IMMUNOCORE

Statistical Analysis Plan

Protocol IMCnyeso-101

A Phase I/II Open-label, Multi-center Study of the Safety and Efficacy of IMCnyeso, an HLA- A*0201-Restricted, NY-ESO-1- and LAGE-1A-specific Soluble T Cell Receptor and Anti-CD3 Bispecific Molecule, as a Single Agent in HLA-A*0201 Positive Patients with Advanced NY-ESO-1 and/or LAGE-1A Positive Cancer

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ADA	Anti-drug antibody
AE	Adverse event
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
AUC	Area under curve
AUClast	Area under the plasma concentration-time curve from time zero to time of last measurable concentration
AUCtau	Area under the concentration time profile over the dosing interval
BLRM	Bayesian Logistic Regression Model
BLQ	Below the limit of quantification
BOR	Best Overall Response
C#D#	Cycle # Day #
CD#	Cluster of differentiation #
CL	The total body clearance of drug from the plasma
C_{max}	Maximum observed concentration
CR	Complete response
CRS	Cytokine release syndrome
CSR	Clinical Study Report
CTCAE	Common Terminology Criteria for Adverse Events
DDS	Dose-determining Set
DETC	Dose-escalation teleconference
DLT	Dose-limiting Toxicity
DoR	Duration of response
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Form
EWOC	Escalation with overdose control
FAS	Full analysis set
FIH	First in human
FSH	Follicle stimulating hormone

hCG	Human chorionic gonadotropin
HLA	Human leukocyte antigen
HLA-A*0201	Human leukocyte antigen-A*0201
HLA-DR	Human leukocyte antigen-DR
ICF	Informed consent form
ICH	International Conference on Harmonization
IL-#	Interleukin-# (e.g. IL-6, IL-10)
IPE	Intra-patient escalation
IRS	Integrated response system
IV	Intravenous
LAGE-1A	L antigen family member-1 isoform A
LAGE-1B	L antigen family member-1 isoform B
[redacted]	[redacted]
MedDRA	Medical Dictionary for Regulatory Activities
[redacted]	[redacted]
MTD	Maximum tolerated dose
N-CRM	N-Continual Reassessment Method
NCI	National Cancer Institute
NSCLC	Non-small cell lung cancer
NY-ESO-1	New York esophageal squamous cell carcinoma-1
ORR	Objective response rate
OS	Overall survival
PBMC	Peripheral blood mononuclear cell
PD	Progressive disease
PD-1	Programmed death-1
PD-L1	Programmed death-ligand 1
PFS	Progression-free survival
PK	Pharmacokinetic
PPS	Per protocol set
PR	Partial response
PT	Preferred Term

QTcF	QT interval corrected by Fredericia's method
QW	Every week
RECIST	Response Evaluation Criteria in Solid Tumors
RP2D	Recommended Phase 2 dose
SAE	Serious adverse event
SAF	Safety Analysis Set
SAP	Statistical Analysis Plan
SD	Stable disease
SOC	System Organ Class
SST	Study Safety Team
$t_{1/2}$	Terminal elimination half-life
T3	Triiodo thyroxine
T4	Thyroxine
TEAE	Treatment-emergent adverse events
TIL	Tumor infiltrating lymphocyte
T_{max}	Time of maximum concentration
[redacted]	[redacted]
TSH	Thyroid stimulating hormone
ULN	Upper limit of normal
US	United States
Vss	Steady state volume of distribution
WBC	White Blood Cell
WHO	World Health Organization

1 Introduction

This statistical analysis plan (SAP) describes the analyses and data presentations for the clinical study protocol IMCnyeso-101 version 4.0, dated 24 Feb 2020. This study is a Phase I/II, open-label, multi-center trial. Phase I of the study is a dose escalation to determine the maximum tolerated dose (MTD) or recommended Phase II dose (RP2D) of IMCnyeso administered weekly as monotherapy in patients with advanced non-small cell lung cancer (NSCLC), melanoma, urothelial cancer and synovial sarcoma; Phase II of the study is expansion in three disease cohorts (NSCLC, urothelial cancer and synovial sarcoma patients).

Any differences between this SAP and protocol version 3.0 are documented in Section 12.

This SAP describes statistical analyses that will be produced in three deliveries:

1. Phase I Summary Report

   Based on a cut-off of Phase I patients once MTD/RP2D has been determined and all patients having completed DLT evaluation.

2. Full Clinical Study Report (CSR) of Phase I and Phase II

   Based on a cut-off at the time where at least 80% of phase II patients in each cohort have completed the follow up for disease progression or discontinued the study for any reason (once each cohort has reached this point, separate reporting will be considered for each cohort).

   - There will be an interim analysis for each Phase II cohort (s). It will only involve BOR endpoint.

3. Follow-up Abbreviated CSR

   Based on the locked database after 100% follow up of all patients from both phases.

1.1 Rationale

Immunocore is developing a new biological entity, IMCnyeso, for the treatment of multiple indications where tumors are positive for the cancer-testis antigens New York esophageal squamous cell carcinoma-1 (NY-ESO-1) and/or L antigen family member-1 isoform A (LAGE-1A). The effector function of IMCnyeso (anti-CD3) works by binding and activating T cells via cluster of differentiation 3 (CD3). The effector T cells that bind to IMCnyeso and the tumor can be tumor-specific cells (tumor-infiltrating lymphocytes [TIL]) but circulating polyclonal T cells may also be activated as they traffic through the tumor through normal blood supply. IMCnyeso-mediated activation of these T cells stimulates the immune system to attack the target tissue.

IMCnyeso was evaluated in a series of in vitro investigations to assess potential anti-tumor activity in patients with tumors that express NY-ESO-1 and/or LAGE-1A. These data can be summarized as follows:

- In vitro, IMCnyeso potently recruits and activates healthy donor and cancer patient peripheral blood mononuclear cells (PBMCs), leading to the release of pro-inflammatory cytokines, chemokines, and killing of cancer cell targets. The fullest extent of redirected T cell killing can take up to 72 hours.

- In vitro, IMCnyeso potently recruits and activates CD3 positive T cells including CD8 positive and CD4 positive T cells resulting in cancer-cell killing, polyfunctional T cell activation, proliferation, and expansion of T cells.

These data demonstrate that IMCnyeso is a potent tumor-killing agent. Therefore, an investigation into the effects of the drug in patients with tumors expressing NY-ESO-1 and/or LAGE-1A is warranted.

For additional clinical information regarding IMCnyeso, refer to the latest version of the Investigator's Brochure.

2 Objectives

2.1 Primary Objectives

The primary objective in Phase I is to identify the MTD and/or the RP2D of IMCnyeso, as a monotherapy, when administered weekly to patients with advanced NSCLC, melanoma, urothelial cancer, and synovial sarcoma. The primary objective in Phase II is to assess the preliminary anti-tumor activity of IMCnyeso as monotherapy in advanced NSCLC, urothelial cancer, and synovial sarcoma.

2.2 Secondary Objectives

The following secondary objectives apply to both Phases I and II (reported separately) unless otherwise noted:

- To characterize the safety and tolerability of IMCnyeso (Phase II only)
- To assess the preliminary anti-tumor activity of IMCnyeso as monotherapy
- To characterize the PK profile of IMCnyeso as monotherapy
- To evaluate the preliminary incidence of anti-IMCnyeso antibody formation following multiple infusions of IMCnyeso

2.3 Exploratory Objectives

[redacted]

3 Investigational Plan

3.1 Overall Study Design and Plan

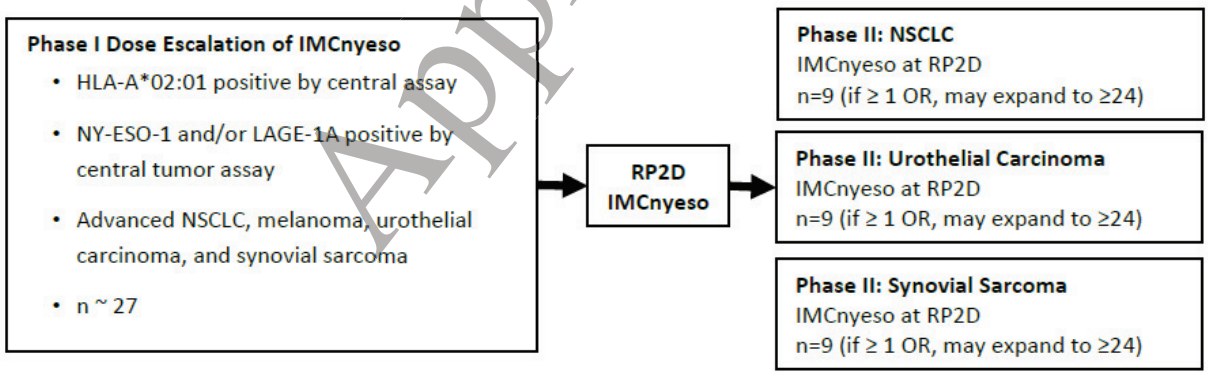
IMCnyeso-101 is a Phase I/II, multi-center, open-label, first in human (FIH), multi-ascending dose study of monotherapy IMCnyeso in HLA-A*0201 positive patients with advanced NY-ESO-1 and/or LAGE-1A positive solid tumors.

The study will be conducted in 2 phases:

- Phase I – dose escalation in 4 diseases (advanced NSCLC, melanoma, urothelial carcinoma, and synovial sarcoma) to determine the MTD and/or RP2D of IMCnyeso as a monotherapy. The decisions regarding dose escalation of IMCnyeso will be made by the Study Safety Team (SST), which will consist of the Study Investigators, the Sponsor Medical Monitor, and a Statistician. Dosing decisions will be made following a review of all relevant data available, from all dose levels evaluated in the ongoing study, including safety information, DLTs, all ⩾ Grade 2 toxicity data, PK, and pharmacodynamic data from evaluable patients in the dose-determining set (DDS) (see Section 4.3.6). The SST will be guided by the recommendation from the Bayesian Logistic Regression Model (BLRM) (see reference 1) since the Phase I design uses N-Continual Reassessment Method (N-CRM) of dose escalation with overdose control (EWOC) (see Section 15.2).
- Phase II – following the identification of the MTD and/or RP2D in Phase I, patients may be enrolled into the 3 Phase II expansion cohorts (NSCLC, urothelial carcinoma, and synovial sarcoma) to make a preliminary assessment of the anti-tumor activity of IMCnyeso as a single agent in these disease settings. Initially, up to 9 patients may be enrolled in each Phase II cohort. If there is at least one response, at the discretion of the sponsor up to an additional 15 patients may be accrued for a total of up to 24 patients.

The design is summarized in **Figure 1** below:

Figure 1 - IMCnyeso-101 Study Design



HLA = human leukocyte antigen; NSCLC = non-small cell lung cancer; RP2D = recommended Phase II dose.

The number of patients in the Phase I escalation part of the study is estimated to be 27 patients. There is no upper limit to the sample size in Phase I. However, in 80% of the simulations conducted, the sample size was < 33 patients (see Section 4.1).

3.2 Study Endpoints

3.2.1 Primary Endpoint

The primary endpoints in Phase I are:

- The incidence of dose limiting toxicities

- The incidence and severity of AE and SAE
- The changes in laboratory parameters, vital signs, and ECGs
- The dose interruptions, reductions, and discontinuations

The primary endpoint in Phase II is the best overall response (BOR) as determined by RECIST v1.1.

3.2.2 Secondary Endpoints

For both phases, the following will be analyzed:

- Progression-free Survival (PFS)
- Duration of Response (DoR) by RECIST v1.1
- Overall Survival (OS)
- Serum PK parameters (e.g. AUC, Cmax, Tmax, $t_{1/2}$) after single and multiple doses
- The incidence of anti-IMCnyeso antibody formation

For Phase I only, the following secondary endpoint will also be analyzed:

- Best Overall Response (BOR)

For Phase II only, the following secondary endpoints will also be analyzed:

- Incidence and severity of AE and SAE
- Changes in laboratory parameters, vital signs, and ECGs
- Dose interruptions, reductions, and discontinuations

3.2.3 Exploratory Endpoints

3.3 Treatments

For this study, the terms investigational drug and study medication refer to IMCnyeso.

Patients enrolled in this study will receive treatment with single agent IMCnyeso, dosed weekly on Days 1, 8, 15 and 22 until disease progression or other reason to discontinue. Patients will be hospitalized for 2 nights following the administration of the first dose (C1D1) of IMCnyeso and

will remain at the site for overnight observation following administration of the second dose (C1D8). In addition, patients receiving intra-patient escalation (IPE) will be hospitalized overnight following the first three doses (C1D1, C1D8, and C1D15). After reviewing safety, PK, and cytokine data from at least 3 patients enrolled at a given dose level, the SST may decide that one night of hospitalization is adequate after the first dose for subsequent patients (with longer hospitalization if indicated). After Phase I is completed and the SST would review all available relevant data for at least 6 patients at the RP2D, the SST may decide to reduce the minimum required monitoring time during the Phase II portion of the study to no less than 8 hours post-end of infusion on C1D1, C1D8, and/or C1D15 (with longer hospitalization if clinically indicated). Patients who experience certain AEs may require additional in-patient monitoring as described in Section 6.15 of Protocol V4.0.

For each patient, the first dose will be infused over 2 hours (±15 minutes); for dose levels $\leqslant$ 30 mcg; the first dose may be infused over 1 hour (±10 minutes). If the first dose is well tolerated without $\geqslant$ Grade 2 infusion and/or a hypersensitivity reaction, a given patient's subsequent infusion times may be reduced to 1 hour (±10 minutes) starting at C1D8, and further reduced to 30 minutes (±10 minutes) starting at C3D1 provided the above conditions continue to be met. Investigators may prolong the infusion time for individual patients if medically indicated at any time.

Cohorts 1- 4 would be fixed dose and cohorts 5 - 7 will introduce an intra-patient escalation (IPE). If the severity of cytokine-mediated AEs tend to become less severe following the initial doses of study drug using a fixed-dose regimen, the SST may initiate a step 1 IPE regimen, in which a lower dose is given on Cycle 1 Day 1 and a higher (target) dose is given on Cycle 1 Day 8 and beyond (for details: Section 6.10.1 of the Protocol V4.0).

3.4 Dose Adjustment/Modifications

All doses administered to subsequent cohorts of patients will be determined by the SST and will be guided by the BLRM and will be subject to both the EWOC principle and the escalation rule. Dose-escalation decisions will be made by the SST, which will consist of the Study Investigators, the Sponsor Medical Monitor, and a Statistician. For each cohort, dose escalation or de-escalation decisions will be based on the SST's review of all relevant data available, from all dose levels evaluated in the ongoing study, including safety information, DLTs, all $\geqslant$ Grade 2 toxicity data, PK, and pharmacodynamic data from evaluable patients (as defined in Section 6.10.2 of protocol version 4.0). The data and BLRM dose recommendations will be discussed and agreed upon during the dose-escalation teleconference (DETC), and all decisions will be documented in the meeting minutes and shared with all participating Principal Investigators.

The actual dose levels that have been tested in this study are shown in **Tab**le 1 below. Actual doses will be determined using the BLRM and must be agreed upon by the SST.

Table 1 - IMCnyeso Dose Levels for Phase I Dose Escalation

Cohort number	Cohort description	IMCnyeso Dose(s) Tested	Enrollment (n)
1	3 mcg fixed dose	3 mcg	4
2	10 mcg fixed dose	10 mcg	3
3	30 mcg fixed dose	30 mcg	5
4	100 mcg fixed dose	100 mcg	3
5	30-100 mcg intra-patient dose escalation	30-100 mcg	5
6	30-100-180 mcg intra-patient dose escalation	30-100-180 mcg	4
7	30-100-300 mcg intra-patient dose escalation	30-100-300 mcg	6 (planned)

To better understand the safety, tolerability, and PK profile of single agent IMCnyeso, additional cohorts of patients may be enrolled at preceding dose levels or intermediate dose levels, before or in parallel, while proceeding with further dose escalation. The outcome from these cohorts will be included in the BLRM.

If the first 2 patients in a previously untested dose level experience a DLT, additional enrollment in that cohort will stop, the BLRM will be updated with this new information, and the SST will evaluate the available safety, PK, and pharmacodynamic data. By incorporating information gained at the preceding dose levels and provided the BLRM predicts that the risk of excessive toxicity remains below 25% (EWOC), additional patients may be enrolled at this dose level or a lower dose level as agreed upon by the SST.

If the severity of cytokine-mediated AEs tend to become less severe following the initial doses of study drug using a fixed-dose regimen, the SST may initiate step 1 intra-patient escalation regimen, in which a lower dose is given on Cycle 1 Day 1 and a higher (target) dose is given on Cycle 1 Day 8 and beyond. Further details can be found in Section 6.10.1 of the protocol.

A subsection on dose escalation decisions will be included in the CSR, and the BLRM outputs produced for the dose escalation meetings will be included in the CSR appendices.

4 General Statistical Considerations

Categorical data will be summarized using frequencies and percentages. The denominator for all percentages will be the number of patients belonging to the analysis set of interest by dose group or disease cohort according to the particular summary. Percentages will be presented as integer numbers with no decimal part given the small number of patients enrolled. Percentages will not be displayed for 0 frequencies. A row denoted “Missing” will be included in count tabulations where necessary to account for missing values.

For continuous data, the mean, standard deviation (SD), median, minimum (Min) and the maximum (Max) will be presented. For PK, if concentration results below a lower limit of detection (LLOD) and LLOD for a parameter is clinically relevant then it will be included in the calculation of standard statistics with that concentration result set at 0; but for cytokines it will be set at the midpoint between 0 and the LLOD. Minimum and maximum will be presented to the same number of decimal places as the raw data, mean and median will be presented to 1 more

decimal place than the raw data, and standard deviation will be presented to 2 more decimal places than the raw data.

No formal statistical hypotheses will be tested. Where appropriate, two-sided 95% confidence intervals will be presented.

All data summaries and statistical analyses will be performed using the SAS software Version 9.4 or higher (SAS Institute, Cary, NC).

The study day of an event that occurred after or on the first dose date will be calculated as:

Event Date – C1D1 Date + 1

whereas the study day of an event that occurred before the first dose date will be calculated as:

Event Date – C1D1 Date

All listings will be sorted for presentation in order of center and patient identification number. Key variables to be displayed on each listing will be: Study phase, center, patient identification number, age, sex, and race.

The following rules will be followed for reporting results unless stated otherwise:

- Screen failure patients are those who signed the ICF, but never started the study treatment for any reason. For these patients, the eCRF data collected will not be included in analyses but will be reported in the clinical study report as separate listing.
- Baseline is defined as the last assessment prior to the first dose of treatment received (e.g. C1D1 pre-dose).
- Tables, listings, and figures will be presented for Phase I and II separately or combined Phase I/II together as appropriate.
- Tables for DLTs will be produced for Phase I and Phase II.
- Visit time points will be presented in the form Cycle x Day y.

Unless otherwise stated in below sections, missing data will not be imputed, but they will simply be noted as missing on appropriate tables/listings.

4.1 Sample Size

Dose decisions will be guided by the BLRM. Among the simulations that were conducted, the mean sample size was 27 patients, and the sample size was less than 33 patients in over 80% of simulations.

A Simon two-stage design will be used for each Phase II cohort using a 10% probability of a Type 1 error, a 20% probability of a Type 2 error, and assuming a target response rate of 20% versus 5% response rate for available treatment options. If there are no responses among the first 9 patients in a cohort, then accrual in that cohort will stop. If there is at least one response, at the discretion of the sponsor up to an additional 15 patients may be accrued for a total of up to 24 patients (with at least 3 responses to support further evaluation).

4.2 Randomization, Stratification, and Blinding

The Integrated Response System (IRS) will be used to control patient allocation to treatment and ensure the dosing intervals and cohort recruitment comply with the protocol.

4.2.1 Treatment and Disease Groups for Reporting

The Phase I safety data will be listed, summarized, and analyzed overall and by dose group where dose groups may incorporate pooling of dose levels; the exact extent of pooling will be defined after Phase I actual doses administered are known, and is expected to use the Recommended Phase 2 dose (RP2D) as threshold (see **Table 2**).

Patients who enroll in multiple cohorts will be represented once for each cohort and once in the total/overall study columns for summaries that are based on baseline data (e.g. demographics, medical history). Listing will be presented for patients who are escalated to a higher dose.

Table 2 – Potential Phase I Dose Groups

Treatment Group	Dose Group (Label for TLF Reporting)*	Patients included
IMCnyeso < x mcg QW	< RP2D	All Phase I dose escalation cohorts receiving a dose less than RP2D
IMCnyeso = x mcg QW	= RP2D	All Phase I dose escalation cohorts receiving the same dose as RP2D
IMCnyeso > x mcg QW	> RP2D	All Phase I dose escalation cohorts receiving a dose greater than RP2D

* x mcg is the Recommended Phase 2 Dose (RP2D) where x is determined during Phase I and administered IV over 1-2 hours.

In Phase II, patients will be analyzed according to the disease cohorts laid out in **Table 3**.

Table 3 - Phase II Disease Cohorts at RP2D

Cohort	Disease Cohort
Cohort 1	Advanced NSCLC
Cohort 2	Urothelial Cancer
Cohort 3	Synovial Sarcoma

4.3 Analysis Sets

The following analysis sets will be defined separately for the Phase I and Phase II parts of the study (except for Safety RP2D Analysis Set which is defined across Phase I and Phase II and the Per-Protocol Set which is defined just for Phase II).

In the Phase I part of the study, HLA-A*0201-positive patients with a diagnosis of NY-ESO-1 and/or LAGE-1A positive advanced NSCLC, melanoma, urothelial carcinoma, or synovial sarcoma will be enrolled. In Phase II, HLA-A*0201 positive patients with NY-ESO-1 and/or

LAGE-1A positive advanced NSCLC, urothelial carcinoma, or synovial sarcoma will be enrolled and treated at the RP2D.

4.3.1 All Patients Set

The All Patients set includes every patient who provided their main informed consent with recorded data in the eCRF. Note that this set includes screening failures.

4.3.2 Full Analysis Set (FAS)

The FAS is a subset of the All Patients Set and it comprises all patients who received at least 1 full dose or partial dose of IMCnyeso. In Phase I, patients will be analyzed according to the planned treatment or as per the dose groups laid out in **Table 2**.
In Phase II, patients will be analyzed according to the disease cohorts laid out in **Table 3**. The FAS will be used for all listings of raw data, demography and baseline characteristics, and all analyses unless specified otherwise.

4.3.3 Safety Analysis Set (SAF)

The SAF is a subset of All Patients Set and it comprises all patients who received at least 1 full dose or partial dose of IMCnyeso. Patients will be classified in this set according to initial treatment received (see **Table 2**) or disease cohort in Phase II (**Table 3**). The SAF will be used for the safety summary of the study. In Phase I, the SAF will be equivalent to FAS if received doses are equal to planned doses (or sufficiently close to be in the same dose grouping).

4.3.4 Safety RP2D Analysis Set

The safety RP2D analysis set is a subset of the All Patients Set and it comprises all patients who received at least 1 full dose at the RP2D level. This will include patients from both phases combined and will be summarized according to disease as per **Table 3** but also including melanoma from Phase I.

4.3.5 Per-Protocol Set (PPS)

The Per-Protocol Set consists of a subset of FAS patients in Phase II who meet below 4 criteria

1. Presence of measurable disease according to RECIST v1.1
2. At least 1 post-baseline tumor assessment or discontinued prior to the first tumor assessment
3. Received at least 1 dose of planned treatment at the RP2D
4. No violation of key inclusion or exclusion criteria.

Patients in the PPS will be classified according to disease cohort as per **Table 3**.

4.3.6 Dose-Determining Analysis Set (DDS)

The DDS consists of all patients from the SAF in Phase I who meet the criteria in Section 3.4.

This set will be used to guide the dose escalation using actual dose received and will not be an analysis set used in final reporting.

4.3.7 Pharmacokinetic (PK) Analysis Set

The PK analysis set consists of all patients in the SAF with at least 1 post-dose blood sample providing evaluable PK data. The PK analysis set will be used for all PK analyses.

Patients may be removed from the estimation of certain PK parameters on an individual basis depending on the number of available blood samples. These patients will be identified at the time of analysis.

5 Patients Disposition

5.1 Disposition

The number and percentage of patients ongoing treatment, ongoing in the study, patients who died with the corresponding reason for death and whether the death was within 30 days of last dose or not, patients who discontinued treatment with the corresponding reason for drop out and patients who discontinued the study with the corresponding reason for drop out will be tabulated by dose group.

In addition, the number and percentage of patients in each analysis set will be shown (as defined in Section 4.2.1).

Percentages will be based on the number of patients assigned to treatment in the FAS.

Patient disposition data will be presented in a listing for the FAS.

5.2 Protocol Deviations

Compliance with the protocol will be assessed by the number and percentage of patients with important protocol deviations. Important protocol deviations will be identified prior to database lock and will be listed and summarized by category for FAS. The impact of important protocol deviations on the study procedures or the analyses will be classified according to the following rules:

- The important protocol deviation resulted in exclusion from one or more analysis sets (as defined in Section 4.3)
- The important protocol deviation resulted in permanent discontinuation of study treatment
- The important protocol deviation resulted in exclusion from one or more analyses

6 Demographics and Baseline Characteristics

Demographics and baseline characteristics will be presented for FAS.

Qualitative data (e.g. sex) will be tabulated by category while quantitative data (e.g. weight) will be summarized by descriptive statistics.

Demographic data, baseline disease characteristics, and other baseline data will be listed in detail.

6.1 Demographics

Demographic data will be summarized and include age group (18-<50, 50-<65, ⩾65), sex, race, ethnicity, weight at baseline and height at baseline.

6.2 Baseline Disease Characteristics

ECOG performance status at baseline will be summarized by grade (0 or 1) and a shift table of baseline to worst on-treatment result will be presented.

The latest set of results/values will be used on demographics (e.g. ECOG, height, weight) summary if a subject has different values for different cohorts.

Listing of ECOG performance status at each visit will be presented for the FAS.

6.3 Smoking Status

Smoking status (smoker, ex-smoker, or non-smoker) at baseline will be summarized together with demographics characteristics (see Section 6.1).

6.4 Medical History

6.4.1 General Medical History

Relevant prior medical history and current medical conditions will be summarized separately, but they will be listed together. Medical history and current medical conditions will be coded by using the International Conference on Harmonization (ICH) Medical Dictionary for Regulatory Activities (MedDRA) version 20.0.

6.4.2 Cancer History

Cancer history will be described by original cancer disease (melanoma, synovial sarcoma, urothelial carcinoma, NSCLC) and stage (0, I, II, III, IV) at trial entry. The type/location on body will be listed only, where collected for melanoma and sarcoma. Also, the histology will be listed only for NSCLC.

The duration in months of diagnosis [(Date of Screening - Date of Initial Cancer Diagnosis + 1)/30.4375] and duration in months of metastatic disease [(Date of Screening - Date of detection of metastatic disease + 1)/30.4375] will be summarized by descriptive statistics.

For calculating the duration of diagnosis and metastatic disease, incomplete dates of initial cancer diagnosis and dates of detection of metastatic disease will be imputed as follows (where UK and UKN indicate unknown or missing day and month respectively):

- UK-MMM-YYYY: Assume 15-MMM-YYYY. If the month and year are the same as the first dose of study drug month and year, then assume the date of first dose of study drug.
- UK-UKN-YYYY: If the year is prior to the year of first dose of study drug, assume 01-JUL-YYYY of the collected year. If the year is the same as the first dose of study drug year, then assume the date of first dose of study drug.

6.5 Prior Anti-Cancer History

Prior anti-cancer therapies classified as systemic therapy (including chemotherapy, immunotherapy, and targeted therapy), radiotherapy, surgery, or "Other" are to be recorded on the Prior Anti-neoplastic Therapy eCRF page during screening. The number of lines of prior anti-cancer therapies and therapy class will be tabulated. The number of lines of prior anti-cancer

therapies will also be summarized by descriptive statistics. The number of lines will be calculated based on the following:

A regimen (i.e. unique regimen number) would count as a line of therapy if

- (therapy class = systemic therapy) AND (treatment setting = [metastatic disease / palliative OR unresectable locally advanced disease / palliative])

or

- (therapy class = systemic therapy) AND (treatment setting = primary / neoadjuvant / adjuvant / curative) AND (date of detection of metastatic disease <= 6 months after [cancer therapy end date in this regimen])

Prior anti-cancer therapies will also be listed for FAS patients.

6.6 Inclusion and Exclusion Criteria

Treated and non-treated patients who did not meet inclusion or exclusion criteria will be listed separately for the All Patients Set.

7 Treatments and Medications

7.1 Prior and Concomitant Medications

Prior and concomitant medications will be documented at screening and updated during the study.

Prior and concomitant medications will be coded using the WHO Drug Dictionary Enhanced Version WHODDRUG Dec16 WHO-DDE B2.

A prior medication is defined as a medication where both the start and end dates are before the date of the initial C1D1 IMCnyeso dose received.

A concomitant medication is defined as one where the end date is either on or after C1D1 date or is missing. The start date of a concomitant medication can be before or after C1D1 date. For a medication with partial or completely missing onset date, unless it can be determined to be "prior to the first infusion" from the incomplete start date or end date (e.g., month, year is before C1D date, or end date is before C1D1 date), the medication will always be assumed to be concomitant. Medications initiated prior to the start of study treatment and continued after the start of study treatment will be counted as both prior and concomitant medications.

For the purpose of categorizing medications as prior or concomitant, incomplete medication start and stop dates will be imputed as follows:

Missing start dates (where UK and UKN indicate unknown or missing day and month respectively):

- UK-MMM-YYYY: Assume 01-MMM-YYYY. If the month and year are the same as the first dose of study drug month and year, then assume the date of first dose of study drug.
- UK-UKN-YYYY: If the year is prior to the year of first dose of study drug, assume 01-JAN-YYYY of the collected year. If the year is the same as the first dose of study drug year, then assume the date of first dose of study drug.

Missing stop dates for concomitant medications data will be handled as follows (where UK, UKN and UNKN indicate unknown or missing day, month, and year respectively).

- UK-MMM-YYYY: Assume the last day of the month.
- UK-UKN-YYYY: Assume 31-DEC-YYYY.
- UK-UKN- UNKN: Assume ongoing and leave it missing.

A listing for both prior and concomitant medications will be created for all FAS patients.

7.2 Study Treatments

7.2.1 Extent of Exposure

Total number of cycles, expected dose, actual dose and duration in months of treatment for IMCnyeso, as well as the dose intensity (total actual dose received/actual duration), the relative dose intensity (the dose intensity as percentage of planned dose/planned duration), number of doses beyond progression, number of doses beyond progression and the actual dose beyond progression will be summarized by descriptive statistics for the SAF.

- The treatment period will begin with the first treatment on Day 1 in the first cycle (C1D1). For the purpose of treatment scheduling, a cycle consists of 4 weeks (28 days). The total number of cycles of study drug received will include also partial cycles and reduced dose cycles.
- The duration is defined as the number of months from the date of the initial C1D1 IMCnyeso dose received to the last date of IMCnyeso dose received as recorded on EX dataset plus the protocol defined post-dose rest (i.e. 1 day).

Duration of Treatment (months) = (date of last dose - the date of first dose + 1) / 30.4375.

- Because study drug reduction may occur during the study, the exposure to study drug will also be characterized by total actual dose received, which is defined as the sum of the actual dose levels during the study.
- Dose intensity is the total actual dose received divided by duration of treatment in weeks.

$$\text{Dose Intensity (mcg/wk)} = \frac{Sum\ of\ Actual\ Doses}{Duration\ of\ Treatment}$$

- The relative dose intensity (%) is 100 x (total actual drug given until treatment discontinuation) / (expected amount of drug given until treatment discontinuation). If there is a difference between the last dose date and the treatment discontinuation date (i.e. the date the *decision* was made to stop treatment), then date of last dose would be used.
- The actual dose beyond progression is defined as the total actual dose taken by the patient after the progression according to RECIST v1.1. Patients who did not progress, will not be included in this calculation. The summary of number of doses taken beyond progression and corresponding time duration (months) will be provided.

7.2.2 Treatment Compliance and Modifications

Study treatment will be administered to the patient at the study site by trained study staff. Patients compliance with the prescribed regimen will be assured as all administrations will be performed by site staff under the supervision of the study investigator or his/her designee. Therefore, no analysis of compliance is planned. However, dose interruptions and reductions may occur (see Section 8.6).

8 Safety Analysis

Safety analysis will be conducted on the SAF for the Phase I dose escalation and separately for the Phase II expansion cohorts. Combined outputs for safety may be produced based on the Safety RP2D Analysis Set.

8.1 Dose-Limiting Toxicity

The incidence of DLTs is the primary endpoint in Phase I. The specific type and grades of AEs classified as a DLT can be found in the protocol in Section 6.12. The DLT observation period for the Phase I dose escalation cohorts is explained in Section 3.4.

The number and percentage of patients with at least one DLT will be presented by dose group (as defined in Section 4.2.1).

A listing of key information for DLTs will be presented including patient identification number, Preferred Term (PT) of corresponding AE and CTCAE grade. DLT information will be reported and summarized for Phase II whenever appropriate

8.2 Adverse Events

All AEs regardless of study drug relationship will either be collected from the signing of consent up to the end of the 30 day follow-up based on current protocol versions 3.0 and 4.0 or 90 day follow up based on the previous protocol versions. Those AEs with onset 31-90 days after the last dose will be flagged in the separate adverse events listing.

1) Treatment-emergent adverse events (TEAEs) are defined as any adverse event after the first dose of study drug within 30 days of the last dose of study drug or prior to subsequent anti-cancer therapy, whichever is sooner. For adverse events on C1D1, the event onset time relative to the first dose time will be considered (if relative or actual times are available), otherwise AE starting on C1D1 will be assumed treatment-emergent.

The AE summary tables include only AEs that are new or worsened during the on-treatment period (TEAEs). However, all safety data (including those from the pre- and post-treatment periods) will be listed and those collected during the pre-treatment and post-treatment period are to be flagged.

The incidence of TEAEs will be summarized by system organ class (SOC) and/or PT, severity (based on NCI CTCAE v.4.03 grades), and relation to study treatment by treatment group (as defined in Section 4.2.1). Serious TEAEs resulting in death and non-fatal serious TEAEs will be listed by patient and tabulated by treatment group. There will be a separate listing for TEAE leading to treatment discontinuation.

AEs will be coded by MedDRA version 20.0.

For the purpose of inclusion in TEAE tables, incomplete AE onset and end dates will be imputed as follows:

- Missing onset dates (where UK and UKN indicate unknown or missing day and month respectively):
    - UK-MMM-YYYY: If the month and year are different from the month and year of the first dose of study drug, assume 01-MMM-YYYY. If the month and year are the same as the first dose of study drug month and year, and the end date (after any imputation) is on or after the first dose of study drug, then assume the date of the first dose of study drug. If the month and year are the same as the first dose of study drug month, and year and the end date (after any imputation) is prior to the first dose of study drug, then assume the end date for the onset date.
- Missing end dates are generally not imputed. However, in the cases of partial missing end dates, the following rules will be applied (where UK and UKN indicate unknown or missing day and month respectively):
    - UK-MMM-YYYY: Assume the last day of the month.
    - DD-UKN-YYYY/UK-UKN-YYYY: Assume 31-DEC-YYYY.

8.2.1 Incidence of Adverse Events

An overall summary of the number and percentage of patients with at least one TEAE in different categories (described here and below) will be provided by treatment group (as defined in Section 4.2.1). Treatment-emergent AEs will also be presented by SOC and PT. At each level of patient summarization, a patient is counted once if the patient reported one or more events. Percentages will be calculated out of the number of patients in the SAF. The table is sorted alphabetically for SOC and by descending frequency overall for PT.

Additionally, a summary of TEAEs will be presented by PT alone sorted in descending order of frequency overall. In addition, AEs of special interest including CRS (i.e. cytokine release syndrome [CRS]) symptoms will be presented in separate tables as needed.

All AEs will be presented in a listing.

8.2.2 Relationship of Adverse Events to Study Drug

A summary of TEAEs related to study drug will be presented in a table by incidence of occurrence. The investigator will provide an assessment of the relationship of the event to the study drug. The possible relationships are “related”, “possibly related” and “unrelated”. All “related” and “possibly related” AEs and SAEs will be defined as related to study drug.

In the TEAE relationship table, if a patient reports multiple occurrences of the same TEAE, the highest grade of the related or possibly related will be presented (e.g. if a patient experiences for example Grade 3 dyspnea that is ‘potentially related’ and Grade 1 dyspnea that is ‘related’, it would give that patient a maximum severity of Grade 3 rather than Grade 1 in the TEAE relationship table). Treatment-emergent AEs that are missing a relationship will be presented in the summary table as “related” but will be presented in the data listing with a missing relationship. Percentages will be calculated based on the number of patients in the SAF.

The TEAE related to study drug data will be presented by SOC, PT and maximum severity (see below), and PT alone in a manner similar to that described in Section 8.2.1.

8.2.3 Severity of Adverse Event

A summary of TEAEs by severity will be presented in a table. The severity that will be presented represents the most extreme severity captured on the eCRF page. The possible severities are measured on the CTCAE scale which goes from 1 to 5 where 1="mild", 2="moderate", 3="severe", 4="life-threatening" and 5="fatal". In the TEAE severity tables, if a patient reported multiple occurrences of the same TEAE, only the most severe will be presented. Treatment-emergent AEs that are missing severity will be presented in tables and listings as "missing". Percentages will be calculated out of the number of patients in the SAF.

The TEAE data will be presented by SOC, PT and maximum severity in a manner similar to that described in Section 8.2.1. Extra columns will be added to show TEAEs having CTCAE grade 3-4 and 5 separately. Additionally, the grade 3 and 4 TEAEs and related TEAEs will be presented by PT alone.

8.2.4 Serious Adverse Events

Treatment-emergent serious adverse events (SAEs) will be presented in a table. Treatment-emergent SAEs related to study drug will be presented in a table. A treatment-related treatment-emergent SAE is a treatment-emergent SAE with any relation to study drug other than "unrelated". Treatment-emergent SAEs that are missing a relationship will be presented in the table as "related" but will be presented in the data listing with a missing relationship. At each level of patient summarization, a patient is counted once if the patient reported one or more events. Percentages will be calculated out of the number of patients in the SAF.

The treatment-emergent SAE data will be categorized and presented by SOC and PT, and PT alone in a manner similar to that described in Section 8.2.1.

8.2.5 Adverse Events Leading to Treatment Discontinuation, Dose Interruption and Dose Reduction

A summary of TEAEs with a study drug action taken of "drug discontinued", "dose interrupted" and "dose reduced" will be presented in separate tables. At each level of patient summarization, a patient is counted once if the patient reported one or more events. Percentages will be calculated out of the number of patients in the SAF.

The tables will be presented by PT in descending order of frequency from the PT with the highest total incidence (that is, summed across all treatment groups, as defined in Section 4.2.1) to the PT with the lowest total incidence.

8.2.6 Deaths

TEAEs with an outcome of "fatal" will be presented in the overall summary table. A patient is counted once if the patient reported one or more events. Percentages will be calculated out of the number of patients in the SAF.

All patients who have a TEAE with an outcome of "fatal" will be presented in a listing. A listing of all deaths recorded during the study will also be produced. This listing will include the cause of

death and the period that the event occurred (i.e. the treatment period plus 30 days from last dose administered or the follow-up period).

8.3 Clinical Laboratory Evaluations

Laboratory parameters assessed for safety purposes will be evaluated locally. Refer to **Tab**le 4 for a summary of the parameters to be evaluated. Local laboratories must provide normal ranges for the parameters being analyzed and accreditation documentation for all local laboratories that perform protocol-required assessment.

Table 4 - Clinical Laboratory Parameters Collection

Test Category	Test Name
Hematology	Hemoglobin, platelets, white blood cells, lymphocytes, and neutrophils
Chemistry	Albumin, alkaline phosphatase, alanine transaminase, aspartate transaminase, bicarbonate, calcium, chloride, creatinine, glucose magnesium, inorganic phosphate, potassium, sodium, total bilirubin (also measure direct and/or indirect bilirubin if total bilirubin is > 1.5 × ULN), blood urea nitrogen or urea, amylase, and lipase
Coagulation	Prothrombin time or international normalized ratio and activated partial thromboplastin time
Urinalysis	Bilirubin, blood, glucose, ketones, pH, protein, specific gravity, and white blood cells (in the event of macroscopic findings, microscopy may be performed at the Investigator's discretion)
Thyroid	Free T4 and thyroid stimulating hormone (also measure free T3 if TSH is suppressed but free T4 is normal)
Pregnancy / menopausal status	hCG (women of childbearing potential) FSH (if required to confirm non-childbearing potential)

hCG = human chorionic gonadotropin; FSH = follicle-stimulating hormone; T3 = triiodo thyroxine; T4 = thyroxine; TSH = thyroid stimulating hormone.

Pregnancy tests will be performed for all women of childbearing potential. Any pregnancy must be reported as described in Section 8.5.6 of the protocol V4.0, and the patient should be withdrawn from treatment. For post-menopausal patients, FSH at screening must be within the laboratory's post-menopausal reference range.

In addition to laboratory parameters obtained by local laboratories, the following parameters will be derived (age and weight will be the values at Cycle 1 Day 1):

- For patients with Albumin<40 g/L, Corrected calcium (mmol/L) = Total calcium (mmol/L) + ([40 – Albumin (g/L)] × 0.02). Otherwise, Corrected calcium (mmol/L) = Total calcium (mmol/L)
- Creatinine clearance (mL/min)
  - For males = [140–age(years)] × weight(kg)/[72 × serum creatinine (mg/dL)]
  - For females = 0.85×[140–age(years)] × weight(kg)/[72 × serum creatinine (mg/dL)]
- If only % lymphocytes reported then:
  Absolute lymphocytes = white blood cell count × % lymphocytes
- If only % neutrophils reported then:
  Absolute neutrophils = white blood cell count × % neutrophils

On dosing days laboratory safety samples will be collected prior to the IMCnyeso infusion. More frequent evaluations may be performed, at the investigator's discretion, if medically indicated; results should be recorded as unscheduled laboratory assessments in the eCRF.

Laboratory parameters obtained by local laboratories and derived parameters will be summarized. Any result below the limit of quantification (BLQ) where BLQ for a parameter is clinically relevant (Hemoglobin, WBC, Lymphocyte count, Neutrophil count, Platelet count, Albumin, Bicarbonate, Calcium, Chloride, Magnesium, Phosphorus, Potassium, Sodium, Glucose, TSH, Free T4, Free T3) will be included in the calculation of standard statistics listed in Section 4 with the result set as 0.

Some results might be expressed as a range rather than a single value (e.g. '<x'). For such results, the value to be considered for summaries is the upper limit of the range if 'x' is greater than the BLQ (e.g. for '<x' results, the value will be 'x'). If 'x' is the BLQ, the result cannot be included in the statistics calculations as explained above.

For laboratory tests covered by the NCI CTCAE version 4.03, the study team will grade laboratory data accordingly and grading programming will be performed at SDTM database. For laboratory tests covered by NCI CTCAE, a grade of 0 will be assigned for all non-missing values not graded as 1 or higher. For laboratory tests where grades are not defined by CTCAE, results will be graded by the low/normal/high classifications based on laboratory normal ranges.

For NCI CTCAE tests, the worst on-treatment result is the maximum grade recorded after baseline. For non-NCI CTCAE tests, the worst on-treatment result will be:

1. "Low", if any result recorded after baseline is lower than the normal range and no post-baseline result is higher.
2. "High", if any result recorded after baseline is higher than the normal range and no post-baseline result is higher.
3. "Both", If both low and high are clinically meaningful, report worst low and worst high separately.

Summaries will be generated separately for hematology and biochemistry. These will include:

- Absolute values and change from baseline summaries, a graph of the results will be plotted.
- Shift tables of laboratory data using CTCAE grades to compare baseline to the worst on-treatment value, a graph of the results will be plotted.
- Listing of all relevant laboratory data with values flagged to show the corresponding CTCAE grades and the classifications relative to the laboratory normal ranges.

Shift tables of baseline to worst on-treatment laboratory grade (low/normal/high) will be presented for the following parameters with their relative worsening direction:

- Low: Hemoglobin, Albumin, Platelets, Neutrophils, and Phosphate.
- High: ALP, ALT, APTT, AST, Total bilirubin, Creatinine, Amylase, Lipase, and INR.
- Both: WBC Count, Lymphocytes, Calcium, Magnesium, Sodium, Potassium, Corrected calcium, and Glucose.

Central laboratory cytokine data (Interferon Gamma, Interleukin 6, Interleukin 8, Tumor Necrosis Factor alpha, Interleukin 10, Interleukin 2) will be summarized and statistics produced as per Section 4. A graph of the results will be plotted by all timepoints. It will also be listed.

8.4 Vital Signs

Vital signs (body temperature, pulse, respiratory rate, and blood pressure) will be performed as scheduled (details see Table 7-2 of the protocol V4.0).

Vital signs pre-dose values and worst absolute values and changes from pre-dose as well as time from start of infusion to worst will be summarized for each dose. See Section 9 of the protocol V4.0 for definition of observation periods.

The relevant vital sign values at each visit will be classified into the categories of low, normal, and high based on the following reference ranges.

- Systolic blood pressure, low is <75 mm Hg or decrease of >=30 mm Hg that results in <=90 mm Hg. High is >=160 mm Hg. (CTCAE V4.03, Grade 1: Prehypertension (systolic BP 120 - 139 mm Hg), Garde 2: Stage 1 hypertension (systolic BP 140 - 159 mm Hg), Grade 3: Stage 2 hypertension (systolic BP >=160 mm Hg))
- Diastolic blood pressure, low is <40 mm Hg or decrease of >=20 mm Hg that results in <=50 mm Hg. High is >=100 mm Hg. (CTCAE V4.03, Grade 1: Prehypertension (diastolic BP 80 - 89 mm Hg), Garde 2: Stage 1 hypertension (diastolic BP 90 - 99 mm Hg), Grade 3: Stage 2 hypertension (diastolic BP >=100 mm Hg))
- Pulse, low is <60 bpm. High is >100 bpm.
- Temperature, low is <=32 ℃. High is >=38 ℃ for any fever and >40 ℃ for CTCAE grade 3 fever. (CTCAE V4.03, 1. Fever- Grade 1: 38.0 - 39.0 degrees C, Garde 2: >39.0 - 40.0 degrees C, Grade 3: >40.0 degrees C for <= 24 hours, Grade 4: >40.0 degrees C for > 24 hours; 2. Hypothermia- Grade 2: 35 - >32 degrees C; Grade 3: 32 - >28 degrees C; Grade 4: <=28 degrees C)
- Weight gain: grade 1 = 5 - <10% from baseline, grade 2 = 10 - <20% from baseline, grade 3= >=20% from baseline.
- Weight loss: grade 1 = 5 - <10% from baseline, grade 2 = 10 - <20% from baseline, grade 3= >=20% from baseline.
- Oxygen saturation, low is < 94% and <88% is Grade 3.

For those parameters where the values might go in multiple directions (low/high), the results will be presented for worst low post-baseline and worst high post-baseline results separately. Figures for vitals during cycle 1, with all timepoints from pre-dose through ~24 hours post-dose will be plotted.

8.5 Electrocardiogram

A standard 12-lead ECG will be performed as per the assessment schedule in Table 7-2: Schedule of Treatment Period Assessments of the protocol V4.0.

PR Interval (msec), RR Interval (msec), QRS Duration (msec), QT Interval (msec), QTcF interval (msec), QTcF derivations (formula QTcF = QT interval/Cube Root of RR interval (seconds), when required), absolute values and change from baseline will be summarized.

QTcF interval absolute values will also be tabulated by the following groups:

- <=450
- >450 - <=480 msec (Grade 1)
- >480 - <=500 msec (Grade 2)
- >500 msec (Grade 3).

Change from Baseline in QTcF interval will be classified as:

- <=30 msec increase from baseline
- >30 - <=60 msec increase from baseline
- >60 msec increase from baseline

A shift table of baseline QTcF to worst on-treatment results will be presented. For rating the worst on-treatment value, 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 (Grade 1)
- >480 - <=500 msec (Grade 2)
- >500 msec (Grade 3)

8.6 Dose Interruptions and Reductions

The number of IMCnyeso dose interruptions, dose reductions, escalations and re-escalations will be summarized. A dose is considered interrupted when it is not administered for any reason during a visit (i.e. investigator answers the question in eCRF: "If No, reason for dose interruption"), when a visit is delayed by $\geq$ 7 days or omitted, or if an infusion is started and then stopped part-way through. If the dose is administered, but the investigator states it is reduced compared to last visit or if there is a reduction compared to the planned dose (for example, if a patient is assigned to 30/100/300 and receives 30 mcg on C1D8 that is a reduction from the planned dose of 100 mcg.), then the dose is considered as reduced (i.e. the investigator' answers the question in eCRF: "If Yes, reason for dose reduction").

Reasons for dose interruptions and dose reductions will be listed by patient and summarized.

9 Efficacy Analysis

Analysis of efficacy endpoints will be performed using the FAS and PPS for Phase II and only on FAS for Phase I.

No sensitivity or exploratory analysis are planned.

9.1 Primary Efficacy Endpoint

The primary efficacy endpoint in Phase II is the BOR as determined by RECIST v1.1.

9.1.1 Objective Response Rate

The primary summary measure of Best Overall Response (BOR) is the ORR, defined as the proportion of patients with a best overall response of CR or PR based on local investigator

assessment, as defined in RECIST v.1.1. The denominator in the calculation of the ORR will be the number of patients with measurable disease at baseline in the FAS / PPS as appropriate. All these patients included in the denominator will be categorized by their BOR (CR, PR, SD, PD, NE).

Confirmation of response is required for declaring PR or CR in the ORR. A confirmed response is defined as a CR or PR followed by a CR or PR at least 4 weeks later (allowing a window, this will need to be at least 3.5 weeks after the original assessment). Patients who have a PD event (progression or death) immediately after 2 or more consecutive missed/non-evaluable tumor assessment visits, will have a BOR of NE. Specifically for patients who die with no evaluable follow-up tumor assessments or no evaluable baseline assessment, if the death occurs immediately after the first 2 scheduled scans, then the BOR will also be NE. An exception to this rule is if the patient (with no evaluable follow-up tumor assessments or no evaluable baseline assessment) dies within 2 visits of first dose of study drug, then the BOR will be PD (for death in the absence of progression).

Tumor response will be determined per local investigator's assessment, according to RECIST v.1.1

Individual lesion measurements and overall response assessments will be listed by patient and assessment date. Best overall response per RECIST v.1.1 will be listed and tabulated. Change in tumor size for individual patients will be shown in spider plots. Duration of Treatment, Tumor Response and Response Duration will be shown in swimmer plots. Best overall change in tumor size for individual patients will be shown in waterfall plots and may be repeated at 13 and 26 weeks (Cycle 3 and Cycle 6).

Best overall response analysis per RECIST v.1.1 will be repeated for PPS. BOR will be summarized for overall and by Synovial cohort.

ORR and DCR (CR + PR + stable disease [SD]) will be summarized with accompanying 95% Clopper-Pearson's confidence interval. A patient is eligible for an assessment of stable disease only after 16 weeks from day of first dose. Any SD assessed before 16 weeks will not be counted as SD in the DCR.

DoR and time-to-response for patients who experience a CR or PR at any time on study will be listed by patient. Duration of response is the time in months from the date of first documented objective response until the date of progression or death (whichever occurs first). If a large proportion of patients achieves a response (e.g. 5/10), Kaplan-Meier plots for DoR will also be produced, and the median DoR will be estimated. The time-to-response is defined as the time from first dose to their first CR or PR.

9.2 Secondary Efficacy Endpoints

9.2.1 Progression-free Survival

PFS is defined as the time from first dose until the date of objective progression, or death from any cause, whichever occurs first. Patients who progressed or died immediately after two or more missed scheduled tumor assessments will be censored at date of last adequate assessment with evidence of no progression. Patients who have not progressed or died at the time of analysis will be censored at the time of the latest date of assessment from their last evaluable RECIST 1.1 assessment. These censoring rules apply regardless of what concomitant medications may have been taken or if the patient discontinued treatment prior to their last assessment. A sensitivity

analysis may be performed if subjects without objective disease progression receive a new anti-cancer therapy potentially affecting their results. In this analysis such patients will then be censored at the date of the last adequate response assessment prior to the new anti-cancer therapy.

PFS (months) = (Event date – date of first dose + 1) / 30.4375

The PFS will be presented graphically using Kaplan-Meier plots including all patients treated at the MTD or RP2D and by overall and Synovial cohort. Median PFS time and the proportion of patients who are progression-free at 3, 6, 9 and 12 months will be estimated for each group. To note, the 95% confidence interval will be calculated using "conftype = loglog" option within the Proc Lifetest procedure in SAS software.

PFS per RECIST v.1.1 will be listed by patient and tabulated.

PFS per RECIST v.1.1 will be repeated for the PPS for Phase II.

9.2.2 Overall Survival

OS is defined as the time from the date of first dose until death due to any cause.

OS (months) = (Death date or censor date – date of first dose + 1) / 30.4375.

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 study completion" (for those patients still alive) on the End of Study eCRF page and (ii) the "Date patient last known to be alive" on the Survival Follow Up eCRF page."

The OS will be treated similarly to PFS. Median OS time and the proportion of patients who are alive at 3, 6, 9 and 12 months will be estimated. OS will be presented graphically using Kaplan-Meier plots by overall and Synovial cohort for the FAS and PPS in Phase II. To note, the 95% confidence interval will be calculated using "conftype = loglog" option within the Proc Lifetest procedure in SAS software.

OS will be listed by patient.

10 Pharmacokinetics, Immunogenicity and Pharmacodynamics

10.1 Pharmacokinetics

The PK analysis set will be used for all PK summaries and listings. All analyses will be reported in the clinical study report (CSR) and/or a stand-alone report. The following summaries/analyses will be provided for PK concentration data:

- Listings of IMCnyeso concentrations by cohort, visits and nominal timepoint.
- Plot of average pre-dose concentrations versus End of infusion at Day 1 of each Cycle.
- Summary of descriptive statistics of IMCnyeso PK concentrations by nominal time point in pg/mL.
    - The statistics to be presented include the n, arithmetic and geometric mean, median, standard deviation (Std), coefficient of variation (%CV), minimum, and maximum.
- Concentration profile plots for individual patients by Phase and cohort.
- Arithmetic mean concentration profile plots by Phase and cohort (colored line for each cohort/expansion) with errors bars (SD).

For calculating summary statistics, the following considerations will be taken into account:

- Concentration values below lower limit of quantitation (LLOQ) will be handled as zero in summary statistics. Values <LLOQ will be reported as is in the data listing of collected PK concentrations. The LLOQ for IMCnyeso is 25 pg/mL.
- 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) for display purposes in the both the individual concentration profiles 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 (i.e. the min is >LLOQ).
- The %CV is calculated as (arithmetic standard deviation / arithmetic mean) × 100.

Pharmacokinetic parameters will be calculated by non-compartmental methods utilizing Phoenix WinNonlin (Certera version 8.2 or higher, Princeton, NJ, US) utilizing the linear/log trapezoidal methods. For parameter calculations, concentration values reported as LLOQ at pre-dose will be treated as zero (0), all other timepoints reported as LLOQ will be treated as missing. The following PK parameters will be calculated for individual patients where possible:

Cycle 1 Day 1

- Tmax – time to maximum concentration observed
- Cmax – maximum concentration observed
- AUClast – area under the concentration time profile from pre-dose to last measurable concentration

Cycle 1 Day 8

- Tmax – time to maximum concentration observed
- Cmax – maximum concentration observed
- AUCtau – area under the concentration time profile over the dosing interval

Cycle 1 Day 15

- Tmax – time to maximum concentration observed
- Cmax – maximum concentration observed
- AUCtau – area under the concentration time profile over the dosing interval

Additional PK parameters may be calculated as the analysts determines meaningful at the time of the analysis (e.g. clearance [CL], terminal elimination half-life [$t_{1/2}$], steady state volume of distribution [Vss], etc.)
The following summaries/analyses will be provided for PK parameters:

- Listings of pharmacokinetic parameters by cohort and dose (Cycle and Day).
- Summary of descriptive statistics of IMCnyeso PK parameters by cohort and dose

- The statistics to be presented include the n, arithmetic and geometric mean, median, standard deviation (Std), coefficient of variation (%CV), minimum, and maximum.

Any missing PK parameter data will not be imputed.

10.2 Immunogenicity

Anti-drug Antibody (ADA) analysis will be used to evaluate immunogenicity responses. The frequency of ADA at baseline and following treatment will be summarized. All analyses will be reported in the CSR and/or a stand-alone report.

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

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

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

- ADA status (Unevaluable, Positive, Negative)
- ADA Characterization (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

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 below.
- The number (%) of evaluable patients – see ADA Evaluable Subset definition below.
- The number (%) of patients who are ADA-positive at follow-up – see Overall ADA *incidence* definition below.
- The number (%) of patients who are ADA-negative at follow-up - see ADA Negative Subjects definition below.
- The number (%) patients with a treatment-induced ADA (from baseline negative) – see Treatment-induced ADA *incidence* definition below.

- The number (%) patients with a treatment-boosted (≥4-fold) (from baseline positive) - see Treatment-boosted (≥4-fold) ADA *incidence* definition below.
- 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.

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 9.6.3 of the protocol V4.0
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-	Subject in the ADA Evaluable Subset who has a Positive

fold) ADA	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).

10.3 **Pharmacodynamics**

Cytokines and lymphocytes are analyzed and are covered by this SAP. No other pharmacodynamics analysis would be performed.

11 Interim Analysis

No formal interim analysis is planned during Phase I. The BLRM will be updated after each dose-escalation cohort and the MTD / RP2D will be determined at the end of Phase I (see Section 3.1).

A formal interim analysis will be conducted during Phase II. ORR will be evaluated for the first 9 patients in each Phase II cohort to determine whether enrollment may continue (see Section 4.1).

12 Changes in the Planned Analysis

There were no substantial changes from the planned analyses described in the protocol version 4.0, dated 24 Feb 2020 to those presented in this SAP. The following minor detail has changed from the protocol:

- All Patients Set has been added to allow for additional disposition summaries to be conducted
- Safety RP2D Analysis Set has been added to allow for some analyses to be conducted on patients pooled across phases if they receive RP2D.

13 References

1. Neuenschwander B, Branson M, Gsponer T. Critical aspects of the Bayesian approach to phase I cancer trials. Stat Med. 2008;27:2420–2439.

14 Appendices

14.1 N-Continual Reassessment Method (N-CRM)

The N-CRM design updates a Bayesian Logistic Regression Model (BLRM) after each cohort of patients. At each decision point, the BLRM provides an estimate of all dose levels of IMCnyeso that do not exceed the MTD and incorporates all DLT information at all dose levels for this estimation (see Section 3.4). In general, the next dose will have the highest chance that the true DLT rate will fall in the target interval (16%–33%) and will always satisfy the EWOC principle (the next recommended dose or MTD should have less than 25% chance that the probability of DLT lies within the excessive toxicity band.). In all cases, the dose for the next cohort will not exceed a 3.34-fold increase from the previous dose. Smaller dose increases may be recommended by the Investigators and Sponsor upon consideration of all available clinical data.

For more information on the BLRM used to make dose recommendations for the Phase I dose escalation cohorts in this study, see appendix 13.3 in the protocol V4.0, the simulation plan, the simulation report and the simulation report addendums 1, 2 and 3.

14.2 Tables and Figures (planned)

Table 14.1.1.1 Patient Disposition – Phase I Full Analysis Set

Table 14.1.2.1.1 Analysis Sets – Phase I All Patients Set

Table 14.1.2.2.1 Important Protocol Deviations – Phase I Full Analysis Set

Table 14.1.3.1 Demographics and Baseline Characteristics – Phase I Full Analysis Set

Table 14.1.4.1.1 Medical History – Phase I Full Analysis Set

Table 14.1.4.1.2 Current Medical Medications – Phase I Full Analysis Set

Table 14.1.5.1 Cancer History – Phase I Full Analysis Set

Table 14.1.6.1 Prior Anti-cancer Therapy – Phase I Full Analysis Set

Table 14.1.6.2 Concomitant Medications – Phase I Full Analysis Set

Table 14.1.6.2.1 Concomitant Medications for Treatment Related Adverse Event – Phase I Full Analysis Set

Table 14.1.6.2.2 Concomitant Medications taken by at least 10% of patients – Phase I Full Analysis Set

Table 14.1.6.2.3 Concomitant Medications that Started within 1 day of the First Study Dose – Phase I Full Analysis Set

Table 14.1.6.2.4 Concomitant Medications that Started within 1 day of the Second Study Dose – Phase I Full Analysis Set

Table 14.1.6.2.5 Concomitant Medications that Started within 1 day of the Third Study Dose – Phase I Full Analysis Set

Table 14.1.6.3 Concomitant Medications by Preferred Term by more than 5% of patients – Phase I Full Analysis Set

Table 14.1.7.1 Drug Exposure – Phase I Safety Analysis Set

Table 14.1.8.1 Dose Interruptions and Reductions – Phase I Safety Analysis Set

Table 14.2.1.1.1 Best Overall Response – Summary of Status Phase I and Phase II Full Analysis Set

Table 14.2.1.1.2 Best Overall Response – Summary of Status Phase I & II Full Analysis Set

Table 14.2.2.1.1.1 Progression Free Survival – Summary of Status – Phase I and Phase II Full Analysis Set

Table 14.2.2.1.1.2 Progression Free Survival – Summary of Status – Phase I and Phase II Full Analysis Set

Table 14.3.1.6.1 Treatment-Emergent Adverse Events of Interest by System Organ Class and Preferred Term – Phase I Safety Analysis Set

Table 14.3.1.7.1.1 Treatment-Emergent Adverse Events Leading to Treatment Discontinuation by Preferred Term – Phase I Safety Analysis Set

Table 14.3.1.7.2.1 Treatment-Emergent Adverse Events Leading to Dose Interruption by Preferred Term – Phase I Safety Analysis Set

Table 14.3.1.7.3.1 Treatment-Emergent Adverse Events Leading to Dose Reduction by Preferred Term – Phase I Safety Analysis Set

Table 14.3.2.1.1.1 Serious Treatment-Emergent Adverse Events Regardless of Causality Overall by System Organ Class and Preferred Term - Phase I Safety Analysis Set

Table 14.3.2.1.2.1 Serious Treatment-Emergent Adverse Events Regardless of Causality Overall by Preferred Term - Phase I Safety Analysis Set

Table 14.3.2.1.3.1 Serious Treatment-Emergent Adverse Events Related to Study Drug by System Organ Class and Preferred Term - Phase I Safety Analysis Set

Table 14.3.2.1.4.1 Serious Treatment-Emergent Adverse Events Related to Study Drug by Preferred Term - Phase I Safety Analysis Set

Table 14.3.2.1.5.1 Adverse Event of Special Interest of Cytokine Release Syndrome - Phase I Safety Analysis Set

Table 14.3.2.2.1 Listing of Deaths – Phase I Safety Analysis Set

Table 14.3.4.1.1 Hematology Laboratory Data Overall - Observed Values and Change from Baseline - Phase I Safety Analysis Set

Figure 14.3.4.2.1.1 Hematology Laboratory Data Overall – Line plot of Absolute Values at Each Scheduled Time Point - Phase I Safety Analysis Set

Figure 14.3.4.2.2.1 Hematology Laboratory Data Overall – Line plot of Change from Baseline at Each Scheduled Time Point - Phase I Safety Analysis Set

Table 14.3.4.3.1.1 Hematology Laboratory Data – Shift Table for CTCAE Grades (Worst On-treatment vs. Baseline) - Phase I Safety Analysis Set

Table 14.3.4.3.2.1 Hematology Laboratory Data – Shift Table for Low/Normal/High Parameters (Worst On-treatment vs. Baseline) - Phase I Safety Analysis Set

Figure 14.3.4.4.1.1 Hematology Laboratory Data – Worst On-treatment vs Baseline Plot - Phase I Safety Analysis Set

Table 14.3.4.5.1 Biochemistry Laboratory Data Overall- Observed Values and Change from Baseline - Phase I Safety Analysis Set

Figure 14.3.4.6.1.1 Biochemistry Laboratory Data Overall – Line plot of Absolute Values at Each Scheduled Time Point - Phase I Safety Analysis Set

Figure 14.3.4.6.2.1 Biochemistry Laboratory Data Overall – Line plot of Change from Baseline at Each Scheduled Time Point - Phase I Safety Analysis Set

Table 14.3.4.7.1.1 Biochemistry Laboratory Data – Shift Table for CTCAE Grades (Worst On-treatment vs. Baseline)- Phase I Safety Analysis Set

Table 14.3.4.7.2.1 Biochemistry Laboratory Data – Shift Table for Low/Normal/High Parameters (Worst On-treatment vs. Baseline) - Phase I Safety Analysis Set

Figure 14.3.4.8.1.1 Biochemistry Laboratory Data – Worst On-treatment vs Baseline Plot - Phase I Safety Analysis Set

Table 14.3.5.1.1 Vital Signs Overall - Observed Values and Change from Baseline - Phase I Safety Analysis Set

Table 14.3.6.1.1 ECGs Overall - Observed Values and Change from Baseline - Phase I Safety Analysis Set

Table 14.3.6.2.1 ECGs – Shift Table for QTcF Abnormalities (Worst On-treatment vs. Baseline) - Phase I Safety Analysis Set

Table 14.3.7.1.1 ECOG Performance Status – Observed Values – Phase I Safety Analysis Set

Table 14.3.7.2.1 ECOG Performance Status – Shift Table - Phase I Safety Analysis Set

Table 14.3.8.1.1.1 Central Cytokine - Phase I Safety Analysis Set

Figure 14.3.8.2.1 Central Cytokine – Line plot of Absolute Values over Time - Phase I Safety Analysis Set

Figure 14.3.8.3.1 Pharmacokinetic concentration – individual patient profile plots on the log scale at C1D1 and C1D15 - Phase I PK Analysis Set

Table 14.3.9.1 Summary of [redacted] Parameters - Phase I PK Analysis Set

Table 14.3.10.1 Immunogenicity anti-drug antibody patient summary – Phase I Safety Analysis Set

Table 14.3.10.2 Immunogenicity anti-drug antibody study summary – Phase I Safety Analysis Set