRC will be separately reported as supportive data for Phase 2 patients.

Phase 1 patients will be reported based on Investigator assessed Modified irRECIST/irRC. Some ICR data may be available for some of the Phase 1 patients and any available ICR data will be listed.

Note: the main differences between (a) Modified irRC criteria by Investigator, (b) irRECIST by ICR, and (c) Modified irRECIST by Investigator are:

- (a) Modified irRC uses measurement of longest diameter of both nodal and non-nodal lesions, whereas (b) irRECIST by ICR and (c) Modified irRECIST uses the longest diameter for non-nodal lesions and the short axis for nodal lesions in line with RECIST v1.1 criteria. Therefore, as described above, in the absence of the new TMTB field being completed for visits prior to RECIST-PD, the RECIST v1.1

SOLD value can be substituted instead for patients following (c) Modified irRECIST.

- (a) Modified irRC and (b) irRECIST by ICR require confirmation of progression at least 4 weeks apart (i.e. two visits of irPD at least 4 weeks apart), whereas (c) Modified irRECIST per the Protocol defines progression as a ≥ 20% increase in TMTB from the **initial RECIST v1.1 progression, or unequivocal progression of non-target lesions or new non-measurable lesions**. Therefore, as mentioned above, the definition of progression differs between (b) irRECIST by ICR and (c) Modified irRECIST by the Investigator.

14.3.1.2. Derivation of Best overall Response using irRECIST by ICR or Modified irRECIST/irRC Criteria

The same basic logic for deriving the best overall response (BOR) will be used as for the Primary Efficacy (see Section 14.1.2). It is the best response a patient has had following the date of first dose of study drug, but prior to either (i) disease progression according to the respective criteria*, (ii) the last evaluable tumor assessment in the absence of disease progression (including death), or (iii) starting any subsequent alternative cancer therapy including another investigational agent, whichever comes first. In other words, for patients who progress and subsequently have a response, the BOR will not include the response after a progression event. Furthermore, tumor assessments performed after initiating another anti-cancer therapy will not be included in the calculation of BOR.

For (a) Modified irRC criteria by Investigator and (b) irRECIST by ICR, a patient's BOR is derived in the following order, checking for best outcome before worst:

1. **irComplete Response (irCR):** At least one confirmed visit response of irCR
2. **irPartial Response (irPR):** If not irCR, at least one confirmed visit response of irPR.
3. **irStable Disease (irSD):** If not irCR/irPR, at least one visit response of irSD (RECIST SD) or irSD (RECIST PD) recorded at least 8 weeks after date of first dose of study drug. Includes unconfirmed irCR or irPR recorded at least 8 weeks after date of first dose of study drug.
4. **irProgressive Disease - irPD (*unconfirmed*):** If not irCR/irPR/irSD, an unconfirmed disease progression. Note: In absence of confirmed irPD, a BOR of unconfirmed irPD may be considered an irSD for reporting purposes.
5. **irProgressive Disease - irPD (*confirmed*):** If not irCR/irPR/irSD, a confirmed disease progression or death in the absence of progression.
6. **Not-Evaluable (NE):** No evidence of irCR, irPR, irSD, or irPD (regardless of confirmation). Either by default or the only visit response entered by the investigator is 'Not evaluable'.

For (c) Modified irRECIST by Investigator, a patient's BOR is derived in the following order, checking for best

outcome before worst:

1. **irComplete Response (irCR):** At least one confirmed visit response of irCR
2. **irPartial Response (irPR):** If not irCR, at least one confirmed visit response of irPR.
3. **irStable Disease (irSD):** If not irCR/irPR, at least one visit response of irSD (RECIST SD) or irSD (RECIST PD) recorded at least 8 weeks after date of first dose of study drug. Includes unconfirmed irCR or irPR recorded at least 8 weeks after date of first dose of study drug.
4. **irProgressive Disease - irPD (*following RECIST 1.1 Progression):*** If not irCR/irPR/irSD, a disease progression (strictly at or after the first RECIST-PD) or death in the absence of progression.
5. **Not-Evaluable (NE):** No evidence of irCR, irPR, irSD, or irPD (regardless of confirmation). Either by default or the only visit response entered by the investigator is 'Not evaluable'.

***Important note**: For (a) Modified irRC and (b) irRECIST by ICR, disease progression has to be confirmed, whereas for (c) Modified irRECIST, progression does not require an unconfirmed irPD followed by a confirmed irPD.

For (c) Modified irRECIST, response categories will be assigned as follows:

- irPD is defined as a ≥ 20% increase in TMTB compared to the initial RECIST v1.1 PD visit, or unequivocal progression of non-target lesions or new non-measurable lesions. For Modified irRECIST response, irPD will be assigned if the Investigator has recorded irPD as the overall visit response on the new *ORRECIST* eCRF page as "irProgressive Disease-irPD (following RECIST 1.1 Progression)".
    - In the absence of irPD on the *ORRECIST* eCRF page, deaths occurring strictly after the first RECIST-PD will also count towards irPD.
    - Investigators may enter irPD, for clinical accuracy reasons, on the same date and visit as when RECIST v1.1 PD occurred.
- irCR, irPR, irSD, and NE are as described above for Modified irRC/irRECIST and as documented on the *ORRECIST* eCRF page.

Further considerations for deriving BOR:

- ***A special note:** As stated above, prior to RECIST v1.1 progression, if (c) Modified irRECIST data are not available (i.e. TMTB and/or overall visit response are missing on the *ORRECIST* eCRF page) then the RECIST v1.1 overall response will be substituted as the Modified irRECIST overall visit response, as it will be exactly the same prior to RECIST v1.1 progression. On or after RECIST v1.1 progression, if no Modified irRECIST data are available then tumor response by Modified irRECIST will be considered missing/not done at these visits.
- For (a) Modified irRC and (b) irRECIST by ICR, if there is an unconfirmed irPD followed by a confirmed irPD with no evaluable responses in between, then the best overall response is

reported as a confirmed irPD.

- According to the eCRF for irRC, irSD can be either "irSD (RECIST SD)" or "irSD (RECIST PD)". This is due to the criteria for SD and PD being different between RECIST and Modified irRC criteria, with irSD (RECIST SD) being a less-severe and better outcome. For the purposes of summarizing the BOR, these have been grouped into a single irSD category.
- Stable disease should be recorded at least 8 weeks ± 1 week, i.e. at least 49 days (to allow for the assessment window), after first dose. For determination of a best response of irSD of either kind, the **earliest** of the dates contributing towards a particular overall visit assessment will be used. The same goes for determining a best response of irSD for any unconfirmed irCR or irPR recorded at least 8 weeks after first dose.
- Per (a) Modified irRC criteria, the irPD definition for analysis of uni-dimensional or bi-dimensional measurements is given in Protocol version 6 and previous versions. The investigator opinion of overall irRC visit response is used for analysis, rather than programmatically-derived overall visit responses.
- All data will be used up until the progression event (irPD or death in absence of irPD) that is used for the analysis. In other words, unconfirmed progressions per Modified irRC criteria/irRECIST by ICR, are not considered progression events, which means that the BOR may be after an unconfirmed progression for some patients. In absence of progression, data will be used up until the last evaluable assessment or starting any subsequent alternative cancer therapy including another investigational agent, whichever comes first.
- A maximum of *two scheduled tumor assessment visits* will be allowed to be missed before an irPD event is considered censored and hence will not contribute to the BOR derivation. See Section 14.1.2 of this SAP under Further considerations for deriving BOR for details.

14.3.1.3. Confirmation of Overall Response Using irRECIST by ICR or Modified irRECIST/irRC Criteria

Confirmation of irCR/irPR:

Confirmation of response is required for declaring irPR or irCR in the ORR using (a) Modified irRC criteria by Investigator, (b) irRECIST by ICR, and (c) Modified irRECIST by Investigator, as it is for the analysis using RECIST v1.1 criteria. A confirmed response is defined as an initial response (irCR or irPR) followed by a response at least 4 weeks later (for irCR this needs to be confirmed by irCR and for irPR this needs to be confirmed by either irPR or irCR). As for confirmation of response per RECIST v1.1 in Section 14.1.3, the initial overall visit assessment which showed a response will use the **latest** imaging date contributing towards a particular overall visit assessment. The same will be done for the confirmation overall visit assessment.

In the case where a patient has two non-consecutive visit responses of irPR, then, as long as the time between the 2 visits of irPR is greater than 4 weeks and there is no PD between the irPR visits, the patient will be defined as a responder. For confirmation of response to count, visit responses of NE are allowed between visit responses of irCR to confirm an irCR, and likewise, visit responses of NE or irSD are allowed in between visit responses of irPR/irCR to confirm an irPR. For example, if a patient has visit responses of irCR, NE, irCR, then, as long as the time between the 2 visits of irCR is greater than 4 weeks, then a best response of irCR will be assigned.

Tumor assessments will be performed every 8 weeks (±1 week) from C3D1 to C11D1, then every 12 weeks (± 1 week) until disease progression or patient withdrawal. See Table 7-2 of the Protocol for the disease assessment collection plan.

Confirmation of irPD:

Disease progression (i.e. irPD) per (a) Modified irRC by Investigator and (b) irRECIST by ICR criteria does typically require confirmation. Once confirmed, the ***original*** date of disease progression entered is used as the date of irPD for analysis purposes. See Section below on PFS for deriving this date.

- Note: For (a) Modified irRC by Investigator, there are some cases where a single visit of automatic irPD confirmed is allowed without having to have a previous consecutive irPD unconfirmed assessment, e.g. if a patient develops new or significant worsening of brain metastases. In this case, the single date of confirmed disease progression entered by the Investigator is used as the date of irPD for analysis purposes. For **irProgressive Disease - irPD (*confirmed*)** to count as a visit response towards BOR in the analysis, all that is required is a single investigator-entered overall response of "irProgressive Disease-irPD (confirmed)". This is irrespective of how many days are in between an unconfirmed irPD and confirmed irPD, and irrespective of if a previous consecutive irPD unconfirmed assessment exists.

For (c) Modified irRECIST by Investigator, confirmation is not required, and therefore the ***earliest*** date irPD was recorded will be used to determine the date of progression. See Section 14.3.3.1 below under "The date of RECIST-PD" for deriving this date.

14.3.2. Missing Data Methods for Exploratory Efficacy Variables

No adjustments for missing data will be made for any response data used for the Exploratory efficacy analyses. However, as per the Phase 2 primary efficacy analysis, an underlying assumption will be made such that missing tumor response data is not indicative of a complete or partial (objective) response, nor of stable disease or progressive disease. Therefore, any missing overall visit responses for tumor assessments are either considered as Not Evaluable in the calculation of the BOR or are ignored in any of the other calculations.

14.3.3. Analysis of Exploratory Efficacy Variables

14.3.3.1. BOR and Duration of Treatment Post RECIST-Progression (PD)

A summary of BOR post RECIST-PD will be presented for irRECIST by ICR for Phase 2 Expansion only. Also, the duration of treatment post RECIST-PD will be presented, using both ICR data and Investigator opinion for RECIST-PD, for both Phase 1 and 2.

For the subset of patients in the FAS that continue treatment beyond RECIST v1.1 progression, the BOR will be derived in the same fashion as described above under Derivation of Best Overall Response using irRECIST by ICR or Modified irRECIST/irRC Criteria in Section 14.3.1.2. However, instead of being the best response following the date of first dose of study drug, the BOR post RECIST-PD will be defined as the best response a patient has had *following the date of RECIST-PD*, but prior to either (i) confirmed disease progression, (ii) the last evaluable tumor assessment in the absence of disease progression (including death), or (iii) starting any subsequent alternative cancer therapy including another investigational agent, whichever comes first. In other words, for patients who progress and subsequently have a response, the BOR will not include the response after a progression event according to the respective criteria. Furthermore, tumor assessments performed after initiating another anti-cancer therapy will not be included in the calculation of BOR. All other considerations above in the derivation of BOR are valid here.

Only patients who have a date of last study drug administration greater than the date of RECIST-PD will be included in the analysis.

In addition to the BOR post RECIST-PD, the duration of treatment post RECIST-PD will be calculated in a similar fashion to the overall duration of treatment (see Section 13.1):

i. *Duration of treatment post RECIST-PD* (days) = (date of last study drug administration – date of RECIST-PD).

The date of RECIST-PD will be derived as per the progression date from the corresponding criteria:

i. irRECIST by ICR: RECIST-PD date will be based on the date of first RECIST progression recorded by ICR (see Section 14.1.2 under Further considerations for deriving BOR).

A swimmer plot may be produced showing the duration of treatment for patients continuing treatment post-RECIST-PD.

A comparison summary listing of the BOR for each patient will be presented for all the following criteria side by side:

- BOR by RECIST v1.1 by ICR
- BOR by RECIST v1.1 by Investigator assessment

- BOR by irRECIST by ICR
- BOR by Modified irRECIST (or Modified irRC in the absence of any Modified irRECIST data) by Investigator assessment
- BOR by irRECIST by ICR post RECIST-PD

15. SAFETY OUTCOMES

All summary outputs for safety outcomes will be based on the SAF analysis set. All safety tables and listings will be presented according to APPENDIX 1 - Presentation of Treatment Groups. Safety tables in general will be presented by cohort (Phase 1 dose escalation cohorts by dose and the Expansion cohort, such that safety outcomes during the first two weeks of cycle 1 where the subject has received 20 mcg, or 30 mcg will not be distinguished from safety outcomes following the escalated dose on C1D15. However, listings will show the actual dose at the time of the AE. Additional plots (as described further below), such as adverse event toxicity plots, may address the timing of safety outcomes.

Unless otherwise stated, the overall observation period will be divided into 3 mutually exclusive segments as follows:

- Pre-treatment period: from day of patient's informed consent (or pre-screening informed consent) to the time of the first dose of study drug
- On-treatment/follow-up period: from immediately after the first dose of study drug to 90 days after last dose of study drug
- Post-treatment/follow-up period: starting at Day 91 after last dose of study drug

For domains such as concomitant medications and adverse events, definitions of concomitance and treatment emergence are included in the associated sections of this SAP.

15.1. DOSE LIMITING TOXICITIES

The primary variable is the incidence (number) of dose limiting toxicities (DLTs) in the Phase 1 dose escalation part of the study. The DLT observation period for the Phase 1 cohorts is the first cycle during IMCgp100 dosing (C1D1 until C1D28).

A DLT is defined as an adverse event or abnormal laboratory value that occurs within the first cycle of treatment and is assessed as (1) having a suspected relationship to study drug, (2) being unrelated to disease, disease progression, inter-current illness, or concomitant medications, and (3) meets any of the criteria included in Table 6-3 of the Protocol. DLTs are recorded on the *Dose-Limiting Toxicity* eCRF page and additionally filled in on the *Adverse Event/Serious Adverse Event* eCRF page.

Further information on a DLT for this study is given in Section 6.4 of the Protocol.

The primary objective is to identify the MTD and/or the RP2D of IMCgp100 in the weekly intra-patient escalation

dosing regimen.

The MTD is defined as the highest dose level with an observed incidence of DLT in fewer than 33% of the patients enrolled in a cohort level. If all evaluated dose levels demonstrate an observed incidence of DLT in fewer than 33% of patients, the MTD has not been reached. If this proves to be the case, then a total of 6 patients will be treated at the highest dose tested to gain additional safety data before proceeding to the dose-expansion part of the study. If a DLT occurs at the MTD, a total of 6 patients must be treated at the MTD.

The RP2D-IE will be defined as the dose level selected for testing in the expansion cohort by the Study Team, based on all available safety, tolerability, PK and pharmacodynamic data. The MTD and RP2D-IE may not be the same dose level; the RP2D-IE will be the same dose or a lower dose than an identified MTD. If the MTD and RP2D are different, the RP2D-IE will be implemented in the expansion cohort. A minimum of 6 patients will be treated at the identified RP2D-IE for the DLT period before the expansion cohort with this dose can begin enrollment.

The determination of the MTD and RP2D-IE is a clinical decision and is not impacted by any analysis performed by IQVIA Biostatistics. For further details of dose escalation guidelines, including the determination of the MTD and RP2D-IE, refer to Section 6.3.4 of the Protocol. The primary and final analysis provided by IQVIA Biostatistics will include a table of the number of DLTs by dose level for the SAF. DLTs will also be listed.

15.2. ADVERSE EVENTS

Adverse Events (AEs) will be coded using Medical Dictionary for Regulatory Activities (MedDRA) central coding dictionary, using 22.0 or later (i.e. a later version MedDRA may be available and used at the time of coding for the reporting period).

Treatment-emergent adverse events (TEAEs) are defined as AEs that started or worsened in severity from the date of first dose (regardless of time) up until 90 days after the last dose of study drug or until start of subsequent alternative cancer therapy, whichever occurs first. Only alternative cancer therapies with start dates that are greater than the date of last dose of study drug (i.e. subsequent), are considered. Therefore, the treatment-emergence period will be at a minimum up until the date of last dose of study drug + 1.

The start date of subsequent alternative cancer therapy is derived as the *earliest* start date from (i) alternative cancer therapies entered on the *Prior and Concomitant Medications* eCRF page (see Section 12.1) which occur after the date of last dose of study drug, and (ii) from therapies entered on the *Antineoplastic therapies since discontinuation* eCRF page (see Section 12.2). See APPENDIX 2 for handling of partial dates for AEs and subsequent alternative cancer therapies. In the case where it is not possible to define an AE as treatment-emergent or not, the AE will be classified by the worst case; i.e. treatment-emergent.

An overall summary of number of patients within each of the categories described in the sub-section below, will be provided as specified in the templates.

An AE Listing will include TEAEs and Non-TEAEs, including those from the screening and post-treatment periods which will be flagged as such. Only TEAEs will be summarized.

AE Structure as Recorded in the eCRF:

AEs will be recorded in the eCRF with a new adverse event record each time the severity of an adverse event changes. This means each unique AE record is not necessarily a distinct event. Where a single event is split across multiple records due to a changing severity grade, these split adverse event records require being grouped using a dataset flag in order to identify the single event for a subject. This will be handled as follows:

- Adverse events that do not change in severity over the course of their duration will be recorded as single event records in the eCRF and require no further manipulation post collection.
- Adverse events that do change in severity over the course of their duration will be grouped using the following algorithm:
    - For a given subject, if the same AE Preferred Term exists across two or more records where the AE Stop Date (+1 day) of the first record equals the AE Start Date of the next record, and so on, or if there is overlap in the dates for the records, these two or more records will be 'grouped' in order to flag they are of the same unique AE.

Notes:

- Severity is defined using the NCI CTCAE version 4.03 Grades as recorded on the eCRF.
- AE records with partial dates will not be grouped.
- This 'grouping' does not entail creating any new combination records nor does it mean truncating the existing records. A flag in the AE dataset will simply be used to indicate these records are of the same unique AE.
- Grouped AEs will be counted as a single event in event-level summaries but will be presented separately (as recorded in the CRF) in the listings.
- For calculating AE durations in a data listing, the duration of each event will be calculated at each distinct severity. Also, the total duration will be calculated for AEs that change in severity over the course of their duration. The total duration will be calculated as the last AE Stop Date - first AE Start Date + 1 in the grouped records for a unique AE. If the last of the AE records within same group is ongoing, then the total duration will be calculated as the last AE Start Date - first AE Start Date + 1. In this case, the total duration will be concatenated with '+' to imply that the total duration is *at least* the calculated number of days.
- The definition of a treatment-emergent AE will be handled appropriately for AEs split across each distinct severity level. Specifically, only when an AE **worsens** in severity within the timeframe from

the date of first dose (regardless of time) up until 90 days after the last dose of study drug or until start of subsequent alternative cancer therapy, whichever occurs first, will it be defined as treatment-emergent. A worsening severity is defined as changing from a less severe (lower) CTCAE grade to a more severe (higher) CTCAE grade.

15.2.1. ALL TEAEs

Incidence of TEAEs by subject count, in addition to number of total TEAEs, will be presented by System Organ Class (SOC) and Preferred Term (PT) and also broken down further by maximum severity.

15.2.1.1. Severity

Severity is based on NCI CTCAE v.4.03 grades and classed as mild, moderate, severe, life threatening, or death related to AE (increasing severity), as represented by Grades 1-5, respectively. TEAEs starting after the first dose of study drug with a missing severity will be classified as 'missing'. If a patient reports the same AE more than once within that SOC/PT, the AE with the worst-case severity will be used in the corresponding severity summaries. In determining maximum severity, response values will be ranked in order from minimum severity to maximum severity as Missing, Grade 1, Grade 2, Grade 3, Grade 4, and Grade 5 (as values: 'missing', 'mild', 'moderate', 'severe', 'life threatening', and 'death related to AE').

A summary table will present TEAEs, showing number of subjects (%) for all grades (including missing grades) and grades ≥ 3 for each SOC/PT. This summary table will also be repeated for TEAEs related to IMCgp100.

15.2.1.2. Relationship to Study Drug (IMCgp100)

Relationship, as indicated by the investigator, is classed as unrelated or related. The categories 'possibly' related or 'related' will be pooled to create the 'related' category. TEAEs with a missing relationship to study drug will be regarded as 'missing'.

15.2.2. TEAEs LEADING TO DOSE INTERRUPTION

TEAEs leading to dose interruption will be identified by using the "Action taken with the study drug" variable collected on the eCRF, where the variable is equal to 'Dose interrupted'. These will be flagged in the listing.

15.2.3. TEAEs LEADING TO DISCONTINUATION OF STUDY DRUG

TEAEs leading to permanent discontinuation of study drug will be identified by using either (1) the "Action taken

with the study drug" variable collected on the eCRF, where the variable is equal to 'Drug permanently discontinued', or (2) the "Did the AE cause the patient to discontinue from the study medication?" variable collected on the eCRF, where the variable is equal to 'Yes'. These will be flagged in the listing.

15.2.4. Serious Adverse Events

Serious adverse events (SAEs) are those events recorded as 'Yes' in response to the "Does the Adverse Event meet seriousness criteria?" question on the *AE/SAE* page of the eCRF. A summary of serious TEAEs by SOC and PT will be presented. These include both deaths as an outcome of SAEs and non-fatal SAEs. Deaths as an outcome of SAEs are those events which have a severity recorded as 'Grade 5 - Death related to AE' and are marked as serious.

A listing of SAEs (including deaths as an outcome of SAEs) will also be created.

A summary of serious TEAEs and Serious TEAEs related to IMCgp100 by SOC and PT will be presented.

15.2.5. Adverse Events Leading to Death

TEAEs leading to death are defined in Section 15.2.4. These events will be summarized as part of the SAE summary table.

Any AE leading to death will be also listed in a separate data listing from SAEs.

15.2.6. Adverse Events of Special Interest

Incidence of TEAEs of Special Interest for IMCgp100 will be presented by the TEAE of special interest category and PT. The investigator response to the question 'Is it an adverse event of special interest?' will not be reported. Based on data from the ongoing and completed clinical trials, the Sponsor considers the following to be IMCgp100 adverse events of special interest (AESI):

- Cytokine release syndrome (CRS)
- Rash
- LFT (Liver Function Tests) elevation

Due to evolution in grading and terminology there may likely be under-reporting of CRS as an AE, the incidence and severity of CRS will be based on a medical review utilizing the ASTCT consensus grading for CRS (Lee, et. al, 2019). By incorporating AE, concomitant medication, and vital sign data, a determination will be made as to

whether CRS occurred after each patient's dose and, if so, at what grade. Using this approach, the incidence of CRS as an AESI will not match reports of CRS as an AE in AE-based tables.

Rash will be identified using a medically-approved list of PTs provided by the Sponsor. See APPENDIX 6 for details.

LFT elevation will be based on the Standard MedDRA Queries (SMQs) "Drug related hepatic disorders – comprehensive search." Both Narrow and Broad scope terms will be considered.

Incidence of TEAEs for AESI will also be summarized broken down by maximum severity (Total, Grade 1, Grade 2, Grade 3, Grade 4, Grade 5) for the AESI category.

Toxicity plots will be produced for AESIs to show the frequency and timing, in respect to when the events occurred while patients were on-treatment.

15.2.7. Adverse Events Beyond Disease Progression

A summary of the number of patients with TEAEs that occurred post RECIST-Progression (PD) by Investigator assessment will be presented by SOC, PT, and CTCAE grade ≥ 3.

In this case, the treatment-emergence definition is altered for "TEAEs occurring post RECIST-PD" such that any AEs that started or worsened in severity from the date of first RECIST-PD up until 90 days after the last dose of study drug, are included. Therefore, the following are included:

- TEAEs that have an AE start date ≥ first RECIST-PD date by Investigator assessment, or
- TEAEs that are ongoing at RECIST-PD date by Investigator assessment that have worsened post RECIST-PD
    - Note: The definition of a "TEAEs occurring post RECIST-PD" will be handled appropriately for AEs split across each distinct severity level. Specifically, only when an AE **worsens** in severity within the timeframe from the date first RECIST-PD up until 90 days after the last dose of study drug or until start of subsequent alternative cancer therapy, whichever occurs first, will it be included. A worsening severity is defined as changing from a less severe (lower) CTCAE grade to a more severe (higher) CTCAE grade.

15.3. Deaths

If any patients die during the study as recorded on the *Death* page of the eCRF, the information will be summarized in a table by primary reason for death and presented in a data listing.

15.4. LABORATORY EVALUATIONS

Results from local laboratory data will be included in the reporting of this study for Hematology, Chemistry, Coagulation, Urinalysis, Thyroid, and Cytokines. All laboratory parameters assessed for safety purposes will be evaluated locally. A list of laboratory assessments to be included in the outputs is included in Table 7-5 of the Protocol, Section 7.3.7. The treatment periods to be used for reporting laboratory data are defined in Section 15.

Presentations will use International System of Units (SI Units).

Quantitative laboratory measurements reported as "< X", i.e. below the lower limit of quantification (BLQ), or "> X", i.e. above the upper limit of quantification (ULQ), will be converted to X for the purpose of quantitative summaries, but will be presented as recorded, i.e. as "< X" or "> X" in the listings.

Handling of retests and unscheduled measurements for laboratory results is included in Section 6.3 of this SAP.

The following summaries will be provided for laboratory data. These summaries will be repeated for hematology, biochemistry (chemistry, coagulation, inflammatory analytes, thyroid function and cytokines), and urinalysis:

- Actual and change from baseline by visit (for quantitative measurements) may be presented.
- Shift from baseline to the worst on-treatment/follow-up value according to NCI CTCAE grading system for quantitative measurements, as well as for urinalysis categorical measurements.
    - For measurements that have a National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) grading system, 'worst' will be defined as the maximum (i.e. most severe) Grade obtained during treatment; see Section 15.4.3 below. A missing value for Grade due to a missing laboratory value is considered to be the least severe. **A special note:** For laboratory tests that have CTCAE grades defined for both a lower and higher level of extremity, separate shift from baseline summaries will be presented for each extreme of abnormality, e.g. (i) Lymphocytes Absolute Count – *Low* and (ii) Lymphocytes Absolute Count – *High*. See Section 15.4.3 below for all relevant tests.
    - For urinalysis categorical measurements, 'worst' will be defined as the maximum (i.e. most severe) result, where the results ranked in order from minimum severity to maximum are: 'Not done', 'NEG', '+', '++', and '+++'.
- Listing of all clinically relevant laboratory data with values flagged to show the corresponding NCI CTCAE grades and the classifications relative to the laboratory normal ranges.

For both hematology and biochemistry, the following plots will be produced:

- Scatter plot of worst on-treatment/follow-up value versus baseline value, with values expressed as

multiples of the lower limit normal or upper limit normal. Note that parameters will be presented separately for both above and below the normal range, since 'worst' will be defined as both extremes of abnormality.

- Plot of patient profiles over time for all patients with at least one CTCAE grade ≥ 3 – for specific Sponsor-decided laboratory tests only

- Plot of individual patient profiles for patients with at least one CTCAE grade ≥ 3 – for specific Sponsor-decided laboratory tests only

To assess potential drug-induced liver injury (DILI) using Hy's Law, the following summaries for liver function tests will be produced:

- Incidence of patients with Alanine aminotransferase (ALT) or Aspartate transaminase (AST) ≥ 3xULN and total bilirubin ≥ 2xULN within specified time intervals. The time intervals that will be summarized are the following:

    - ALT/AST and total bilirubin elevation results at any time during on-treatment/follow-up.

    - ALT/AST elevation result within one week (+/- 7 days) of total bilirubin elevation result, during on-treatment/follow-up.

    - ALT/AST elevation result within one day (+/- 1 day) of total bilirubin elevation result, during on-treatment/follow-up.

    - ALT/AST elevation results within one day (+/- 1 day) of total bilirubin elevation results with a duration of ≥ 7 days, during on-treatment/follow-up. Duration is calculated as consecutive days (subsequent laboratory date – previous laboratory date) where the elevated levels of both (ALT or AST ≥ 3xULN) and total bilirubin ≥ 2xULN are maintained, without going below the potential Hy's Law criteria.

- A scatter plot of worst on-treatment/follow-up value for ALT versus total bilirubin, with values expressed as multiples of the upper limit normal will be produced. This scatterplot will be repeated for AST versus total bilirubin.

15.4.1. LABORATORY SPECIFIC DERIVATIONS

The following laboratory parameters will be derived as follows:

- Corrected Calcium [mmol/L]* = Serum Calcium [mmol/L] + 0.02 (40 - Serum Albumin [g/L])
  - *This correction will only be applied for records at the patient/visit level where albumin is less than the lower limit of normal. For records where albumin is greater than or equal to the lower limit of normal, no correction will be applied, and the Corrected Calcium value will equal the calcium (uncorrected) value, as collected on the eCRF.
  - Note: The reference ranges for Corrected Calcium will be derived on a patient by patient, visit by visit level, as the same reference ranges collected locally for calcium (uncorrected), which is a parameter collected directly from eCRF.

All other laboratory parameters are available from the data collected on the eCRF. Local laboratory results will be converted into SI units and presentations will use SI Units.

15.4.2. Laboratory Reference Ranges and Markedly Abnormal Criteria

The following laboratory tests do not have grades defined by NCI CTCAE:

Hematology:

- Hematocrit
- Absolute basophils
- Absolute eosinophils
- Absolute monocytes

Biochemistry:

- Bicarbonate
- Chloride
- Lactate dehydrogenase (LDH)
- C-reactive protein (CRP)
- Blood urea nitrogen

- Urea
- Total T3 (Triiodothyronine) – only for some patients; list only
- Free T4 (Thyroxine, Free)
- Thyroid stimulating hormone (Thyrotropin)
- Prothrombin time (in seconds) – when collected in %; list only
- Gamma-interferon - only for some patients; list only
- Interleukein-6 - only for some patients; list only

Urinalysis:

- Macroscopic panel (dipstick) (bilirubin, blood, glucose, ketones, pH, protein, specific gravity, white blood cells)

For these laboratory tests, results will be graded by the low/normal/high classifications based on laboratory normal ranges. In this case, quantitative laboratory measurements will be compared with the relevant laboratory reference ranges in SI units and categorized as:

- Low: Below the lower limit of the laboratory reference range.
- Normal: Within the laboratory reference range (upper and lower limit included).
- High: Above the upper limit of the laboratory reference range.

The lower and upper limit will be referred to in outputs as LLN = Lower Limit Normal and ULN = Upper Limit Normal, respectively.

15.4.3. NCI CTCAE GRADING FOR LABORATORY DATA

Laboratory measurements will be graded by the study team using NCI CTCAE version 4.03 as defined in the following link: https://www.eortc.be/services/doc/ctc/CTCAE_4.03_2010-06-14_QuickReference_5x7.pdf

Laboratory tests covered by NCI CTCAE are as follows (found under 'Investigations' in the link above unless otherwise specified):

Hematology:

- Hemoglobin – presented in shift tables as 'Low' and 'High'
- White blood cell count (Leukocytes) – presented in shift tables as 'Low' and 'High'
- Platelet count
- Absolute neutrophils count
- Absolute lymphocyte count – presented in shift tables as 'Low' and 'High'

Biochemistry:

- Creatinine
- Sodium (see hypernatremia/hyponatremia) – presented in shift tables as 'Low' and 'High'
- Potassium (see hyperkalemia/hypokalemia) – presented in shift tables as 'Low' and 'High'
- Albumin (see hypoalbuminemia)
- Total bilirubin (and direct/indirect)
- Alkaline phosphatase
- ALT
- AST
- Magnesium (see hypermagnesemia/ hypomagnesemia) – presented in shift tables as 'Low' and 'High'
- Corrected Calcium (see hypercalcemia/hypocalcemia) – see Section 15.4.1– presented in shift tables as 'Low' and 'High'
- Glucose (see hyperglycemia/hypoglycemia) – presented in shift tables as 'Low' and 'High'
- Amylase

- Inorganic phosphate (see hypophosphatemia)
- Lipase
- Prothrombin international normalized ratio (see INR increased)
- Activated partial thromboplastin time

For laboratory tests covered by NCI CTCAE, a grade 0 will be assigned for all non-missing values not graded as 1 or higher. Any missing laboratory value will consequently have a missing CTCAE Grade.

If the NCI CTCAE version 4.03 documentation above, requires LLN/ULN, to derive Grade 1, then follow the rules below:

For LLN:

- If LLN is above or equal to the lower value of the range for the Grade 1, then continue with the process as specified in the NCI CTCAE version 4.03 documentation.
- If LLN is below the lower value of the range for the Grade 1 then check if the laboratory test value is equal to the lower value, if yes set this to Grade 1. If the laboratory test value is above the lower value of the range for the Grade 1, then set to Grade 0. Else grade as per the rules for Grade 2 onwards.

For ULN:

- If ULN is below or equal to the higher value of the range for the Grade 1, then continue with the process as specified in the NCI CTCAE version 4.03 documentation.
- If ULN is above the higher value of the range for the Grade 1 then check if the laboratory test value is equal to the higher value, if yes set this to Grade 1. If the laboratory test value is below the higher value of the range for the Grade 1, then set to Grade 0. Else grade as per the rules for Grade 2 onwards.

15.5. ECG EVALUATIONS

Results from the Electrocardiogram (ECG) as recorded by the Investigator on the eCRF will be included in the reporting of this study. The treatment periods to be used for reporting ECG data are defined in Section 15.

The following ECG parameters will be reported for this study:

- PR Interval (msec)
- QRS Interval (msec)
- QT Interval (msec)
- QTcB Interval (msec)
- QTcF Interval (msec)
- Overall assessment of ECG (Investigator's judgment):
    - Normal
    - Abnormal, Not Clinically Significant (ANCS)
    - Abnormal, Clinically Significant (ACS)

The following summaries will be provided for ECG data:

- Shift from baseline to the worst on-treatment/follow-up value according to the predefined criteria for varying degrees of abnormality for prolonged QTcB and QTcF. Section 15.5.2 below states the exact criteria used to grade ECGs. A value below the lowest threshold of concern, i.e. ≤ 450 msec, will be assigned a value of 'Normal'. The 'worst' on-treatment/follow-up value will be defined as the maximum (i.e. most severe) abnormality criterion obtained during treatment. A missing value due to a missing ECG value is considered to be the least severe.

- Shift from baseline to worst on-treatment/follow-up value for PR and QRS interval abnormalities. Normal range criteria will be used to define 'worst' as both extremes of abnormality (lowest and highest); see Section 15.5.2 below. A missing value due to a missing ECG value is considered to be the least severe.

Values meeting markedly abnormal criteria will be flagged in the listing.

15.5.1. ECG Specific Derivations

- QTcF Interval (msec) post-baseline is not collected directly on the eCRF. Therefore, at all visits after screening, $QTcF$ will be derived using QT and $QTcB$ as collected in milliseconds from the *Electrocardiogram – Study* eCRF page:
- Convert QT and $QTcB$ from milliseconds to seconds:
  - $QT\ (\text{sec}) = QT\ (\text{msec})/1000$
  - $QTcB\ (\text{sec}) = QTcB\ (\text{msec})/1000$
- Calculate $QTcF\ (\text{sec}) = \frac{QT}{\frac{QT^{\ 2/3}}{QTcB}} = QT\ (\text{sec})^{1/3} \times QTcB\ (\text{sec})^{2/3}$
- Convert $QTcF$ in seconds to milliseconds:
- $QTcF\ (\text{msec}) = QTcF\ (\text{sec}) \times 1000$

Note that this will be done for both pre-dose and 1-hour (±5 min) post dose ECG measurements taken post baseline.

15.5.2. ECG Markedly Abnormal Criteria

Markedly abnormal quantitative ECG measurements will be identified in accordance with the following predefined criteria for varying degrees of abnormality for prolonged QTc (based on ICH – E14 standard ranges, https://database.ich.org/sites/default/files/E14_Guideline.pdf.

For rating the 'worst' on-treatment/follow-up value for QTcB and QTcF *absolute values*, the following categories will be used based on the varying degrees of abnormality above, in the order of least to most severe (top to bottom):

- Missing result
- ≤ 450 msec (i.e. 'Normal')
- >450-480 msec

- >480-500 msec
- >500 msec

For rating the 'worst' on-treatment/follow-up value for QTcB and QTcF *change from baseline values*, the following categories will be used based on the varying degrees of abnormality above, in the order of least to most severe (top to bottom):

- Missing result
- ≤ 30 msec increase from baseline
- 30 to ≤ 60 msec increase from baseline
- > 60 msec increase from baseline

For rating the 'worst' on-treatment/follow-up value for PR and QRS intervals the values will be graded by the following low/normal/high classifications based on the normal range criteria, in order of least to most severe (top to bottom):

PR Interval:

- Missing result
- <120 msec (i.e. 'Low')
- 120-200 msec (i.e. 'Normal')
- >200 msec (i.e. 'High')

QRS interval:

- Missing result
- <80 msec (i.e. 'Low')
- 80-120 msec (i.e. 'Normal')
- >120 msec (i.e. 'High')

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15.6. VITAL SIGNS

The treatment periods to be used for reporting vital signs data are defined in Section 15. The following Vital Signs measurements will be reported for this study:

- Systolic Blood Pressure (mmHg)
- Diastolic Blood Pressure (mmHg)
- Respiratory Rate (breaths/min)
- Pulse Rate (bpm)
- Temperature (^{o}C)
- Weight (kg)

All measurements apart from weight are taken in a sitting position after at least 5 minutes rest.

The following summaries will be provided for vital signs data:

- Shift from baseline to the worst on-treatment/follow-up value (for all quantitative measurements) according to the predefined criteria for varying degrees of abnormality. Section 15.6.2 below states the exact criteria used to grade vital signs. The 'worst' on-treatment/follow-up value will be defined as the maximum (i.e. most severe) abnormality criterion obtained during treatment. A missing value due to a missing vital signs value is considered to be the least severe.
    - Note: Systolic blood pressure will have separate shift from baseline summaries presented for (i) highest and lowest absolute values and (ii) maximum increase and decrease changes from baseline values.
- The following plots will be produced twice separately for: 1. All assessment time points and 2. All assessments after first dose of study drug up to a specific period of time.
    - Plot of patient profiles over time for all patients with at least one hypotension or cytokine release syndrome event of CTCAE grade ≥ 3
    - Plot of patient profiles over time for all patients with at least one SBP decrease from baseline ≥ 35mmHg

[redacted]

Values meeting markedly abnormal criteria will be flagged in the listing.

15.6.1. VITAL SIGNS SPECIFIC DERIVATIONS

Weight can be entered on the eCRF in kg or lbs. Any weight assessments entered in lbs will be converted to kg by dividing by 2.205.

15.6.2. VITAL SIGNS MARKEDLY ABNORMAL CRITERIA

Markedly abnormal quantitative Vital Signs measurements will be identified in accordance with the following predefined markedly abnormal criteria:

Variable	Unit	Low	High
SBP	mmHg	< 90 mmHg Post-baseline: Decrease from baseline of: (1) < 15 mmHg (2) ≥ 15 mmHg and < 35 mmHg (3) ≥ 35 mmHg	CTCAE Grade 1: 120 to 139 mmHg CTCAE Grade 2: 140 to 159 mmHg CTCAE Grade 3: ≥ 160 mmHg Post-baseline: Increase from baseline of: (1) < 15 mmHg (2) ≥ 15 mmHg and < 35 mmHg (3) ≥ 35 mmHg
DBP	mmHg	< 60 mmHg	CTCAE Grade 1: 80 to 89 mmHg CTCAE Grade 2: 90 to 99 mmHg CTCAE Grade 3: ≥ 100 mmHg

Variable	Unit	Low	High
Respiratory Rate	breaths/ min	<10 breaths/min	Baseline: ≥ 20 breaths/min Post-baseline: Do 1 of following: (1) If Low/Normal at baseline: ≥ 20 breaths/min OR change from baseline ≥ 10 breaths/min (2) If High at baseline: ≥ 20 breaths/min
Pulse rate	bpm	Baseline: ≤ 60 bpm Post-baseline: Do 1 of following: (1) If Normal/High at baseline: ≤ 50 bpm AND change from baseline ≤ -15 bpm (2) If Low at baseline: ≤ 50 bpm	Baseline: ≥ 100 bpm Post-baseline: Do 1 of following: (1) If Low/Normal at baseline: ≥ 100 bpm AND change from baseline ≥ 15 bpm (2) If High at baseline: ≥ 100 bpm
Body Temperature	˚C	N/A	CTCAE Grade 1: 38.0 – 39.0 ˚C CTCAE Grade 2: >39.0 – 40.0 ˚C CTCAE Grade 3: >40.0 ˚C for consecutive ≤ 24 hours CTCAE Grade 4: >40.0 ˚C for consecutive >24 hours
Weight	kg	Baseline: N/A Post-baseline: percentage change from baseline ≤ -10.0 %	Baseline: N/A Post-baseline: percentage change from baseline ≥ 10.0 %

Note: Since Weight at baseline has no Low or High markedly abnormal criteria, the baseline value will be represented in summary tables and listings as “Baseline”. For other vital signs variables and weight post-baseline,

a value that is not Low nor High will be represented as “Normal”.

15.7. PHYSICAL EXAMINATION

Physical Examination results will be listed, and abnormalities will be flagged.

Ophthalmologic and audiologic assessment data will be separately listed and abnormalities will be flagged.

15.8. OTHER SAFETY ASSESSMENTS

15.8.1. ECOG PERFORMANCE STATUS

Eastern Cooperative Oncology Group performance status is collected at screening, on Day 1 of every odd-numbered cycle and at the EOT visit. The status is determined as follows at each visit:

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

ECOG performance status at each visit will be listed.

Also, a summary will be presented for the shift from baseline to the best on-treatment/follow-up value and the shift from baseline to the worst on-treatment/follow-up value. Here, ‘best’ is defined as the lowest ECOG grade (Grade 0 being the lowest). Likewise, ‘worst’ is defined as the highest ECOG grade (Grade 5 being the highest). A missing value due to a missing ECOG performance status is the last value considered in either the ‘best’ or ‘worst’ case.

16. PHARMACOKINETICS

Samples for pharmacokinetic analysis are drawn at many visits and at the following time-points: pre-dose, end of infusion, 4-hour post dose, 8-hour post dose, and 12-24-hour post dose. See **Table 7-7** in the Protocol, Section 7.3.8 for the schedule of PK assessments.

16.1.1. PK VARIABLES & DERIVATIONS

The PK parameters to be derived and analyzed by Immunocore and/or a third-party vendor and summarized/listed by IQVIA. These are given in Table A below:

Table A Pharmacokinetic Parameters to be Analyzed

AUC_{last}	The area under the curve (AUC) from time zero to the last measurable concentration sampling time (t_{last}) (mass × time × volume-1)
AUC_{inf}	The AUC from time zero to infinity (mass × time × volume-1) for Cycle 1 Day 1 only
AUC_{tau}	The AUC over the dosing interval for Cycle 1 Day 15 only
C_{max}	The maximum (peak) observed plasma, blood, serum, or other body fluid drug concentration after single dose administration (mass × volume-1)
T_{max}	The time to reach maximum (peak) plasma, blood, serum, or other body fluid drug concentration after single dose administration (time)
$T_{1/2}$	The elimination half-life associated with the terminal slope (λz) of a semi logarithmic concentration-time curve (time). Use qualifier for other half-lives
CLSS	The clearance steady state (dose/ AUC_{tau}) for Cycle 1 Day 15 only
CL	The total body clearance of drug from the plasma (volume × time-1) for Cycle 1 Day 1 only
Vz	The apparent volume of distribution during terminal phase (associated with λz) (volume)

Additional parameters may be calculated as deemed necessary based on the final data available.

16.1.2. ANALYSIS OF PK

The SAF will be used for all PK summaries and listings. The following summaries/analyses will be provided for PK parameter data:

- Summary of descriptive statistics of all derived parameters for IMCgp100. The statistics to be presented include the arithmetic and geometric mean, median, standard deviation (Std), coefficient of variation (%CV), geometric mean ± standard deviation, minimum, and maximum.
- Summary of descriptive statistics for the collected pharmacokinetic concentrations for IMCgp100 in pg/mL.
- Concentrations profile plots for individual patients by Phase and cohort.
- Arithmetic mean concentration profile plots by Phase and cohort (coloured line for each cohort/expansion) with errors bars.
- Plot of pre-dose concentrations versus End of infusion at Day 1 of each Cycle.
- Listings of pharmacokinetic parameters and concentrations.

The following considerations will be taken into account:

- Concentration values below lower limit of quantitation (LLOQ) will be handled as zero in summary statistics and reported as is in the data listing of collected PK concentrations. The LLOQ for IMCgp100 is 25 pg/mL. Please note the following:
    - If the arithmetic mean is below the LLOQ value (i.e. < 25 pg/mL) then the arithmetic mean will be displayed as '<LLOQ' in the summary table. The same holds for the following statistics: min, max, and median. The standard deviation and %CV will be reported as Not Calculable (NC).
    - Concentration values and arithmetic means that are below the LLOQ value will be set to 12.5 pg/mL (half the LLOQ value) in the both the concentration and arithmetic mean profile plots.
- The geometric mean will be calculated as the exponential of the arithmetic mean calculated from data on a natural log scale.
    - The geometric mean will only be calculated at timepoints where all patients have concentration values above the LLOQ.

- Geometric mean ± standard deviation will be calculated as exp[μ±s]), where μ is arithmetic mean calculated from data on a natural log scale, and s is the standard deviation of the data on a natural log scale.
    - The geometric mean ± standard deviation will only be calculated at timepoints where all patients have concentration values above the LLOQ.
- The %CV is calculated as (arithmetic standard deviation / arithmetic mean) $\times 100$.
- Since T_{max} is generally evaluated by a non-parametric method, only the median, minimum, and maximum will be presented for this parameter.

The concentration-/AE-immunogenicity relationship will be explored graphically and tabulated to characterize a relationship between the changes from confirmed immunogenicity presence and serum concentration of IMCgp100. All these analyses will be described outside of this SAP and reported either in the Clinical Study Report or a stand-alone report.

16.1.3. Missing Data Methods for Pharmacokinetic Data

Missing PK concentration values will be reported as is in data listings, as 'No Result' or 'No Sample'. Any missing PK parameter data will not be imputed.

16.1.4. Reporting of Pharmacokinetic Data

For all PK data, descriptive statistics will follow the rounding convention described in Table B below.

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Table B: Reporting Accuracy of Pharmacokinetic Data

Variable / Parameter	Listing	Mean & Geometric mean	Std & Geometric mean +/- geometric Std	%CV	Median	Min	Max
Plasma concentrations	As reported	+1sf	+1sf	1dp	+1sf	3sf	3sf
Single dose parameters							
AUC_{last}	3sf	4sf	4sf	1dp	4sf	3sf	3sf
AUC_{inf}	3sf	4sf	4sf	1dp	4sf	3sf	3sf
AUC_{tau}	3sf	4sf	4sf	1dp	4sf	3sf	3sf
C_{max}	As reported	+1sf	+1sf	1dp	+1sf	3sf	3sf
T_{max}	As reported	NA	NA	NA	As reported	As reported	As reported
$T_{1/2}$	3sf	NA	NA	NA	4sf	3sf	3sf
CL	3sf	4sf	4sf	1dp	4sf	3sf	3sf
CLSS	3sf	4sf	4sf	1dp	4sf	3sf	3sf
Vz	3sf	4sf	4sf	1dp	4sf	3sf	3sf

sf= significant figures; dp = decimal places; NA = Not Applicable

"As reported" means that the plasma concentrations or parameters will be reported to the same precision as the source data.

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17. IMMUNOGENICITY

Blood samples for the evaluation of the development of immunogenicity responses are drawn at many visits' pre-dose as well as at the end of treatment visit. See Table 7-7 in the Protocol, Section 7.3.8 for the schedule of immunogenicity assessments.

Anti-drug Antibody (ADA) analysis will be used to evaluate immunogenicity responses.

17.1.1. ADA VARIABLES & DERIVATIONS

Sample ADA values at each visit and time-point will be collected in the following formats, from a third-party vendor:

- Binding ADA result
    - Positive: Final result in sample results spreadsheet (SRS) is Positive
    - Negative: Final result in SRS is Negative and PK value is < drug tolerance limit of assay (200 ng/mL, which is equivalent to 200,000 pg/mL)
    - Inconclusive: Final result in SRS is Negative and PK value is ≥ drug tolerance limit of assay (200 ng/mL, which is equivalent to 200,000 pg/mL) or unknown
    - Unevaluable: Sample was unable to be analyzed (insufficient volume, wrong matrix, etc.)
- Binding ADA Titer value
- Neutralizing ADA (NAb) result
- Neutralizing ADA titer value

The following table gives the variables that will be derived for the binding ADA results and titers.

Variable	Definition
Baseline ADA result & Baseline ADA titer	See Section 6.2
Pre-existing ADA	Subject with Positive baseline ADA result (without a boost in titer in response to study drug administration). See below for definition of Treatment-boosted (≥4-fold) ADA.
ADA *prevalence* at Baseline	The number of subjects with a Positive ADA result at baseline as a

	percentage of the total number of subjects tested at baseline for ADA.
ADA Evaluable Subset	All subjects who received at least one dose of study drug and have at least one ADA assessment post-baseline. This subset of the SAF will be used for determining ADA incidence.
Max titer	Highest titer value post-baseline.
Peak (or max) fold increase in titer	Ratio of max post-baseline titer to baseline titer (calculated only for subjects with a Positive ADA result at baseline).
Treatment-induced ADA	Subject in the ADA Evaluable Subset who has a positive ADA sample post-baseline with a Negative ADA result at baseline.
Treatment-induced ADA Incidence	Number of treatment-induced ADA subjects / Number of subjects in ADA Evaluable Subset with a Negative ADA result at baseline.
Treatment-boosted (≥4-fold) ADA	Subject in the ADA Evaluable Subset who has a Positive ADA sample at baseline and a Positive ADA sample post-baseline with a titer that has a peak (or max) fold increase in titer ≥4 compared to baseline.
Treatment-boosted (≥4-fold) ADA *incidence*	Number of treatment-boosted (≥4-fold) ADA subjects / Number of subjects in ADA Evaluable Subset with a Positive ADA result at baseline.
Overall ADA Incidence (ADA Positive Subjects)	All subjects with a treatment-induced or treatment-boosted ADA response (see definitions above) or subjects with positive post-baseline ADA sample but do not have a baseline ADA sample in the ADA Evaluable Subset.
ADA Negative Subjects	All subjects without a treatment-induced nor treatment-boosted ADA response in the ADA Evaluable Subset (can include subjects classified as Pre-existing ADA).
ADA Status	Three categories: a. Unevaluable: Patient has no post-baseline ADA samples.

	b. Positive: See "ADA Incidence (ADA Positive Subjects)" definition above. c. Negative: See "ADA Negative Subjects" definition above (can include subjects classified as Pre-existing ADA).
ADA Onset (as applicable)	For subjects with a treatment-induced ADA response: number of days from first dose of study drug to the first instance of Positive ADA. Therefore, ADA Onset = (date of first instance of Positive ADA – date of first dose of study drug + 1).
ADA Duration (as applicable)	For subjects with a treatment-induced ADA response: number of days from the first instance of Positive ADA to last instance of Positive ADA for a subject, such that a subsequent Negative ADA follows the last instance of Positive ADA. Therefore, ADA Duration = (date of last Positive ADA* – date of first instance of Positive ADA + 1). *The last Positive has to exist such that a Negative ADA follows the last instance of Positive ADA. If the date of last Positive ADA result is the *final* ADA assessment, then ADA duration will be calculated above, but in this case, the duration will be concatenated with '+' to imply that the ADA duration is *at least* the calculated number of days.
Transient ADA response	ADA Positive subject (post-baseline) with at least one subsequent Negative result, after the last Positive result and the ADA Duration is < 20 weeks (i.e. < 140 days).
Persistent ADA response	Subject with either (i) an ADA Duration ≥ 20 weeks (i.e. ≥ 140 days), regardless of whether intervening sample results are Positive or Negative; or, (ii) if last sample is ADA Positive (i.e. where ADA Duration is concatenated with '+'as described above).

The following table gives the variables that will be derived for the neutralizing ADA results and titers.

Variable	Definition
Neutralizing ADA status	• Positive: All binding ADA positive subjects with at least one positive neutralizing ADA result. • Negative: All binding ADA positive subjects with a negative result for neutralizing ADA.
Neutralizing ADA max titer	Maximum value of the neutralizing ADA titer per subject.
Overall neutralizing ADA incidence	Number of positive neutralizing ADA subjects / Number of positive binding ADA subjects

17.1.2. Missing Data Methods for ADA

Missing ADA values will be reported as is in data listings, as 'No Result' or 'No Sample'.

17.1.3. Analysis of ADA

The ADA analysis comprises two parts; the ADA status summary at patient-level and the study ADA summary. The SAF will be used for all ADA summaries and listings. Details are summarized below:

17.1.3.1. Patient ADA Status

For each patient, the final ADA status (that considers the cumulative ADA sample results for that patient) will be summarized. This will include:

- ADA status (Unevaluable, Positive, Negative)
- ADA Characterisation (Treatment-induced, Treatment-boosted, or Pre-existing ADA)
- Time to ADA Onset for treatment-induced ADA patients
- ADA Duration category (Transient ADA response or Persistent ADA response)

- Max titer for treatment-induced ADA patients
- Peak fold increase in titer for treatment-boosted ADA patients
- Neutralizing ADA status (Positive, Negative)
- Neutralizing ADA max titer

17.1.3.2. Study ADA Summary

At a study level, the ADA data summaries will include:

- The number (%) of patients who are ADA-positive at baseline – see ADA *prevalence* at Baseline definition above.
- The number (%) of evaluable patients – see ADA Evaluable Subset definition above.
- The number (%) of patients who are ADA-positive at follow-up – see Overall ADA *incidence* definition above.
- The number (%) of patients who are NAb positive at follow-up - see Overall NAb *incidence* definition above.
- The number (%) patients with a treatment-induced ADA (from baseline negative) – see Treatment-induced ADA *incidence* definition above.
- The number (%) patients with a treatment-boosted (≥4-fold) (from baseline positive) - see Treatment-boosted (≥4-fold) ADA *incidence* definition above.
- The max titer from patients with treatment-induced ADA. Descriptive statistics including the median, IQR of the max titer will also be shown.
- The peak fold increase in titer among patients with treatment-boosted (≥4-fold) ADA. Descriptive statistics including the median, IQR of peak titer fold increases will also be shown.
- A graphical representation of time to ADA onset and ADA duration for patients with treatment-induced ADA. Descriptive statistics (median, minimum and maximum) may also be summarized for time to ADA onset and ADA duration.

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For all patients, all Sample ADA values (including regular ADA results and NAb results) collected at baseline and post-baseline will be listed.

18. EXPLORATORY OBJECTIVES

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18.2.1.2. [redacted]

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18.2.1.3. [redacted]

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18.2.1.4. [redacted]

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18.2.2.1. [redacted]

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18.4. [redacted]

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19. DATA NOT SUMMARIZED OR PRESENTED

The other variables and/or domains not summarized or presented are:

- Whole blood for DNA HLA typing (central)
- Disease Progression Follow Up and Safety Follow Up eCRF pages
- Collection of tumor sample in the setting of PD eCRF page
- Free text comments for any domains that are not listed specifically in the Listing Output Templates

These domains and/or variables will not be summarized or presented, but will be available in the clinical study database, SDTM and/or ADaM datasets. Also note that the eCRF pages pertaining to [redacted] exploratory endpoints will be covered outside of this SAP and output templates.

[redacted]

20. REFERENCES

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EORTC Quality of Life Group. (2001). *EORTC-QLC-C30 scoring manual.* Retrieved from EORTC: https://qol.eortc.org/manuals/

Kalbfleisch, J. D., & Prentice, R. L. (1980). *The Statistical Analysis of Failure Time Data* (First ed.). John Wiley & Sons, Inc.

Lee, D. W. (2019). ASTCT Consensus Grading for Cytokine Release Syndrome and Neurologic Toxicity Associated with Immune Effector Cells. *Biology of Blood and Marrow Transplantation, 25*, 625-638.

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APPENDIX 1. PROGRAMMING CONVENTIONS FOR OUTPUTS

IQVIA OUTPUT CONVENTIONS

Outputs will be presented according to the following IQVIA output conventions.

1. ABBREVIATIONS

- ASCII American standard code for information interchange file format
- CGM Computer graphics metafile
- ODS Output Delivery System
- RTF Rich text file format

2. INTRODUCTION

This document applies to standards used for outputting tables, listings and figures. It is intended to provide specifications to guide the statistician or statistical programmer in setting up specifications for programming tables, listings and figures. These standards should be used in the absence of customer specific standards.

3. OUTPUT FILE NAMING CONVENTIONS

File names should only consist of lowercase letters, digits (0 to 9) and underscores. A period should only be used to indicate a separator between the file name and the extension. No spaces, other special characters or punctuation marks are permitted.

Output files should be in RTF format.

The program, program log and output file name should reflect the type and number of the statistical output. If this is not possible, then the output name should be at least as descriptive as possible. A prefix can be used to distinguish between a Table, Listing and Figure document ('t' for table, 'l' for listing and 'f' for figure). If there is only

1 digit in the number of the table, listing or figure in the place where 2 digits are possible, a leading zero should be added in the file name to make sorting consistent with the sequence (e.g. T14_3_01_1.RTF)

4. PAPER SIZE, ORIENTATION AND MARGINS

- The size of paper will be A4.
- The page orientation should preferably be landscape, but portrait is also permitted.
- Margins should provide at least 3 centimeters of white space all around the page, regardless of the paper size.
- The number of columns per page (line size) should be 132 for A4.
- The number of rows per page (page size) should be 46 for A4.

5. FONTS

The font type 'Courier New' should be used as a default for tables and listings, with a font size of 8. The font color should be black. No bolding, underlining italics or subscripting should be permitted. Try to avoid using super-scripts, unless absolutely necessary. Single spacing should be used for all text.
Figures should have a default font of "Times Roman", "Arial", or "Courier New".
This can be achieved by using the following options in SAS for figures created using SG Procedures or GTL:

```
proc template;
 define style newfont;
 parent = styles.rtf;
 style GraphFonts from GraphFonts /
 'GraphDataFont' = ("Courier New", 10pt)
 'GraphLabelFont' = ("Courier New", 10pt)
 'GraphValueFont' = ("Courier New", 10pt)
 'GraphFootnoteFont' = ("Courier New", 10pt);
 end;
run;
ods rtf style=newfont;
```

6. HEADER INFORMATION

Headers should be defined as follows:

- The header should be placed at the top of the page (same place on each page) regardless of the size or orientation of the table or listing.
- The sponsor name and Protocol number should appear in rows 1 and 2, left-aligned.
- The output identification number should appear in row 4, centered after a blank line in row 3.
- The output title should start in row 5, centered.
- The output population should appear in row 6, centered. The population should be spelled out in full, e.g. Full Analysis Set in preference to FAS.
- Row 7 should be a blank line.
- Row 8 should be a continuous row of underscores ('_') (the number of underscores should equal the line size).
- Sentence case should be used for titles.
- The output titles should be designed so that they are arranged consistently through all outputs. For example, content (e.g. Vital signs) followed by metric (e.g. change from baseline) e.g. Vital signs – change from baseline.
- Titles should not contain quotation marks or footnote references.
- The column headings should be underlined with a row of underscores ('_').
- Column headings spanning more than one column should be underlined and have underscores on either side of the title and should be centered.
- Column headings containing numbers should be centered.
- Column headings should be in proper case or sentence case.
- In general, the population count should appear in the column header in the form "(N=XXX)".
- "Statistic" should be the column header over n, Mean, SE, n (%) etc.

- As a rule, all columns should have column headings if possible.

7. TABLE AND LISTING OUTPUT CONVENTIONS

General:

- The first row in the body of the table or listing should be blank.
- The left-hand column should start in column 1. No indenting or centering of the output should occur.
- Rounding should be done with the SAS function ROUND.
- Numbers in tables should be rounded, not truncated.
- Alphanumeric output should be left aligned.
- Numbers should be decimal point aligned, where possible.
- Whole numbers should be right aligned.
- Text values should be left aligned.
- The first letter of a text entry should be capitalized.
- Listings of adverse events, concomitant medications, medical histories etc. should be sorted in chronological order, with earliest adverse event, medication or history coming first.
- The study drug should appear first in tables with treatments as columns.
- All listing outputs should be sorted (preferably by Treatment, Patient Identifier [Site Number + Patient Number]).
- Do not use superscripts and subscripts.
- Exponentiation will be expressed without superscripts, i.e., m^2 will be displayed as m2.
- The width of the entire output should match the line size.

Univariate Statistics:

- Statistics should be presented in the same order across tables (i.e., n, Mean, Std, Median, Minimum, Maximum).
- Table statistics should line up under the N part of the (N=XXX) in the table header. All decimal points should line up. If the minimum and maximum are output on one line as Minimum, Maximum then the comma should line up with the decimal point.
- If the original data has N decimal places, then the summary statistics should have the following decimal places:
    - Minimum and maximum: N,
    - Mean, median and CV%: N + 1,
    - Std: N + 2.

Note: An exception to this rule is for demography and other baseline characteristics summaries, in which the precision of the original data can be ignored, if fewer decimal places suit the statistical summary better. The full decimal precision (places) will be shown in Listings in these cases.

Frequencies and percentages (n and %):

- Percent values should be reported inside parentheses, with one space between the count and the left parenthesis of the percentage. Parentheses should be justified to accept a maximum of 100.0 as a value and padded with blank space if the percent is less than 100.0. An example is given below:

77 (100.0%)

50 (64.9%)

0 (0.0%)

- Percentages will be reported to one decimal place, except percents <100.0% but >99.9% will be presented as '>99.9%' (e.g., 99.99% is presented as >99.9%); and percents < 0.1% will be presented as '<0.1%' (e.g., 0.08% is presented as <0.1%). Rounding will be applied after the <0.1% and >99.9% rule. For example:

(<0.1%)

[redacted]

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(6.8%)

(>99.9%)

- Percentages may be reported to 0 decimal places as appropriate (for example, where the denominator is relatively small).
- Where counts are zero, percentages will not appear in the output.

Confidence Intervals:

- As a rule, confidence intervals are output to one place more than the raw data, and standard deviations and standard errors to two places more than the raw data.
- Confidence intervals should be justified so that parentheses displayed on consecutive lines of a table "line up". However, parentheses do not have to be used.
- Boundary values of confidence intervals should be separated by a comma.
- Boundary values should be padded as necessary to accept negative values and to allow alignment of the decimal place.
- An example is given below:

-0.12, -0.10
9.54, 12.91

Ratios:

- Ratios should be reported to one more decimal place than the original data.

Spacing:

- There must be a minimum of 1 blank space between columns (preferably 2).

Denominators:

[redacted]

- If a different count other than the population count is used for a denominator (within the table) to calculate percentages, there should be a row in the table that identifies that number "n".
- Alternatively, a footnote should be included in each table with percentages to indicate the denominator for percentages.

Missing values:

- A "0" should be used to indicate a zero frequency.
- A blank or '-' will be used to indicate missing data in an end-of-text table or patient listing.
- In the case that only a single value is used in the creation of summary statistics (i.e. n=1) then only n, mean, median, minimum and maximum will be presented.

8. FIGURE OUTPUT CONVENTIONS

- Figures should be provided in RTF files using the SAS Output Delivery System (ODS). Formats such as Computer Graphics Metafile (CGM), PNG (Portable Network Graphic), etc. should be used for the formatted graphical output generated by SAS.
- The CGM/PNG/etc. graphical file itself may or may not contain the title or footer.
- The image should be clear and of high quality when viewed in the Word document, and when printed.
- In general, boxes around the figures should be used.

9. FOOTNOTE INFORMATION

Footers should be defined as follows:

- A continuous line of underscores ('_') will follow the body of the table or listing prior to any footnotes at the bottom of the page.
- Table footnotes should be defined using compute statements in the proc report and should appear

directly after the body of the table.

- The program path and name and version number (if applicable) should appear as the last footnote at the bottom of the page.
- The date/time stamp should appear directly after the program path and name.
- Footnotes should be left-aligned.
- Footnotes should be in sentence case.
- Only “typewriter” symbols should be used where possible – e.g. “*”, “$”, “#”, “@”, “&” and “+”. However, other symbols may be added as required.
- The choice of footnote symbols should be consistent. E.g. if you have the footnote “# indicates last observation carried forward” for one table, the same symbol and footnote should indicate LOCF for all tables.
- If text wraps across more than one line (for a note), the first letter for all lines of text after the first one will be indented to align beneath the first letter of the text in the first line (if possible).
- The page identification in the format Page X of Y (where Y is the total number of pages for the output) will appear at the bottom of the page, right aligned.

Ordering of footnotes should be as follows:

1.) Abbreviations and definitions
2.) Formulae
3.) Symbols
4.) Specific notes
5.) Source data listing reference, if necessary

- Common notes from table to table should appear in the same order.

- The symbols should appear in the same order as what they are defined in the table or listing, from left to right.

10. PROGRAMMING INSTRUCTIONS

Programming instructions must appear in blue font at the end of each table or listing shell. Programming instructions, where necessary, should follow the table or listing shells in blue font, beginning with the words "Programming Note" followed by a colon. These include notes on the output, reminders of how to handle missing values, repeat shells for similar tables etc.

DATES & TIMES

Depending on data available, dates and times will take the form `DDMMMYYYY HH:MM`.

SPELLING FORMAT

English US

PRESENTATION OF TREATMENT GROUPS

EFFICACY

For all primary and secondary efficacy Tables and most Figures, treatment groups will be represented differently for each Phase of the study. For listings, each cohort of patients will be listed separately.

For Phase 1 dose escalation cohorts: Patients will be pooled into a total treatment group

Treatment Group	For Tables and Figures	For Listings
IMCgp100 xx mcg	Phase 1 dose escalation cohorts - Total	Cohort x: IMCgp100 xx mcg

For the Phase 1 dose escalation cohorts, some efficacy figures will additionally be presented by IMCgp100 dose level.

For Phase 2 dose expansion cohort: Patients presented by a single treatment arm, presented as follows. There is

a single dose, which will be known before this cohort of patients is assigned to treatment.

Treatment Group	For Tables and Figures	For Listings
IMCgp100 xx mcg	Expansion: IMCgp100 xx mcg	Cohort x: IMCgp100 xx mcg

For the Phase 2 dose expansion cohort, some efficacy tables and figures will be presented by subgroup, as per Section 7.5.

NON-EFFICACY

For all other Tables and Figures (including Study Population, Exposure, and Safety) treatment groups will be represented differently for each Phase of the study, as follows:

For Phase 1 dose escalation cohorts: Patients treated with the same dose will be pooled into treatment 'groups', defined by a unique set of doses. 'Groups' will be presented as follows from minimum to maximum protocol-assigned dose level (at C1D15).

Treatment Group	For Tables and Figures	For Listings
IMCgp100 xx mcg	Phase 1 dose escalation cohorts: IMCgp100 xx mcg	Cohort x: IMCgp100 xx mcg

For Phase 2 dose expansion cohort: Patients presented by a single treatment arm, presented as follows. There is a single dose, which will be known before this cohort of patients is assigned to treatment.

Treatment Group	For Tables and Figures	For Listings
IMCgp100 xx mcg	Expansion: IMCgp100 xx mcg	Cohort x: IMCgp100 xx mcg

For Screen Failures and Not Assigned:

Treatment Group	For Tables and Figures	For Listings
Not Assigned	-	Not Assigned
Screen Failure	-	Screen Failures

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PRESENTATION OF VISITS

For outputs, visits will be represented as follows and in that order:

Long Name (default)	Short Name
Screening	Scr
Baseline	BL
Treatment Period	
Cycle 1 Day 1	C1D1
Cycle 1 Day 2	C1D2
Cycle 1 Day 8	C1D8
Cycle 1 Day 15	C1D15
Cycle 1 Day 16	C1D16
Cycle 1 Day 22	C1D22
Cycle 2 Day 1	C2D1
…	…
End of Treatment record	
End of Treatment	EoT

LISTINGS

All listings will be ordered by the following (unless otherwise indicated in the template):

[redacted]

- Phase (Phase 1 dose escalation cohorts, followed by Expansion cohort)
- Phase 1 dose escalation cohorts should be presented in ascending dose order,
- Center-patient ID,
- Visit (where applicable)
- Date and time (where applicable),
- For listings where Screen Failures are included, these will appear in a category after the randomized/actual treatment groups labelled as 'Screen Failures'.

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APPENDIX 2. PARTIAL DATE CONVENTIONS

Imputed dates will NOT be presented in the listings.

ALGORITHM FOR TREATMENT EMERGENCE OF ADVERSE EVENTS:

Note: The start date of subsequent alternative cancer therapy will only be considered below, if the start date of alternative cancer therapy is greater than the study drug end date*. The start date of subsequent alternative cancer therapy is derived as the *earliest* start date from (i) alternative cancer therapies entered on the *Prior and Concomitant Medications* eCRF page (see Section 12.1) which occur after the date of last dose of study drug, and (ii) from therapies entered on the *Antineoplastic therapies since discontinuation* eCRF page (see Section 12.2).

START DATE	STOP DATE	ACTION
Known	Known	If start date < study drug start date, then not TEAE If start date ≥ study drug start date and start date ≤ Minimum[study drug end date + 90, start date of subsequent alternative cancer therapy*], then TEAE If start date > Minimum[study drug end date + 90, start date of subsequent alternative cancer therapy*], then not TEAE Note: If study drug end date is missing, then as long as start date ≥ study drug start date, then TEAE
	Partial	If start date < study drug start date, then not TEAE If start date ≥ study drug start date and start date ≤ Minimum[study drug end date + 90, start date of subsequent alternative cancer therapy*], then TEAE If start date > Minimum[study drug end date + 90, start date of subsequent alternative cancer therapy*], then not TEAE Note: If study drug end date is missing, then as long as start date ≥ study drug start date, then TEAE
	Missing	If start date < study drug start date, then not TEAE If start date ≥ study drug start date and start date ≤

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START DATE	STOP DATE	ACTION
		Minimum[study drug end date + 90, start date of subsequent alternative cancer therapy*], then TEAE If start date > Minimum[study drug end date + 90, start date of subsequent alternative cancer therapy*], then not TEAE Note: If study drug end date is missing, then as long as start date ≥ study drug start date, then TEAE
Partial, but known components (month/year or year) show that start date cannot be on or after study drug start date	Known	Not TEAE
	Partial	Not TEAE
	Missing	Not TEAE
Partial, could be on or after study drug start date (i.e. same month/year or after, or year after)	Known	If stop date < study drug start date, then not TEAE If stop date ≥ study drug start date, then impute start date as earliest possible date (i.e. first day of month if day unknown or 1st January if day and month are unknown). Then, consider the following: -If start date ≤ Minimum[study drug end date + 90, start date of subsequent alternative cancer therapy*], then TEAE -If start date > Minimum[study drug end date + 90, start date of subsequent alternative cancer therapy*], then not TEAE Note: If study drug end date is missing, then as long as start is same month/year or same year as study drug start date, then TEAE
	Partial	Impute stop date as latest possible date (i.e. last day of month if day unknown or 31st December if day and month

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START DATE	STOP DATE	ACTION
		are unknown), then: If stop date < study drug start date, then not TEAE If stop date ≥ study drug start date, then impute start date as earliest possible date (i.e. first day of month if day unknown or 1st January if day and month are unknown). Then, consider the following: -If start date ≤ Minimum[study drug end date + 90, start date of subsequent alternative cancer therapy*], then TEAE -If start date > Minimum[study drug end date + 90, start date of subsequent alternative cancer therapy*], then not TEAE Note: If study drug end date is missing, then as long as start is same month/year or same year as study drug start date, then TEAE
	Missing	Impute start date as earliest possible date (i.e. first day of month if day unknown or 1st January if day and month are unknown). Then, consider the following: -If start date ≤ Minimum[study drug end date + 90, start date of subsequent alternative cancer therapy*], then TEAE -If start date > Minimum[study drug end date + 90, start date of subsequent alternative cancer therapy*], then not TEAE Note: If study drug end date is missing, then as long as start is same month/year or same year as study drug start date, then TEAE
Missing	Known	If stop date < study drug start date, then not TEAE If stop date ≥ study drug start date, then TEAE
	Partial	Impute stop date as latest possible date (i.e. last day of month if day unknown or 31st December if day and month are unknown), then:

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START DATE	STOP DATE	ACTION
		If stop date < study drug start date, then not TEAE If stop date ≥ study drug start date, then TEAE
	Missing	Assumed TEAE

ALGORITHM FOR PRIOR / CONCOMITANT MEDICATIONS:

START DATE	STOP DATE	ACTION
Known	Known	If stop date < study drug start date, assign as prior If stop date ≥ study drug start date and start date ≤ end of treatment, assign as concomitant If stop date ≥ study drug start date and start date > end of treatment, assign as post treatment
	Partial	Impute stop date as latest possible date (i.e. last day of month if day unknown or 31st December if day and month are unknown), then: If stop date < study drug start date, assign as prior If stop date ≥ study drug start date and start date ≤ end of treatment, assign as concomitant If stop date ≥ study drug start date and start date > end of treatment, assign as post treatment
	Missing	If stop date is missing could never be assumed a prior medication If start date ≤ end of treatment, assign as concomitant If start date > end of treatment, assign as post treatment
Partial	Known	Impute start date as earliest possible date (i.e. first day of month if day unknown or 1st January if day and month are unknown), then: If stop date < study drug start date, assign as prior If stop date ≥ study drug start date and start date ≤ end of treatment, assign as concomitant If stop date ≥ study drug start date and start date > end of treatment, assign as post treatment

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START DATE	STOP DATE	ACTION
	Partial	Impute start date as earliest possible date (i.e. first day of month if day unknown or 1st January if day and month are unknown) and impute stop date as latest possible date (i.e. last day of month if day unknown or 31st December if day and month are unknown), then: If stop date < study drug start date, assign as prior If stop date ≥ study drug start date and start date ≤ end of treatment, assign as concomitant If stop date ≥ study drug start date and start date > end of treatment, assign as post treatment
	Missing	Impute start date as earliest possible date (i.e. first day of month if day unknown or 1st January if day and month are unknown), then: If stop date is missing could never be assumed a prior medication If start date ≤ end of treatment, assign as concomitant If start date > end of treatment, assign as post treatment
Missing	Known	If stop date < study drug start date, assign as prior If stop date ≥ study drug start date, assign as concomitant Cannot be assigned as 'post treatment'
	Partial	Impute stop date as latest possible date (i.e. last day of month if day unknown or 31st December if day and month are unknown), then: If stop date < study drug start date, assign as prior If stop date ≥ study drug start date, assign as concomitant Cannot be assigned as 'post treatment'
	Missing	Assign as concomitant

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ALGORITHM FOR ANTI-NEOPLASTIC THERAPIES POST TREATMENT DISCONTINUATION:

START DATE	STOP DATE	ACTION
Known	Known	If stop date < study drug start date, assign as prior If stop date ≥ study drug start date and start date ≤ end of treatment, assign as concomitant, If stop date ≥ study drug start date and start date > end of treatment, assign as post treatment
	Partial	Impute stop date as latest possible date (i.e. last day of month if day unknown or 31st December if day and month are unknown), then: If stop date < study drug start date, assign as prior If stop date ≥ study drug start date and start date ≤ end of treatment, assign as concomitant If stop date ≥ study drug start date and start date > end of treatment, assign as post treatment
	Missing	If start date ≤ end of treatment, assign as concomitant If start date > end of treatment, assign as post treatment
Partial	Known	Impute start date as latest possible date (i.e. last day of month if day unknown or 31st December if day and month are unknown, provided the stop date is not before the imputed start date (if so set to: stop date)), then: If stop date < study drug start date, assign as prior If stop date ≥ study drug start date and start date ≤ end of treatment, assign as concomitant If stop date ≥ study drug start date and start date > end of treatment, assign as post treatment

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START DATE	STOP DATE	ACTION
	Partial	Impute start date as latest possible date (i.e. last day of month if day unknown or 31st December if day and month are unknown, provided the imputed stop date is not before the imputed start date (if so set to: imputed stop date)) Impute stop date as latest possible date (i.e. last day of month if day unknown or 31st December if day and month are unknown), then: If stop date < study drug start date, assign as prior If stop date ≥ study drug start date and start date ≤ end of treatment, assign as concomitant If stop date ≥ study drug start date and start date > end of treatment, assign as post treatment
	Missing	Impute start date as latest possible date (i.e. last day of month if day unknown or 31st December if day and month are unknown), then: If start date ≤ end of treatment, assign as concomitant If start date > end of treatment, assign as post treatment
Missing	Known	Impute start date as stop date, then: If stop date < study drug start date, assign as prior If stop date ≥ study drug start date and start date ≤ end of treatment, assign as concomitant If stop date ≥ study drug start date and start date > end of treatment, assign as post treatment
	Partial	Impute start date as stop date Impute stop date as latest possible date (i.e. last day of month if day unknown or 31st December if day and month are unknown), then: If stop date < study drug start date, assign as prior If stop date ≥ study drug start date and start date ≤ end of treatment, assign as concomitant If stop date ≥ study drug start date and start date > end of treatment, assign as post treatment
	Missing	Impute start date as “study drug end date + 91”. Assign as post treatment. Cannot be assigned as ‘prior’ or ‘concomitant’

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[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

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[redacted]

APPENDIX 5. DATA CUT-OFF APPROACH FOR SDTM DATA

IMCgp100-102 Data Cut-off Approach for SDTM Data

Version 6.0

12 May 2020

Protocol Number: IMCgp100-102

Project Code: UXA32889

[redacted]

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1. Modification History

UNIQUE IDENTIFIER FOR THIS VERSION	DATE OF THE DOCUMENT VERSION	AUTHOR	SIGNIFICANT CHANGES FROM PREVIOUS VERSION
1.0	06 Aug 2019	[redacted]	NA – Initial version
2.0	16 Aug 2019	[redacted]	Additional updates to the whole document to align with the Immunocore study requirements. In particular updates Section 5.5 Findings for the Tumor domains TU, TR and RS.
3.0	29 Aug 2019	[redacted]	Updates to Section 5.4 Events for the AE domain.
4.0	10 Sep 2019	[redacted]	Updates to Section 5.5 for the RS tumor domain.
5.0	26 Sep 2019	[redacted]	Updates to Section 5.5 for the TR and RS tumor domains.
6.0	24 Apr 2020	[redacted]	Added Section 5.1.6 and updated Section 5.1.1 to cover survival status requirements in the DS and DM domains. Updated Section 5.2 to provide cut-off date for primary analysis.

[redacted]

2. Acronyms & Definitions

ADaM	Analysis Data Model
CRO	Contract Research Organization
DM	Demographics
DSUR	Drug Safety Update Reports
DTHDTC	Date/Time of Death
DTHFL	Subject Death Flag
EXDOSE	Exposure Dose
IDSMC	Independent Data Safety Monitoring Committee
RFENDTC	Subject Reference End Date/Time
RFICDTC	Date/Time of Informed Consent
RFPENDTC	Date/Time of End of Participation
RFSTDTC	Subject Reference Start Date/Time
RFXENDTC	Date/Time of Last Study Treatment
RFXSTDTC	Date/Time of First Study Treatment
SDTM	Study Data Tabulation Model
SVSTDTC	Start Date/Time of Visit

Cut-off subject: A cut-off subject refers to a subject on which cut-off rules are applied.

Data-cut-off: A process where clinical data cut into subsets. The cut is based on the rule set described in this document. Data-cut-off could be executed for i.e. DSUR, Interim Analysis, IDMC, or regulatory requests.

--DTC: Date/Time for the relevant Domain where – indicates the Domain

--ENDTC: End date for the relevant Domain where – indicates the Domain

--ENRF: End Relative to Reference Period for the relevant Domain where – indicates the Domain

--STDTC: Start Date/Time for the relevant Domain where – indicates the Domain

Treated subject: A “treated subject” in terms of the cut-off is defined as a subject where RFSTDTC is not blank and who has at least one exposure record.

[PLUS] datasets: Datasets containing the parent SDTM data merged with their supplemental variables and consists of comments (from Comments Domain) where a reference to a record in a parent dataset exists. These datasets are indicated as [PLUS] datasets.

3. Introduction

3.1. Purpose of the plan

The scope of this document is to describe the SDTM-cut off approach for the study IMCgp100-102. The below rules are applied to filter data for SDTM package and prior to creation of ADaM, for IDMC analyses and other analyses requiring a data cut off. The rules will be documented in the Reviewer's Guides.

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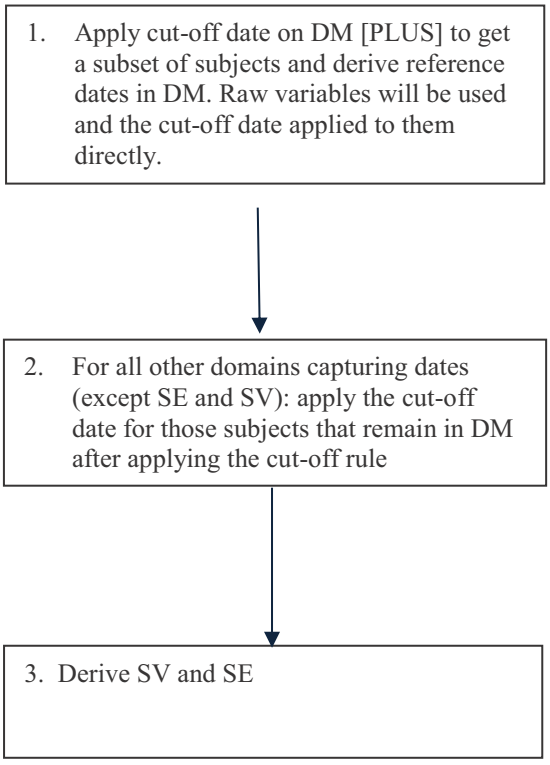
4. Assumptions

- The cut-off program is done on [PLUS] datasets. No cut-off will be applied specifically on dates in supplementary domains.
- The cut-off will first be applied the DM (Demographics) [PLUS] domain. This includes the reference dates. The cut-off will then be applied to all the other [PLUS] domains, as explained section 5. This will ensure that needed values form the DM domain is ready for use in the other domains as needed.

Figure 1: Cut-off Workflow



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5. SDTM Domains

5.1. Special Purpose Domains

5.1.1. Demographics (DM)

RFICDTC (Informed consent date) is used as reference date for all non-treated subjects (i.e. screen failures and not assigned), and RFSTDTC (First treatment date) is used as reference data for treated subjects. Please follow the steps below for derivation of reference variables and filtering of the DM dataset based on the data cut-off date.

Step 1: Selection of subjects to be included in the Cut-off DM [PLUS] Dataset

General rules for most deliveries:

- Include all treated subjects where RFSTDTC <= cut-off date
  - Note: No data in EX (Exposure) domain will be available for these subjects.
- Include all non-treated subjects (i.e. screen failures and not assigned) where RFICDTC <= cut-off date

Special rules for Interim Analysis Sep-2019 (and other deliveries as desired by sponsor):

Phase 1 dose escalation subjects:

- Phase 1 dose escalation subjects are those noted as ESCALATION=Y in 'Escalation Subjects' worksheet
- Include all Phase 1 treated subjects where RFSTDTC <= cut-off date
- Include all Phase 1 non-treated subjects (i.e. screen failures and not assigned) where RFICDTC <= cut-off date

Phase 2 expansion subjects:

- Phase 2 dose escalation subjects are those which do *not* have ESCALATION=Y in 'Escalation Subjects' worksheet
- Include only the *first* 75 Phase 2 treated subjects where RFSTDTC <= cut-off date. Sorting by non-missing RFSTDTC, for only the Phase 2 subjects, subset on the *first* 75 subjects
- Include all Phase 2 non-treated subjects (i.e. screen failures and not assigned) where RFICDTC <= the *latest* RFICDTC among the *first* 75 treated Phase 2 subjects. (This can be achieved after the step

above, by sorting by non-missing RFICDTC, for only the *first* 75 Phase 2 subjects, and taking the latest RFICDTC).

Records in *all other SDTM* domains (apart from Trial datasets) will be merged with the DM dataset by USUBJID. If USUBJID does not exist in DM, then delete subject completely from *other SDTM datasets*.

Step 2: Assumptions for reference variables in Dataset DM [PLUS]

Derivation of variables like RFSTDTC, RFENDTC, RFXSTDTC, RFXENDTC, RFPENDTC, DTHDTC, DTHFL.

- After Step1, the variables in DM such as RFSTDTC, RFENDTC, RFXSTDTC, RFXENDTC, DTHDTC and DTHFL should be derived. Only observations where the study drug dose is larger than 0 will be used for the derivation of RF(X)STDTC.

- RFPENDTC: is derived based on information from the latest information available in different disposition pages. If the RFPENDTC is after the cut-off date, then the RFPENDTC will be set to missing.

- DTHDTC/DTHFL: only dates before or equal to the cut-off date will be kept.

- Note1: For the reference dates, the cut-off will be applied using raw variables in the derivation.

- Note2: When using exposure dates for deriving reference variables, any records with a start date before or equal to the cut-off date will be kept, even if the end date is after the cut-off date.

In order to confirm that survival status is correctly shown in the study, a programming check should be completed to ensure that the death status and death dates are consistent across data sets/domains (DS, DM) – if a patient dies after the DCO date this death shouldn't be present in DM/DS (see section 5.1.6).

5.1.2. Comments (CO)

Records of the CO domain which have a link to records in other subject-level data sets are merged beforehand to the respective dataset in the PLUS structure. These data are then automatically cut.

Records in CO domain where there is no related record will be merged with the DM dataset by USUBJID. If USUBJID does not exist in DM, then delete subject completely from CO domain.

5.1.3. Subject Elements (SE)

The Subject element domain is derived based on records from Subject visits after the data cut has been applied. Therefore, a separate data cut in the SE domain is not applied. It is important that the SE domain is generated after the cut-off.

5.1.4. Subject Visits (SV)

The Subject visits domain is derived based on records from Subject visits after the data cut has been applied. Therefore, a separate data cut in the SV domain is not applied. It is important that the SV domain is generated after the cut-off.

5.1.5. RELREC (Relrec)

The Related Record domain is derived based on other domains where Cut-off date filter is already applied. Therefore, a separate cut-off filter is not applied in this dataset.

5.1.6. Disposition (DS)

The Disposition dataset contains information about the patients' survival status at each survival follow-up visit. In order to correctly cut off the status of each patient, the following steps are to be adhered to when performing the data cut-off:

a. On the Survival follow-up page, data where the date of last contact (T_SURVIVAL.SURCONDAT) is after the cut-off date should be handled as follows:
    i. If the survival status is any of the options ("dead", "alive", "lost to follow-up", or "unknown") and the last known alive date (T_SURVIVAL.SURDAT) is after the cut-off date, then change the SDTM.DSSTDTC value associated with the last known alive date to the cut-off date.
        - If the status (T_SURVIVAL.SURSTAT) is "dead" change to "alive".
    ii. If the last known alive date (T_SURVIVAL.SURDAT) is prior to the cut-off, then keep as it is.
    iii. Keep the date of last contact (T_SURVIVAL.SURCONDAT) unchanged and allow the record through the filter.

In order to confirm that survival status is correctly shown in the study, a programming check should be completed to ensure that the death status and death dates are consistent across data sets/domains (DS, DM)

– if a patient dies after the DCO date this death shouldn't be present in DM/DS (see section 5.1.1).

5.2. Trial Design datasets

No cut-off rules are applied on Trial Design datasets. Cut-off date and Cut-off description will be populated in TS domain.

For the Interim Analysis Sep-2019, the cut-off date will be 26-June-2019.

For the Primary Analysis Jun-2020, the cut-off date will be 20-Mar-2020.

5.3. Intervention Class Domains

Cut-off rule will be applied to all interventions domains for those subjects that remain in DM after applying the cut-off rule based on RFSTDTC/RFICDTC.
For the domains CM and EX, any records where --STDTC > cut-off date, will be excluded. All data elements will be kept for the records, except for the following changes to --ENDTC and --ENRF (where these variables exist):

- If --ENDTC > cut-off date then change --ENDTC to missing
- If --ENDTC > cut-off date then change --ENRF to "ONGOING"

5.4. Events

Cut-off rule should be applied to all events domains for those subjects that remain in DM after applying the cut-off rule based on RFSTDTC/RFICDTC.
For the domains AE, DS, DV, HO and MH, any records where --STDTC > cut-off date will be excluded. All data elements will be kept for the records, except for the following changes to --ENDTC and --ENRF (where these variables exist):

- If --ENDTC > cut-off date then change --ENDTC to missing
- If --ENDTC > cut-off date then change --ENRF to "ONGOING"

A special rule will be handled for the AE domain where:

- If --ENDTC > cut-off date and AEOUT is "RESOLVED" or "RESOLVED WITH SEQUELAE" then change AEOUT (Outcome of Adverse Event) to "NOT RECOVERED/NOT RESOLVED"

- If –ENDTC > cut-off date and AE led to death, then change AEOUT to "DOSE NOT CHANGED"
- If TRTEDT > cut-off date and AE led to discontinuation, then change AEACN to "DOSE NOT CHANGED"

5.5. Findings

Cut-off rule should be applied to all findings domains for those subjects that remain in DM after applying the cut-off rule based on RFSTDTC/RFICDTC.
For the domains EG, IE ,IS, LB, MI, PC, PE, QS, RP, RS, SR, SU, TR, TU, and VS and where --DTC > cut-off date, will be excluded.

- The only exception to this rule is for TU, TR, and RS where the following will be done:
  - **TU:**
    - Exclude any record from TU where TUDTC > cut-off date.
  - **TR:**
    - If TREVAL = "INVESTIGATOR" and TRCAT equals ("RECIST 1.1" or "IRRC" or "MODIFIED IRRECIST") and TRSCAT = null, then create a new variable TRCAT_temp = "RECIST 1.1/IRRC".
      - Otherwise, set TRCAT_temp = TRCAT.
    - Calculate the *latest* visit date TR [PLUS].TRDTC for each unique combination of USUBJID, TREVAL, TREVALID, TRCAT_temp, TRSCAT, ASMNTVIS, and VNUMICR. Call this latest/maximum visit date "max TR date".
      - Note: This is because there can be multiple tumor imaging scan dates for a subject at each ASMNTVIS (Assessment Visit) and VNUMICR (Independent Central Review Visit Number), per evaluator (investigator or independent assessor), evaluator identifier (radiologist 1 or 2), tumor criteria (RECIST 1.1, irRECIST, etc.), and tumor criteria sub-category (regular, special investigator hepatic MRI scan criteria).
      - This creates a temporary TR tumor dataset containing one record per each unique combination of records above, with a populated "max TR date".
    - Merge the "temporary" TR tumor dataset with the original TR [PLUS] by USUBJID, TREVAL, TREVALID, TRCAT_temp, TRSCAT, ASMNTVIS, and VNUMICR.
    - Exclude any record that has a "max TR date" per {USUBJID/TREVAL/TREVALID/ TRCAT_temp/TRSCAT/ASMNTVIS/VNUMICR} > cut-off date. This creates a "cut" TR tumor dataset containing only the tumor assessments that start and end in their entirety before or on the cut-off date. Also, records are conservatively kept which do not have a corresponding "max TR date".
  - **RS:**

- Two different methods will be used to cut the RS dataset for RSEVAL = INVESTIGATOR and RSEVAL = INDEPENDENT ASSESSOR. The investigator data will rely on cutting visit records from RS using TR dates (TRDTC), whereas independent assessor data will rely on dates from RS (RSDTC).

- Step 1: Investigator data
  - Use the "cut" TR tumor dataset containing only the tumor assessments that start and end in their entirety before or on the cut-off date, as created above from TR [PLUS].

  - Before merging this "cut" TR tumor dataset with RS [PLUS], the following manipulations are necessary to ensure an accurate merge.

  1. Manipulations for the "cut" TR tumor dataset from TR [PLUS]:
  - Subset on TREVAL = "INVESTIGATOR".
  - Remove all records from "cut" tumor dataset where TREVAL = "INVESTIGATOR" and TRSCAT = "HEPATIC MRI SCAN", as there are no associated records in RS.
  - If TREVAL = "INVESTIGATOR" and TRCAT equals ("RECIST 1.1" or "IRRC" or "MODIFIED IRRECIST"), then create a new variable TRCAT_temp = "RECIST 1.1/IRRC".
    - Otherwise, set TRCAT_temp = TRCAT.
  - Remove any duplicate records by USUBJID, TREVAL, TREVALID, TRCAT_TEMP, ASMNTVIS before the next merge.

  2. Manipulations for RS [PLUS]:
  - Subset on RSEVAL = "INVESTIGATOR".
  - In RS [PLUS], if RSEVAL = "INVESTIGATOR" and RSCAT equals ("RECIST 1.1" or "IRRC", or "MODIFIED IRRECIST"), then create a new variable RSCAT_temp = "RECIST 1.1/IRRC"
    - Otherwise, set RSCAT_temp = RSCAT.

- Merge the manipulated "cut" TR tumor dataset from TR [PLUS] with manipulated RS [PLUS], by RS.USUBJID=TR.USUBJID, RS.RSEVAL = TR.TREVAL, RS.RSEVALID = TR.TREVALID, RS.RSCAT_temp =TR.TRCAT_temp, and RS.ASMNTVIS=TR.ASMNTVIS. Then, only keep records that exist in both datasets. Call this final dataset RS_CUT_INVESTIGATOR.

- Step 2: Independent assessor data

- Create a subset dataset from RS [PLUS] where RSEVAL = "INDEPENDENT ASSESSOR". Call this dataset RS_ICR.
- Calculate the latest RS_ICR.RSDTC for each unique combination of USUBJID, RSEVAL, RSEVALID, RSCAT, ASMNTVIS, and VNUMICR from the RS_ICR dataset.
- Exclude any latest RS_ICR.RSDTC per {USUBJID/RSEVAL/RSEVALID/RSCAT/ASMNTVIS/VNUMICR} > cut-off date. This creates a temporary "cut" RS tumor dataset containing only the tumor assessments that start and end in their entirety before or on the cut-off date.
- Merge the "cut" RS tumor dataset with the RS_ICR dataset by USUBJID, RSEVAL, RSEVALID, RSCAT, ASMNTVIS, and VNUMICR, and then only keep records in RS_ICR which exist in the temporary "cut" RS tumor dataset. Call this final dataset RS_CUT_INDEPENDENT.

▪ Step 3: Finalize RS

- Set together the final datasets RS_CUT_INVESTIGATOR and RS_CUT_INDEPENDENT, created above in Step 1 and Step 2.

5.5.1. FA

Cut-off rule should be applied to FA for those subjects that remain in DM after applying the cut-off rule based on RFSTDTC/RFICDTC. This will correctly cut-off the records from Disease at Baseline (where FADTC is missing) and where data collected at screening.

Dose-Limiting Toxicity records will be cut, such that records with FADTC > cut-off date, will be excluded for FATESTCD="PROTDLT". The same FADTC from FATESTCD="PROTDLT" will be temporarily used for FATESTCD=" DLTTYPE", in order to apply the cut-off, since these records come from the same Dose-Limiting Toxicity eCRF page.

6. Handling of dates when applying cut-off rules

Rules for handling partial or incomplete dates in the dates that are used when applying the data cut-off.

- Instruction: If replacing the missing date part (year, month, day) allows a date to be on or before the cut-off date, then the respective record should be kept in the dataset; otherwise the respective record is excluded

from the dataset. Using the worst-case scenario principle, records with missing date part should be included in the data cut unless the relevant date is likely to be after the clinical cutoff date.

- If the day of the date is missing:
  - If year is earlier than the cut-off year, then the observation is included
  - If year is the same as the cut-off year, and the month is earlier or the same as the cut-off month, then the observation is included

- If day and month of the date are missing:
  - If the year is earlier or the same as the cut-off year, then the observation is included

- If the date is completely missing:
  - The entire record is included

- Example: Cut-off date = 20 Nov 2015.
  - Full Date for applying cut-off = 21 Nov 2015. The full date is after the cut-off date, therefore the respective record will not be kept in SDTM

  - Day is missing: If the respective date in the record is Nov 2015, then the date will be kept in SDTM, i.e. this record will be included

  - If the respective date in the record is Dec 2015, the date will not be kept in SDTM, i.e. this record will be dropped

  - Month is missing: If the respective date in the record is 2015, then the date will be kept in SDTM, i.e. this record will be included

  - If the respective date in the record is 2016, then this date will not be kept in SDTM, i.e. this record will be dropped

  - If Year and Day are available, but Month is missing (possibly due to unclean data) then the same rule as for missing day and month apply: If the respective date is 2015---15, the date will be kept in SDTM, i.e. the record will be included

  - If the respective date is 2016---15, the date will be not kept in SDTM, i.e. this record will be dropped

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APPENDIX 6. PROCESS FOR CATEGORIZING SKIN TOXICITIES ASSOCIATED WITH TEBENTAFUSP, INCLUDING RASH

Since gp100 is expressed on melanocytes on the skin, tebentafusp was expected to induce a skin rash and indeed this was observed. These adverse events may present in different ways and be reported by investigators using different AE preferred terms (PTs). Therefore, for the purpose of detailed safety evaluations, Immunocore designed a process to determine a composite list of rash:

1. All unique MedDRA PTs under the System Organ Class (SOC) of "Skin and subcutaneous tissue disorders" from study IMCgp100-102 were listed and reviewed by the study's medical monitor.
2. PTs were then grouped into only one of several skin toxicity composite terms based this medical review:
    a. Rash
    b. Pruritis
    c. Pigment change
    d. Erythema
    e. Edema
    f. Dry skin
    g. Other changes
3. Due to their suspected relationship to the tebentafusp mechanism of action, the following PTs from other SOCs were also added to these categories:
    a. Eye pruritus (to Pruritis)
    b. Eyelash hypopigmentation (to Pigment change)
    c. Periorbital oedema (to Edema)
4. The process was repeated for the first-in-human study IMCgp100-01, which included some new PTs in the Skin and subcutaneous tissue disorders SOC that were not reported in study IMCgp100-102 and a few PTs from other SOCs (Eyelash discolouration, Erythema of the eyelid, Skin abrasion, Eyelid eodema). All of these PTs were added to the relevant composite lists.
5. The composite lists were reviewed by oncologists who were high volume enrollers on the tebentafusp clinical trials. Based on their input, only a few PTs were adjusted by from one composite list to another.
6. The resulting list of rash PTs is: Blister, Dermatitis acneiform, Dermatitis allergic, Dermatitis bullous,

[redacted]

Dermatitis exfoliative, Drug eruption, Eczema, Palmar-plantar erythrodysaesthesia syndrome, Papule, Psoriasis, Rash, Rash erythematous, Rash generalised, Rash macular, Rash maculo-papular, Rash papular, Rash pruritic, Rash vesicular, Skin abrasion, Skin exfoliation, Urticaria.