Clinical Study 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

Sponsor:	Immunocore, Ltd. United Kingdom
EUDRACT Number:	2017-002243-15
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Development Phase:	I/II

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Protocol Versions:

Current:	v.4.0
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Previous:	v.3.0 (12 June 2019)
	v.2.0 UK (07 August 2018)
	v.2.0 (15 January 2018)
	v.1.0 (22 November 2017)

This study will be conducted in compliance with the Declaration of Helsinki (with amendments), and in accordance with local legal and regulatory requirements.

NCT03515551

PROTOCOL VERSION HISTORY

Version	Title	Date
1.0	Original Protocol	22 Nov 2017
2.0	Amendment 1	15 Jan 2018
2.0UK	Local UK Amendment 1	07 Aug 2018
3.0	Global Amendment 2	12 Jun 2019
4.0	Global Amendment 3	24 Feb 2020

GLOBAL AMENDMENT 3

Amendment Rationale

This amendment includes changes to improve patient safety and efficiency of dose escalation. The amendment also includes changes to simplify study logistics during Phase II while maintaining appropriate safeguards for patient safety. A detailed description of changes to the protocol and rationale for each change is provided in Section 13.5; key changes are summarized as follows:

Key Changes to the Protocol

1. Intra-patient escalation (IPE) regimens have been shown to improve tolerability of other CD3 bispecifics, including blinatumomab and the related ImmTAC molecule tebentafusp (Saber, 2017). Per Protocol Amendment 2, the Study Safety Team may initiate a 1-step or 2-step IPE regimen; a new higher dose level must be tested using a fixed-dose regimen before it is assessed in a 1-step IPE regimen and, similarly, a new higher dose level must be assessed using a 1-step IPE regimen before that dose can be assessed using a 2-step IPE regimen. However, it is anticipated that the risk to patients from acute mechanism-related toxicities is progressively reduced when moving from a fixed-dose regimen to a 1-step IPE regimen, and further reduced when moving from 1-step to a 2-step IPE regimen. Therefore, the dose-escalation rules have been updated, so that at any escalation step, a new permitted dose level based on the Bayesian Logistic Regression Model (BLRM) can be assessed using the same regimen as the prior cohort or using a regimen with additional steps. Furthermore, because ImmTAC-associated toxicities are generally acute, a 28-day DLT period will be used for all schedules.

2. Based on the observation that all signs/symptoms of cytokine release syndrome (CRS), to date, have occurred rapidly (within a few hours) following administration of IMCnyeso, once dose-escalation is completed and the Study Safety Team (SST) has reviewed all available relevant data for at least 6 patients at the recommended Phase II dose (RP2D), the SST may decide to reduce the minimum required post-end of infusion monitoring time to no less than 8 hours on Cycle 1 Day 1 (C1D1), C1D8, and/or C1D15 during the Phase II portion of the study. Such a decision will take into account the initial assessment of safety at the RP2D including whether treatment is well-tolerated at the selected RP2D and if any signs/symptoms of CRS occur within 2-4 hours post-end of infusion. Consistent with prior versions of the protocol, hospitalization would be extended if clinically indicated for any given patient.

3. Eligibility criteria were updated based on Investigator feedback as follows:

a. Patients with a clinically stable, asymptomatic Grade 2 endocrine disorder due to prior anticancer therapy (previously restricted to hypothyroidism) are permitted to be enrolled in the study

b. The minimum allowed creatinine clearance (calculated using Cockcroft-Gault formula or measured) was reduced from 50 mL/min to 40 mL/min

c. The washout period for oral antibiotics was reduced from 14 days to 7 days prior to the first dose of study drug (note: no change was made to the washout period for IV antibiotics).

4. Instructions for allowed and prohibited concomitant medications were edited to include guidance regarding vaccine use.

5. If dose escalation proceeds to a dose of >150 mcg according to BLRM output and treatment at this dose level is well-tolerated, additional BLRM simulations may be performed to predict rates of toxicity for higher dose levels.

GLOBAL AMENDMENT 2

Amendment Rationale

This amendment includes changes to improve study enrollment and efficiency while maintaining appropriate safeguards for subject safety. This amendment incorporates formatting changes, removes redundant information, and corrects inconsistencies and errors noted by sites working on the study. Changes made in Local United Kingdom (UK) Amendment 1 were incorporated globally in this amendment. A detailed description of changes to the protocol and rationale for each change is provided in Section 13.5; key changes are summarized as follows:

Key Changes to the Protocol

1. Description of potential risks was revised to incorporate emerging data from related molecules including the immune mobilizing T cell receptor against cancer (ImmTAC) IMCgp100). The cytokine release syndrome section was updated to include frequencies of relevant adverse events (AEs). Potential risks of hepatic and pulmonary events were added, as inflammation of tumors within the liver and lungs has been associated with AEs following treatment with other immunotherapies.

2. Added provision to allow enrollment in expansion cohorts to be increased from n=9 to n=24 (previously fixed at n=10), based on a Simon two-stage design, to enable a more robust assessment of efficacy. Updated the primary objective and endpoint for Phase II from additional characterization of safety to preliminary anti-tumor activity (best overall response [BOR] per Response Evaluation Criteria in Solid Tumors [RECIST v1.1]) and incorporated interim analysis.

3. Response will no longer be evaluated per modified immune-related RECIST (irRECIST). Treatment discontinuation will be required when unequivocal disease progression is confirmed (defined as an additional ≥ 5 mm increase in tumor burden (sum of diameters of both target and new lesions) and/or identification of additional new lesions, at least 4 weeks after the initial progressive disease (PD) assessment), aligning with more current standards (Seymour, 2017).

4. Standardized infusion duration for all cohorts to require a slower infusion on Cycle 1 Day 1 (C1D1; 2 hours) for all patients, with provisions to reduce the infusion time in subsequent infusions, to support patient safety and simplify protocol compliance.

5. Intra-patient dose-escalation approaches have proven beneficial for other CD3 bispecifics, including blinatumomab and the related ImmTAC molecule IMCgp100 (Saber, 2017). If the emerging safety profile indicates that treatment-related AEs

(eg, cytokine release) are more severe following initial doses and less severe after later doses, the Study Safety Team may initiate a 1-step or 2-step intra-patient escalation regimen and/or allow pre-medication. A longer dose-limiting toxicity (DLT) evaluation period and adjusted Cycle 1 schedule were added for patients receiving intra-patient escalation.

6. The first three patients at each dose level will be hospitalized for 2 nights after the first dose of IMCnyeso. After reviewing safety, pharmacokinetic (PK), and cytokine data from at least 3 patients enrolled at a given dose level, the Study Safety Team (SST) may decide that 1 night of hospitalization is adequate after the first dose for subsequent patients with longer hospitalization if indicated. ImmTACs have short (<24 hour) serum half-life and rapid pharmacodynamic effects; when a treatment-related AE occur, the onset is anticipated to be rapid (<24 hours post dose). Studies for the related ImmTAC molecule IMCgp100 require 1 night of hospitalization after the first dose.

7. The prior assumptions for the Bayesian Logistical Regression Model (BLRM) were updated to emphasize emerging clinical data rather than preclinical assumptions of maximum tolerated dose (MTD) in guiding escalation increments. Higher dose levels (up to 200 mcg) were included in the model. The operating characteristics, example dose levels, and potential escalation schemes were updated accordingly.

8. Eligibility criteria were organized for ease of use and updated based on Investigator feedback to allow enrollment of patients with Grade 2 hypophosphatemia due to prior cancer treatment (if receiving appropriate replacement therapy), Grade 2 hypothyroidism (if on stable replacement doses), Grade 2 lymphopenia, and Gilbert's syndrome. Laboratory criteria for hematology must be met with adequate washout from growth factors / transfusions. Laboratory criteria for electrolytes were removed. Washout for prior antibiotics reduced to 2 weeks prior to first dose (versus before start of Screening). Prior treatment requirements for Phase I were clarified. Washout for prior anti-cancer therapy clarified as for disease under study. Exclusion for patients with prior hypersensitivity to other biologic drugs or monoclonal antibodies was removed.

9. DLT criteria for Grade 3 liver function test elevations were adjusted to apply stricter criteria for high Grade 3 elevations while allowing more time for low Grade 3 elevations to resolve. DLT criteria for concurrent ALT/AST and bilirubin increases were aligned with Potential Hy's Law criteria. DLT criteria regarding amylase / lipase increase were added. DLT criteria for hypotension was modified to align with CRS treatment guidelines (vasopressor use does not automatically trigger DLT). The Sponsor must be notified within 24 hours of any serious adverse event (SAE), DLT, ≥ Grade 2 cytokine

release syndrome (CRS), or ≥ Grade 3 hepatic function abnormality (rather than notified immediately for any unexpected ≥ Grade 3 AE).

10. Allowed/prohibited concomitant medications was edited to provide more flexibility in modifying ongoing hypertensive medications, in cases where withholding anti-hypertensive medications is contraindicated, allow the monoclonal antibody denosumab (as supportive care for patients with bone metastasis), clarify that prohibition of anti-cancer therapies refers to systemic therapies for the cancer under study (eg, adjuvant tamoxifen for prior breast cancer would not be prohibited), allow corticosteroids for known allergy to contrast reagents, and allow SST to recommend pre-medication based on the emerging safety profile.

11. Toxicity management guidelines were updated to align with protocols for other ImmTAC molecules. Dose modification requirements were added for each toxicity and grade if not already present. Requirements for Sponsor notification were added. Cytokine-release syndrome (CRS) grading will follow the most recent consensus guidelines (Lee; 2019); additional information regarding the definition of CRS and recovery from CRS were incorporated in a new Appendix.

12. The schedule of assessment tables were reformatted for ease of use with a few clarifications. Acceptable time windows were added if not previously included and adjusted in some cases to improve operational feasibility. The frequencies of electrocardiogram (ECG), chemistry, hematology, and PK evaluations during later cycles and cytokine testing on Cycle 1 Day 22 were reduced; the revised plans are adequate to assess study endpoints.

13. Safety Follow-Up changed to 30 days, based on the <24-hour half-life of ImmTAC. Added safety assessments at the 30-day post-last-dose visit to allow evaluation of resolution of any abnormal findings or laboratory values at End of Treatment. Clarified that patients who initiate subsequent anti-cancer treatment will proceed directly to Survival Follow-Up. Any treatment-related SAE must be reported even if Safety Follow-Up has completed.

14. Additional [redacted] assessments [redacted] were incorporated to further characterize the pharmacodynamic effects of IMCnyeso treatment. Study objectives and endpoints, schedule, and rationale and description of assessments were updated accordingly.

15. On-study paired biopsies are required for ≥10 patients (previously all patients) in Phase II, as this provides an adequate number of biopsies to meet study objectives and allows enrollment of patients who cannot safely undergo multiple on-study biopsies. The

optimal timing for the on-treatment biopsy sample is between Cycle 1 Day 9 and Cycle 1 Day 16 (previously during Cycles 1 and/or 3, 1-3 days following dosing). Archival biopsies may be used to determine New York esophageal squamous cell carcinoma-1 (NY-ESO-1) / L antigen family member-1 isoform A (LAGE-1A) status throughout the study (previously new biopsies were required for Pre-Screening in Phase II). Added biopsied lesions may not be followed as target lesions for disease assessments per RECIST v1.1 unless the lesion is > 2 cm and, in the opinion of the Investigator, the biopsy will not appreciably impact the dimensions of the lesion.

Institutional Review Board/Independent Ethics Committee

A copy of this amended protocol will be sent to the Institutional Review Board (IRB) or Independent Ethics Committee (IEC) and Health Authorities. If the original protocol had been previously submitted and approved, the changes described in this amended protocol will require IRB or IEC approval. Changes herein are reflected in the Informed Consent.

LOCAL UK AMENDMENT 1

Amendment Rationale

This amendment updates the contraception requirement in the protocol to be consistent with Clinical Trial Facilitation Group recommendations.

The end of trial definition was updated to take into account assessment of the secondary endpoints of objective response rate, overall survival, progression-free survival and duration of response.

The criteria for study drug discontinuation was updated.

Changes to the Protocol

1. Update to contraception requirement in Section 6.14.1
2. Update to end of study definition in Section 3.6
3. Update to study drug discontinuation in Section 6.16.
4. Administrative update to the Sponsor emergency contacts on page 1.

Institutional Review Board/Independent Ethics Committee

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AMENDMENT 1

Amendment Rationale

This amendment will implement changes to the dose-limiting toxicity (DLT) definition and inclusion criteria.

As this is the first-in-human (FIH) assessment of the safety and tolerability of IMCnyeso and the safety profile is currently not known, the DLT definition will be modified to include any Grade 5 event of uncertain etiology. The DLT definition will be amended to specify that any death that is not clearly due to the underlying disease or extraneous causes will be considered a DLT.

Patients enrolled in this FIH clinical trial should have exhausted existing approved therapies. As recommended in the National Comprehensive Cancer Network guidelines for non-small cell lung cancer (NSCLC), patients with sensitizing epidermal growth factor receptor (EGFR) mutations or anaplastic lymphoma kinase (ALK) rearrangements should receive targeted therapy as first-line treatment. For the Dose-Escalation Phase (Phase I), inclusion criterion #9 ensures that enrolled patients are refractory or intolerant to all existing therapies. This amendment specifies for the Dose Expansion Phase (Phase II) that patients with NSCLC and an EGFR or ALK genomic tumor aberration must have disease progression after treatment with the approved targeted therapy for the specific aberration.

As this is the first clinical trial with IMCnyeso, any remaining [redacted] samples will be stored for additional testing to better understand the cancer, the drug response, or to validate diagnostic/[redacted] assays. Specification of storage duration for these samples has been added.

Changes to the Protocol

1. Additional DLT criterion added (Section 6.12)
2. Updated inclusion criteria #10 (Section 5.2) to require that during Phase II patients with NSCLC harboring ALK rearrangements or EGFR mutations have had prior treatment with Health Authority-approved targeted therapies
3. Duration of sample storage has been added (Sections 7.1, 7.10.2)
4. Additional emergency contact added on cover page
5. Corrected typographical errors and inconsistencies and inserted minor clarifications throughout to improve the readability and content presentation

Institutional Review Board/Independent Ethics Committee

A copy of this amended protocol will be sent to the Institutional Review Board (IRB) or Independent Ethics Committee (IEC) and Health Authorities. If the original protocol had been previously submitted and approved, the changes described in this amended protocol will require IRB or IEC approval. Changes herein are reflected in the Informed Consent.

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Protocol Signatures

Sponsor's Signatures

I have read the clinical study protocol and confirm that the protocol follows the current Good Clinical Practice guidelines.

Approved By:

[redacted]

24 FEB 2020

Date

Immunocore, Ltd.

PRINCIPAL INVESTIGATOR'S SIGNATURE

I, the undersigned, have reviewed the protocol, including the appendices, and I will conduct the clinical study as described and will adhere to the tripartite International Conference on Harmonisation (ICH) guideline E6 (R1): Guideline for Clinical Practice (GCP) and all the ethical and regulatory considerations stated.

The study will not commence without the prior written approval of an appropriately constituted Institutional Review Board (IRB) or Independent Ethics Committee (IEC). No changes will be made to the study without prior written approval of the Sponsor and the IRB/IEC, except where necessary to eliminate immediate hazard to the study subjects.

Signed By:

_____ _____

Principal Investigator Date

_____

Print Name

_____

Institution Name

PROTOCOL SYNOPSIS

Study Number	IMCnyeso-101
Title	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*02:01 Positive Patients with Advanced NY-ESO-1 and/or LAGE-1A Positive Cancer
Brief Title	Phase I/II, FIH/dose expansion study of IMCnyeso as monotherapy in HLA-A*02:01 positive Patients with Advanced NY-ESO-1 and/or LAGE-1A positive Cancer
Sponsor and **Clinical Phase**	Immunocore, Ltd. Phase I/II
Study Drug	IMCnyeso: HLA-A*02:01-restricted, NY-ESO-1- and LAGE-1A-specific soluble T cell receptor and scFv anti-CD3 bispecific molecule
Study Type	Interventional
Study Purpose and Rationale	IMCnyeso-101 is a Phase I/II multi-center, open-label, first-in-human (FIH), multi-ascending dose study of monotherapy IMCnyeso in human leukocyte antigen (HLA)-A*02:01 positive patients with advanced New York esophageal squamous cell carcinoma-1 (NY-ESO-1) and/or L antigen family member-1 isoform A (LAGE-1A) positive solid tumors. Patients with a diagnosis of non-small cell lung cancer (NSCLC), melanoma, urothelial carcinoma, or synovial sarcoma with antigen positivity for NY-ESO-1 and/or LAGE-1A are eligible for study participation. IMCnyeso is an immune mobilizing T cell receptor against cancer (ImmTAC), a bispecific protein therapeutic comprising a soluble, affinity-enhanced T cell receptor (TCR) fused to an antibody single-chain variable fragment (scFv). The IMCnyeso TCR recognizes a peptide from the tumor-associated antigen NY-ESO-1 and/or LAGE-1A, presented by HLA-A*02:01. Once the soluble TCR is engaged, the scFv effector end can bind to CD3 on any T cell, redirecting the T cell to produce effector cytokines and/or kill the cell presenting the target peptide. In addition, IMCnyeso-mediated tumor lysis may prime an endogenous anti-tumor immune response. NY-ESO-1 is expressed in a variety of human malignancies. Based on quantitative, real-time, reverse transcription polymerase chain reaction (qRT-PCR) testing of tumor samples conducted by the Sponsor, the frequency of expression of NY-ESO-1 and/or LAGE-1A is approximately 65% in synovial sarcoma, 35% in melanoma, 25% in urothelial carcinoma, and 15% in NSCLC. For patients with the advanced malignancies to be studied in this trial, few treatment options are available. IMCnyeso represents a novel approach for treating these patients.

Study Design	**Phase I Dose Escalation:** Dosing will begin with the minimum anticipated biological effect level (MABEL) dose as determined by in vitro toxicology studies. Cohorts will initially enroll 3 to 6 patients. If necessary and deemed appropriate by the Study Safety Team (SST), additional patients may be enrolled in a given cohort to make informed dosing decisions. Cohorts of 2 patients may be considered for the first 2 doses. The initial dosing of patients in Phase I will be staggered, with at least a 1-week interval between the first 2 patients treated at each dose level. Patients will be observed for dose-limiting toxicities (DLTs) for a period of 1 cycle (28 days). Dose-escalation or de-escalation decisions will be determined following review of all available safety, PK, and efficacy data, and the dosing recommendations will be primarily guided by the Bayesian Logistic Regression Model (BLRM). The key decisions of dose escalation or de-escalation and identification of the MTD and/or the RP2D will be made by the SST and will occur during the dose-escalation teleconferences (DETC), which will be held once all patients in a given dosing cohort have completed DLT evaluation. All dosing decisions will be agreed upon and documented in the DETC meeting minutes. The SST will include the Study Investigators, the Sponsor Medical Monitor, and a statistician. If the emerging safety profile indicates that the severity of cytokine-mediated AEs tends to become less severe following repeated dosing, the SST may initiate a 1-step or 2-step intra-patient escalation (IPE) regimen and/or allow pre-medication as these approaches have been beneficial for related therapeutics. Approximately 27 patients are predicted to be enrolled in Phase I. **Phase II Expansion:** 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 single-agent IMCnyeso at the RP2D in these disease settings. A Simon two-stage design will be used for each Phase II cohort. 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).
Study Treatment	IMCnyeso will be supplied as a sterile, frozen solution, in individual, single-use glass vials at a concentration of 0.5 mg/mL. IMCnyeso will be administered via weekly (QW) intravenous (IV) infusions. For each patient, the first dose will be infused over 2 hours (±15 minutes); for dose levels ≤ 30 mcg; the first dose infusion time may be reduced to 1 hour (±10 minutes). If the first dose is well tolerated without ≥ 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. For all study medication administration, a physician must be present at the site, or immediately available to respond to emergencies. Patients will be hospitalized for 2 nights following administration of the first dose (C1D1) of IMCnyeso and will remain at the site for overnight observation following the second dose (C1D8). After reviewing safety, PK, and cytokine data from at least 3 patients enrolled at a given dose level, the SST may decide that 1 night of hospitalization is adequate after the first dose for subsequent patients (with longer hospitalization if indicated). During Phase I, patients receiving IPE over three doses will be hospitalized overnight after each of the first three doses (C1D1, C1D8, and C1D15). The SST may decide to reduce the minimum required monitoring time during Phase II to no less than 8 hours post-end of infusion for C1D1, C1D8, and/or C1D15. Fully functional resuscitation equipment and medications to handle acute infusion-related emergencies (eg, anaphylaxis, cytokine release syndrome [CRS]) must be available at each study site.
Population Under Study	In Phase I, HLA-A*02:01-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, patients with HLA-A*02:01 positive and NY-ESO-1 and/or LAGE-1A positive advanced NSCLC, urothelial carcinoma, or synovial sarcoma will be enrolled and treated at the RP2D. Patients must meet all eligibility criteria to commence dosing.
Efficacy Assessments	Tumor response will be determined locally according to RECIST v.1.1. During the study, Immunocore may decide to have a central review of the radiological assessments performed.
Safety Assessments	Safety assessments will include physical examination, electrocardiogram (ECG), vital signs, weight, performance status, hematology, chemistry, coagulation, urinalysis, thyroid function, cytokine testing and the collection of AEs. Events of CRS should be assessed in accordance with the American Society of Transplantation and Cellular Therapy (ASTCT) Consensus Guidelines (Lee, 2019); all other AEs should be graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 4.03. The Investigator must notify the Sponsor within 24 hours of any SAE, DLT, ≥ Grade 2 CRS, or ≥ Grade 3 hepatic function abnormality. Based on the available IMCnyeso preclinical data and clinical safety information from the related ImmTAC molecule tebentafusp (IMCgp100), IMCnyeso may induce rash, tumor flare/pain, lymphopenia (associated with lymphocyte trafficking), and CRS. Conservative monitoring and management guidelines as well as definitions of DLT have been implemented.
Statistical Considerations	Categorical data will be presented as frequencies and percentages. For continuous data, mean, standard deviation, median, minimum, and maximum will be presented.

	In Phase I, the primary variable is the incidence of DLTs. An adaptive BLRM guided by the escalation with overdose control (EWOC) principle, which mandates the dose for the next cohort to have less than 25% chance of excessive toxicity, will be used to make dose recommendations and to estimate the MTD/RP2D. In Phase II, the primary variable is the best overall response (BOR) based on local Investigator assessment per RECIST v.1.1. A formal interim analysis will be performed for each Phase II cohort; ORR will be evaluated for the first 9 patients to determine whether enrollment may continue.
Keywords	ImmTAC, NY-ESO-1, LAGE-1A, melanoma, NSCLC, urothelial carcinoma, synovial sarcoma

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition of Term
ADA	Anti-drug antibody
AE	Adverse event
AESI	Adverse event of special interest
ALK	Anaplastic lymphoma kinase
ALT	Alanine aminotransferase
ANC	Absolute neutrophil count
AST	Aspartate aminotransferase
ASTCT	American Society for Transplantation and Cellular Therapy
AUC	Area under the curve
BLRM	Bayesian Logistic Regression Model
BOR	Best overall response
BP	Blood pressure
C#D#	Cycle # Day #
CD#	Cluster of differentiation #
CL	The total body clearance of drug from the plasma
C_{max}	Maximum observed concentration
CNS	Central nervous system
CR	Complete response
CRO	Contract research organization
CRS	Cytokine release syndrome
CT	Computed tomography
CTA	Cancer Testis Antigen
[redacted]	[redacted]
CTL	Cytotoxic T lymphocyte
CTLA-4	Cytotoxic T lymphocyte associated protein-4
DCR	Disease control rate
DDS	Dose-determining set
DETC	Dose-escalation teleconference
DLT	Dose-limiting toxicity
DNA	Deoxyribonucleic acid

Abbreviation	Definition of Term
DoR	Duration of response
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
EDC	Electronic data capture
EGFR	Epidermal growth factor receptor
EOT	End of treatment
EWOC	Escalation with overdose control
FAS	Full analysis set
FDA	Food and Drug Administration
FIH	First-in-human
FSH	Follicle-stimulating hormone
GCP	Good clinical practice
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
HLA	Human leukocyte antigen
HLA-A*02:01	Human leukocyte antigen-A*02:01
HLA-DR	Human leukocyte antigen-DR
HSA	Human serum albumin
ICANS	Immune effector cell-associated neurotoxicity syndrome
ICF	Informed consent form
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IFN-γ	Interferon-gamma
IHC	Immunohistochemistry
IL-#	Interleukin-# (eg, IL-6, IL-10)
ImmTAC	Immune mobilizing monoclonal T cell receptor against cancer
IPE	Intra-patient escalation
IRB	Institutional Review Board
IRS	Integrated response system

Abbreviation	Definition of Term
IUD	Intrauterine device
IUS	Intrauterine system
IV	Intravenous
kDa	Kilodalton
LAGE-1A	L antigen family member-1 isoform A
LAGE-1B	L antigen family member-1 isoform B
LFT	Liver function test
MABEL	Minimum anticipated biological effect level
[redacted]	[redacted]
MRI	Magnetic resonance imaging
MTD	Maximum tolerated dose
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
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	Pharmacokinetics
pM	Pico molar
PPS	Per-protocol set
PR	Partial response
QD	Every day
qRT-PCR	Quantitative, real-time, reverse transcription polymerase chain reaction
QTcF	QT interval corrected by Fredericia's method
QW	Every week
REB	Research ethics board

Abbreviation	Definition of Term
RECIST	Response Evaluation Criteria in Solid Tumors
[redacted]	[redacted]
RP2D	Recommended Phase 2 dose
SAE	Serious adverse event
SAP	Statistical Analysis Plan
scFv	Single-chain variable fragment
SD	Stable disease
SST	Study safety team
SUSAR	Serious unexpected adverse drug reaction
$t_{1/2}$	Terminal elimination half-life
TCR	T cell receptor
TIL	Tumor-infiltrating lymphocyte
T_{max}	Time of maximum concentration
TMTB	Total measured tumor burden
TNF-α	Tumor necrosis factor-alpha
[redacted]	[redacted]
UK	United Kingdom
ULN	Upper limit of normal
US	United States
WHO	World Health Organization

1 BACKGROUND

1.1 Overview of IMCnyeso

Immunocore is developing a new biological entity, IMCnyeso, for the treatment of advanced cancers that 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). IMCnyeso is an immune mobilizing T cell receptor against cancer (ImmTAC), a bispecific protein therapeutic comprising a soluble, affinity-enhanced T cell receptor (TCR) fused to an antibody single-chain variable fragment (scFv). One other investigational ImmTAC drug, tebentafusp (IMCgp100), is currently in development and being tested in patients with metastatic melanoma (Middleton, 2016).

1.2 Mechanism of Action of IMCnyeso

IMCnyeso is a 77 kilodalton (kDa) protein which is manufactured in *Escherichia coli.* Affinity and binding half-life data were generated using soluble proteins and surface plasmon resonance (BIAcore) methods, as shown in Figure 1-1.

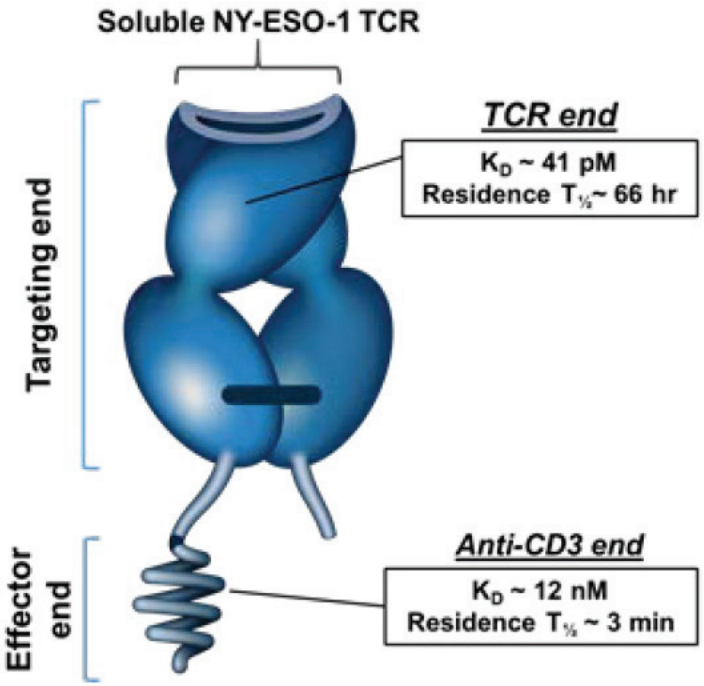

Figure 1-1: IMCnyeso Structure and Functional Domains

Anti-CD3 = anti-cluster of differentiation 3; K_D = dissociation constant; LAGE-1A = L antigen family member-1 isoform A; NY-ESO-1 = New York esophageal squamous cell cancer-1; $T_{½}$ = half-life; TCR = T cell receptor.

The targeting portion of IMCnyeso (the soluble TCR) binds to a peptide fragment of the NY-ESO-1 or LAGE-1A tumor antigen presented by human leukocyte antigen (HLA)-A*02:01 on the surface of cancer cells (Liddy, 2012). HLA molecules are polymorphic; the HLA-A*02:01 allele is expressed by approximately 40% to 50% of the Caucasian population in the Western World (http://www.allelefrequencies.net/). The scFv effector end can bind to CD3 on any T cell, redirecting the T cell to produce effector cytokines and/or kill the cell presenting the target (see Figure 1-2). In addition, IMCnyeso-mediated tumor lysis may prime an endogenous anti-tumor immune response.

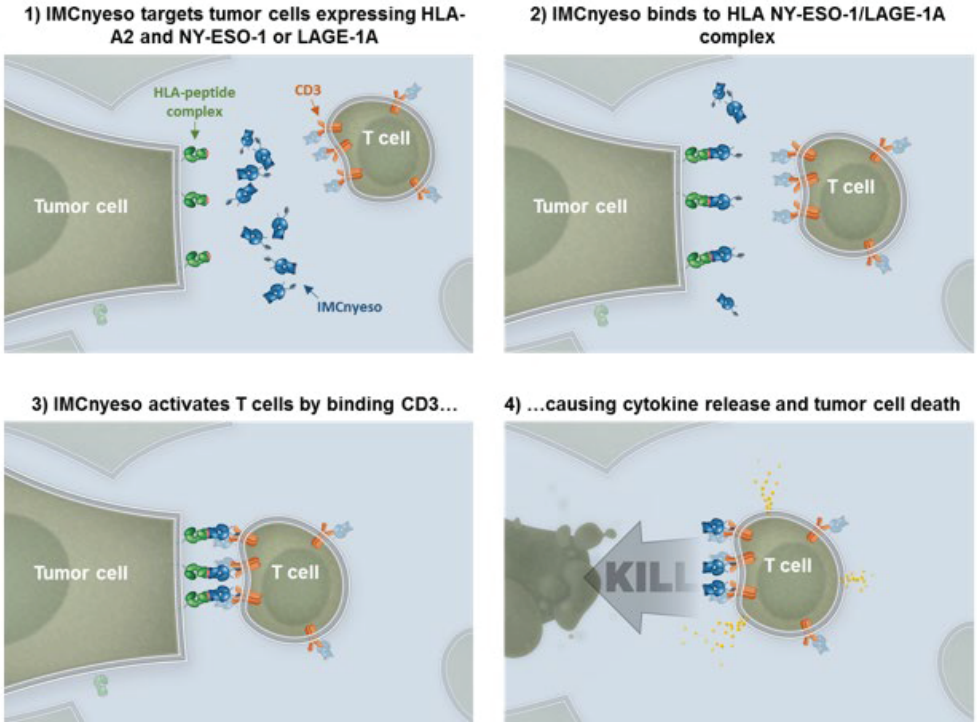

Figure 1-2: Schematic Representation of IMCnyeso Mechanism of Action

CD3 = cluster of differentiation 3; HLA = human leukocyte antigen; LAGE-1A = L antigen family member-1 isoform A; NY-ESO-1 = New York esophageal squamous cell carcinoma-1.

1.2.1 New York Esophageal Squamous Cell Carcinoma-1 and L Antigen Family Member-1 Isoform A

The peptide recognized by IMCnyeso is found in NY-ESO-1 and LAGE-1A (Figure 1-3). In contrast, a related tumor antigen, L antigen family member-1 isoform B (LAGE-1B) does not contain the specific peptide recognized by IMCnyeso molecule.

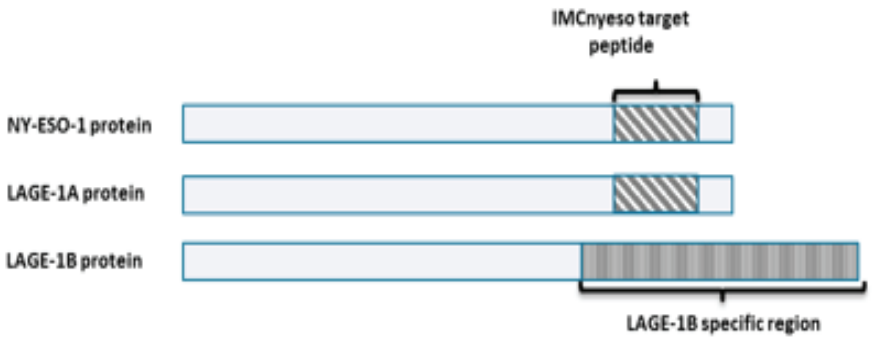

Figure 1-3: Comparison of NY-ESO-1, LAGE-1A, LAGE-1B Protein, and Peptide Expression

LAGE-1A = L antigen family member-1 isoform A; LAGE-1B = L antigen family member-1 isoform B; NY-ESO-1 = New York esophageal squamous cell carcinoma-1.

Expression of NY-ESO-1 and LAGE-1A is restricted to cell types related to human testis and human cancers. The testis is not susceptible to systemic T cell responses and is considered immune-privileged (Zhao, 2014). NY-ESO-1 and LAGE-1A are aberrantly expressed in a wide range of cancer indications at varying frequencies (Nicholaou, 2006; National Cancer Institute, 2017). For these reasons, NY-ESO-1 / LAGE-1A is an attractive target in cancer immunotherapy.

1.3 Non-Clinical Experience with IMCnyeso

The hypothesis of the IMCnyeso preclinical and clinical development programs is that tumors with high expression of the NY-ESO and/or LAGE-1A antigen would be most sensitive to the mechanism of action of IMCnyeso: T cell redirection against cells presenting the HLA-A*02:01-restricted NY-ESO-1 / LAGE-1A peptide.

The soluble TCR targeting end of IMCnyeso is highly specific for human NY-ESO-1 / LAGE-1A peptide presented by human HLA-A*02:01 and does not bind to peptide/HLA complexes from non-human species. The anti-CD3 effector end of IMCnyeso is specific for human CD3 and does not bind to or activate T cells from other species. Therefore, there is no relevant species in which IMCnyeso pharmacology or toxicology can be tested, and the relevance of non-human pharmacokinetic (PK) studies are considered limited.

1.3.1 Non-Clinical Pharmacology of IMCnyeso

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:

- IMCnyeso could redirect T cell activity to tumor cells that express NY-ESO-1 and/or LAGE-1A.
- 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, and proliferation and expansion of T cells.
- T cell activation occurs from 5 picomolar (pM) IMCnyeso and the induction of target-cell killing from 10 pM. Above this concentration, tumor cell killing increases in a dose-dependent fashion, reaching a plateau at 1 nanomolar (nM). These assays were used to determine the minimum anticipated biological effect level (MABEL) and the starting dose for this study (see Section 6.9).

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.

1.3.2 IMCnyeso Single-Agent Pharmacokinetics

Preclinical PK studies allow determination of parameters including the maximum observed concentration (C_{max}), the time of maximum concentration (T_{max}) to C_{max}, the mean residence time, half-life in the plasma, and clearance. Together, these PK data can be modelled to form a basis for predictions of how the drug may be dealt with by the human body. When examined alongside distribution and excretion studies these models may provide insight into the fate of IMCnyeso following administration.

A single-dose, intravenous (IV) PK study was conducted in C57BL/6 mice. Nine mice were flat dosed (0.1 mg/kg) followed by micro-sampling over 24 hours (Report GSK01-IMC076). Data indicate a C_{max} 1.33 mcg/mL, and a $t_{1/2}$ of approximately 2 hours.

1.3.3 Non-Clinical Toxicology of IMCnyeso

In the absence of a relevant toxicology species, IMCnyeso was investigated for potential reactivity to normal tissues in vitro. Given the testis-restricted expression profile of NY-ESO-1 and LAGE-1A, these assays were a measure of the specificity of IMCnyeso to antigen-negative tissues.

ImmTAC tissue cross-reactivity studies with IMCnyeso give no evidence of cross-reactivity of IMCnyeso with a standard panel of normal human tissues. Normal tissue immunohistochemistry (IHC) studies using a commercially available antibody that recognizes NY-ESO-1 were performed to better understand the protein expression of NY-ESO-1 in normal tissues and thus the potential for tissue cross-reactivity. These studies provide evidence for strong NY-ESO-1 protein expression in human testis, as expected with the expression profile of a cancer-testis antigen gene. Weak staining was observed with infrequent cells of the spinal cord and cerebral cortex indicating there may be rare but low expression of the NY-ESO-1 protein found in the central nervous system (CNS).

The tissue type to exhibit activity with the lowest concentration of IMCnyeso was normal melanocytes (500 pM); however, higher concentrations of IMCnyeso (approximately 100-fold greater than the minimal anticipated biological effect level, MABEL) were required to elicit an effect in these normal tissue cells (as compared with tumor cell assays). These data indicate that there is a therapeutic window between a dose of drug required to effect NY-ESO-1 and/or LAGE-1A positive cancer cells and the doses that may cause potential organ-specific toxicity. Additionally, with some healthy donors tested, low levels of cytokines (ie, tumor necrosis factor-alpha [TNF-α] and interferon-gamma [IFN-γ]) were detected when IMCnyeso was incubated with fresh whole blood at concentrations 50–100 fold above the MABEL. However, this activity was not broad and was low level indicating that even at these higher levels of drug, IMCnyeso is unlikely to cause general broad cytokine release syndrome (CRS). Collectively, these data suggest that monitoring blood cytokines and skin toxicity will be important when making dose-escalation decisions regarding IMCnyeso.

1.3.4 Non-Clinical Safety Summary

In the absence of a relevant toxicology species, IMCnyeso was investigated for potential reactivity to tissues other than NY-ESO-1/LAGE-1A positive tissue (ie, testes) in vitro. Findings can be summarized as follows:

- The use of IHC with 37 human tissue samples did not reveal any cross-reactivity against any of the tissue sections for the TCR portion of IMCnyeso. Binding via the anti-CD3 portion of IMCnyeso to lymphatic cells was observed as expected.

- NY-ESO-1 protein expression was determined by IHC with 37 human tissue samples using a commercially available antibody where strong expression was detected in the immune-privileged testis. Low and infrequent expression was detected in cells within the spinal cord and cerebral cortex, in more than 1 donor. Expression of LAGE-1A protein could not be determined due to the lack of specific reagents, however ribonucleic acid (RNA) analysis in publicly available datasets and literature studies have indicated that the expression profile of LAGE-1A is very similar to NY-ESO-1 in normal tissues.

- IMCnyeso did not cause significant reactivity within the anticipated clinical dose range against a panel of HLA-A*02:01 positive, NY-ESO-1/LAGE-1A negative normal cells derived from various normal tissue types.

- The tissue type to exhibit activity with the lowest concentration of IMCnyeso was normal melanocytes (500 pM, approximately 100-fold greater than the minimal anticipated biological effect level, MABEL).

- Within the anticipated clinical dose range, IMCnyeso did not cause broad cytokine release against whole blood.

- Within the anticipated clinical dose range, IMCnyeso did not cause reactivity against platelets or cells displaying most other known HLA types (allo-reactivity).

1.4 Clinical Safety and Experience

This is the first-in-human (FIH) study of IMCnyeso. As of 22Jan2020, 15 patients have been enrolled and treated (n=4 at 3 mcg; n=3 at 10 mcg; n=5 at 30 mcg, and n=3 at 100 mcg). No dose-limiting toxicity (DLT), treatment-related ≥ Grade 3 adverse event (AE), AE leading to discontinuation, or fatal AE has been reported. Treatment-related serious AEs (SAEs) were reported in 2 patients; a Grade 1 overdose (attributed to dose-preparation error) was reported in Cohort 1 (3 mcg) and an event of Grade 2 CRS was reported in Cohort 4 (100 mcg). The most commonly reported AEs (including reported signs and/or symptoms of CRS) were headache (n=10, 67%) and fatigue and pyrexia (each n=9, 60%). These data are from an ongoing study, are not fully validated, and potentially subject to change prior to final database lock. Characterization of safety, tolerability, PK, pharmacodynamics, and efficacy are ongoing.

Based on the available IMCnyeso preclinical data, the IMCnyeso mechanism of action, and clinical safety information from the tebentafusp clinical trials, IMCnyeso may elicit the following adverse drug reactions:

Cytokine Release Syndrome: Release of pro-inflammatory cytokines (eg, IL-6, IFN-γ, TNF-α) is a predicted pharmacodynamic effect of IMCnyeso. Based on experience with tebentafusp,

symptoms such as pyrexia, chills, nausea, hypotension, and edema were observed in most patients, typically 4-24 hours after the first 2-3 doses. As of August 2018, 2% of patients in the IMCgp100-102 study experienced severe (Grade 3) CRS with tebentafusp. Based on a shared mechanism of action with tebentafusp and non-clinical assessments of both molecules in whole blood assays, the risk of CRS with IMCnyeso is anticipated to be similar to tebentafusp. Fully functional resuscitation equipment and medications to handle acute infusion-related emergencies (eg, anaphylaxis, CRS) must be available at each study site. Patients will be hospitalized after the initial doses of IMCnyeso for monitoring (see Section 6.2). Scheduled samples will be taken for cytokine monitoring and additional samples should be taken in the event of suspected CRS. The protocol provides instructions on the recognition and conservative management of associated symptoms.

Rash/Pruritus and Skin Toxicity: Effects in human melanocytes were noted in the non-clinical toxicology studies at IMCnyeso concentrations of 500 pM (100-fold above MABEL). In this FIH study, special attention is placed on the monitoring of adverse effects of IMCnyeso in the skin and conservative management guidance and DLT criteria are implemented for the effects of IMCnyeso in the skin.

Local tumor inflammation: Based on the mechanism of action of IMCnyeso, it may cause inflammation within the tumor microenvironment. Depending on the location of the tumors, various AE may occur, including:

- **Hepatic Events:** Increased transaminase levels may be observed, especially in patients with liver metastasis. Increased bilirubin may also be observed.
- **Pulmonary Events:** Patients with lung metastasis may experience events such as dyspnea, pulmonary edema, pulmonary infiltrates, or pleural effusion.
- **Tumor Flare/Pain**: Severe pain at the site of known tumors is predicted with IMCnyeso, especially following the first 1–4 weekly (QW) doses. Patients receiving tebentafusp have required admission for IV pain medication.

Lymphopenia: Monitoring of patients' white cell counts will be conducted during the study of IMCnyeso. It is important to note that the trafficking of lymphocytes is a desired effect of IMCnyeso. The lymphopenia observed with tebentafusp has been shown to be transient and self-resolving, with lymphocyte counts returning to baseline levels by Day 8.

Full details can be found in the single reference safety document, which is the current IMCnyeso Investigator's Brochure.

1.5 NY-ESO-1 and LAGE-1A Patient Screening Strategy

IMCnyeso targets the same peptide derived from both the NY-ESO-1 and LAGE-1A proteins. Based on in-house and publicly available gene expression datasets (The Cancer Genome Atlas, http://cancergenome.nih.gov/), it is known that tumors may express NY-ESO-1, but not LAGE-1A. They may express LAGE-1A, but not NY-ESO-1, and they may express both antigens, or neither one. While the frequencies of these expression patterns vary between indications, a significant fraction of tumors in each relevant indication do not express either target protein. In addition, there is substantial intra-tumor heterogeneity of expression of positive tumor cells ranging from 0%–100%. Both factors necessitate selecting patients for trial inclusion based on the level of NY-ESO-1 and LAGE-1A expression.

While specific antibodies are available for NY-ESO-1, they are not available for LAGE-1A. Thus, a protein-based (immunohistochemistry [IHC]) patient selection assay is not appropriate for the detection of expression of both target antigens. As a result, the Sponsor has developed a quantitative, real-time, reverse transcription polymerase chain reaction (qRT-PCR) assay to detect gene expression of both NY-ESO-1 and LAGE-1A.

The cut-point for each antigen was determined from a constellation of data including expression in human metastatic tumors and normal human tissues, in vitro efficacy assays, and quantitative, real-time, reverse transcription polymerase chain reaction (qRT-PCR) validation studies with human tumor samples.

Based on both IHC and qRT-PCR (NY-ESO-1) and qRT-PCR (LAGE-1A) testing of tumor samples conducted by the Sponsor, the frequency of expression of NY-ESO- 1 and/or LAGE-1A is approximately 65% in synovial sarcoma, 35% in melanoma, 25% in urothelial carcinoma, and 15% in non-small lung cell lung cancer (NSCLC); note that expression frequencies are significantly lower in uveal melanoma and NSCLC adenocarcinoma (Immunocore internal data).

The assay used for patient selection for NY-ESO-1 and/or LAGE-1A positive tumor samples is an investigational device and is only to be used to determine inclusion in this study protocol.

1.6 Overview of Disease Setting

The targeted indications will include patients with advanced NSCLC, melanoma, urothelial cancer, or synovial sarcoma that are refractory or resistant to standard treatment regimens, or for which no standard treatment exists. The unmet therapeutic need for these patients remains high and access to novel targeted therapies, such as IMCnyeso, may provide clinical benefit.

1.6.1 Non-Small Cell Lung Cancer

NSCLC accounts for approximately 85% of all lung cancers. Histologically, NSCLC is divided into adenocarcinoma, squamous cell carcinoma, and large cell carcinoma. NSCLC is often insidious, producing no symptoms until the disease is well advanced. At initial diagnosis, 20% of patients have localized disease, 25% of patients have regional metastasis, and 55% of patients have distant spread of disease. Over 200,000 new cases and over 150,000 deaths are expected from lung cancers in the United States (US) in 2017 (American Cancer Society, 2017).

Surgery, chemotherapy, and radiation are the main treatment options for localized NSCLC (Pallis, 2012). Only 30%–35% of patients with NSCLC present with sufficiently localized disease at diagnosis that curative, surgical resection may be attempted, and approximately 50% of patients who undergo surgical resection experience local or systemic relapse. Thus, approximately 80% of all patients with lung cancer are considered for systemic therapy at some point in their illness.

The first-line treatment for NSCLC can include a platinum combination in all patients or immunotherapy with immune checkpoint inhibition, with pembrolizumab (Keytruda® [Merck]; a programmed death 1 [PD-1] inhibitor) in patients with programmed death-ligand 1 (PD-L1) positive disease. Patients with NSCLC that overexpress the epidermal growth factor receptor (EGFR) have been shown to have increased resistance to therapy and are suitable for treatment with EGFR tyrosine kinase inhibitors such as Gefitinib (Iressa®) and erlotinib (Tarceva®) (Derman, 2015). These drugs have improved survival rates compared with placebo in the second- and third-line setting. The presence of an anaplastic lymphoma kinase (ALK) gene rearrangement in NSCLC is associated with responsiveness to ALK tyrosine kinase inhibitors, with recent studies demonstrating improved efficacy of alectinib (Alecensa® [Genentech]) over crizotinib (Xalkori® [Pfizer]) in the first-line setting (Peters, 2017).

In addition to the first-line setting, immune checkpoint inhibitors have gained increasing importance in NSCLC therapy across treatment lines. Nivolumab (Opdivo® [Bristol-Myers Squibb]) is a monoclonal antibody inhibitor of PD-1/PD-L1 approved for use in NSCLC with squamous pathology in October 2015 (Zappa, 2016). Pembrolizumab was approved for metastatic NSCLC in October 2015, and in 2017, in combination with pemetrexed. In addition, atezolizumab (Tecentriq® [Roche], a PD-L1 inhibitor) was approved in October 2016, for patients with metastatic NSCLC who have disease progression during or following platinum-containing chemotherapy.

1.6.2 Melanoma

Malignant melanoma continues to represent a major public health problem globally. Approximately 87,110 new diagnoses of melanoma and almost 10,000 deaths are expected in the US in 2017 (American Cancer Society, 2017). The rising incidence of melanoma combined with

poor outcomes with standard chemotherapy (10%–15% response rate) has led to intense investigation of novel approaches using immunotherapy and various combinations in an attempt to enhance the anti-tumor immune response.

Until 2011, the alkylating agent, dacarbazine, was the standard of care for patients, despite the lack of survival benefit. However, due to an improved understanding of the biology of melanoma and the discovery of oncogenic mutations contributing to disease progression (eg, BRAF mutations), the BRAF kinase inhibitor, vemurafenib (Zelboraf® [Genetech]), was approved by the Food and Drug Administration (FDA) in 2011, and a second BRAF inhibitor, dabrafenib (Tafinlar® [Novartis]), was approved in 2013. Both drugs demonstrated an overall survival (OS) improvement and a response rate of nearly 50% in clinical trials (Shih, 2015; Johnson, 2015). However, responses to treatment with BRAF inhibitors alone or in combination with MEK pathway inhibitors are generally of a shorter duration than those responses noted with checkpoint immunotherapy. During tumorigenesis, cancer cells from a wide range of tumor types exploit the immune checkpoint pathways (eg, PD-1, PD-L1 and cytotoxic T lymphocyte associated protein 4 [CTLA-4]) to avoid detection by the adaptive immune system (Murphy, 2016; Chen, 2013). Blockade of immune checkpoint inhibitors such as CTLA-4, PD-1, and PD-L1 have recently been shown to have significant clinical activity in melanoma, leading to the approval of a new treatments, which include the PD-1 inhibitors, pembrolizumab and nivolumab, as well as ipilimumab, a CTLA-4 inhibitor.

1.6.3 Urothelial Carcinoma

Urothelial cancers encompass carcinomas of the bladder, ureters, and renal pelvis, which occur at a ratio of 50:3:1, respectively. Patients with cancer of the upper urinary tract have a 30%–50% chance of developing cancer of the bladder at some point in their lives. However, patients with bladder cancer have only a 2%–3% chance of developing cancers of the upper urinary tract. In the US in 2017, it is estimated that there will be 146,650 new diagnoses of urinary system cancers, with an estimated 79,030 of these being bladder cancer, and approximately 32,190 deaths, making urothelial cancer the fourth most common malignancy in American men, and the ninth most common in women (American Cancer Society, 2017).

Approximately 25% of patients with urothelial carcinoma will have muscle-invasive disease and either present with or later develop metastases. Systemic chemotherapy is the standard approach for the initial treatment of patients with inoperable, locally advanced or metastatic urothelial malignancies. Although initial response rates are high, the median survival with multi-agent chemotherapy (cisplatin and gemcitabine or carboplatin and gemcitabine or M-VAC [methotrexate, vinblastine, doxorubicin and cisplatin]) shows an increase in long-term survival compared to treatment with cisplatin alone (Yafi, 2011).

Checkpoint inhibitor immunotherapy has offered an additional option for patients progressing after their initial systemic cytotoxic therapy (Wu, 2015). In February 2017, the FDA granted accelerated approval to nivolumab (Opdivo®) for the treatment of patients with locally advanced or metastatic urothelial carcinoma who have disease progression during or following platinum-containing chemotherapy or have disease progression within 12 months of neoadjuvant or adjuvant treatment with a platinum-containing chemotherapy. In addition, multiple PD-1 and PD-L1 inhibitors have been approved in this setting.

1.6.4 Synovial Sarcoma

Synovial sarcoma is the fourth most common type of soft tissue sarcoma (STS) and the synovial subset represents approximately 5%–10% of all soft tissue sarcomas. Approximately 700 to 1200 new cases of synovial sarcoma are expected in the US in 2017 (American Cancer Society, 2017). It generally arises in the extremities (approximately 70% of cases) from undifferentiated mesenchymal stem cells (Thway, 2014; Kimura, 2016).

Standard treatment for localized synovial sarcoma is tumor resection, frequently accompanied by radiotherapy and/or chemotherapy. There is a high incidence of late metastasis, occurring in up to 50% of patients (Krieg, 2011). Common sites of metastasis include lung (80%), bone (9.9%), and liver (4.5%) (Vlenterie, 2016). There are currently no approved systemic therapies for synovial sarcoma and no consensus treatment guidelines. An anthracycline / ifosfamide combination is commonly used for first-line treatment (Riedel, 2018).

Beyond the first-line chemotherapy treatment, the options are more limited and include multiple single-agent and combination chemotherapy, although this setting represents an area of high, unmet medical need. Some sarcomas express highly immunogenic antigens and although previous immunotherapy attempts in sarcomas have largely been disappointing, more recently immunotherapy has regained significant attention and novel targets and immunotherapeutic strategies are being investigated. Recent data with NY-ESO-1 specific TCR transduced autologous T cells (NY-ESO SPEAR® TCR) suggest that immune activation against the NY-ESO-1 antigen may provide therapeutic benefit to patients with prior therapy and expression of the antigen (Mackall, 2017). Other immunotherapy options include checkpoint inhibitors (PD-1/PD-L1), vaccine therapies and adoptive immunotherapy approaches (Mitsis, 2016).

2 STUDY RATIONALE

2.1 Rationale for Study Design

This study is an open-label, Phase I/II FIH, dose escalation/expansion study of single-agent IMCnyeso in HLA-A*02:01 positive patients with advanced NY-ESO-1 and/or LAGE-1A positive NSCLC, melanoma, urothelial cancer, or synovial sarcoma.

In the Phase I portion of the study, the Bayesian Logistic Regression Model (BLRM) guided by the escalation with overdose control (EWOC) principle will be used to guide dose-escalation decision making and to determine the maximum tolerated dose (MTD) of IMCnyeso as monotherapy in NSCLC, melanoma, urothelial cancer, and synovial sarcoma patients. The adaptive BLRM EWOC method controls the risk of DLTs in future patients on study. This approach is likely to provide a more accurate estimate of the MTD than a 3 + 3 design.

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. The SST will be guided by the adaptive Bayesian methodology. Dosing decisions will be made following review of all available data, including safety, PK, and efficacy data (see Section 6.10).

The Phase II expansion cohorts are designed to make a preliminary assessment of the anti-tumor activity of single-agent IMCnyeso at the recommended Phase 2 dose (RP2D) in NSCLC, urothelial carcinoma, and synovial sarcoma.

2.2 Overall Benefit-Risk Assessment

The study is being conducted with several parameters identified to maximize the benefit of and minimize the risks to patients enrolled in the study. There is significant unmet need for therapies that provide durable clinical benefit to patients with advanced NSCLC, urothelial carcinoma, or melanoma who have progressed following treatment with PD-1 / PD-L1-targeted therapy, and for patients with metastatic synovial sarcoma. T cell-based therapy and immunotherapies in general have produced profound clinical effects in patients with advanced cancers across a range of diagnoses.

Measures taken to minimize the risks to patients participating in the study include eligibility criteria designed to exclude patients at potentially high risk for experiencing treatment-related toxicity (Section 5), staggered dosing of the first 2 patients in each cohort (Section 3.2), conservative dose-escalation guidelines with implementation of a Bayesian dose-selection parameter and overdose control (Section 6.10), as well as management guidance and stopping rules for potential IMCnyeso-related AEs (Section 6.15).

Based on these measures, the Sponsor believes that the benefit-risk ratio for patients enrolled in this study is positive (IMCnyeso-101 FIH Study, "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").

3 STUDY DESIGN

IMCnyeso-101 is a Phase I/II, multi-center, open-label, FIH, multi-ascending dose study of monotherapy IMCnyeso in HLA-A*02:01 positive patients with advanced NY-ESO-1 and/or LAGE-1A positive solid tumors.

The study will be conducted in 2 phases (see Figure 3-1).

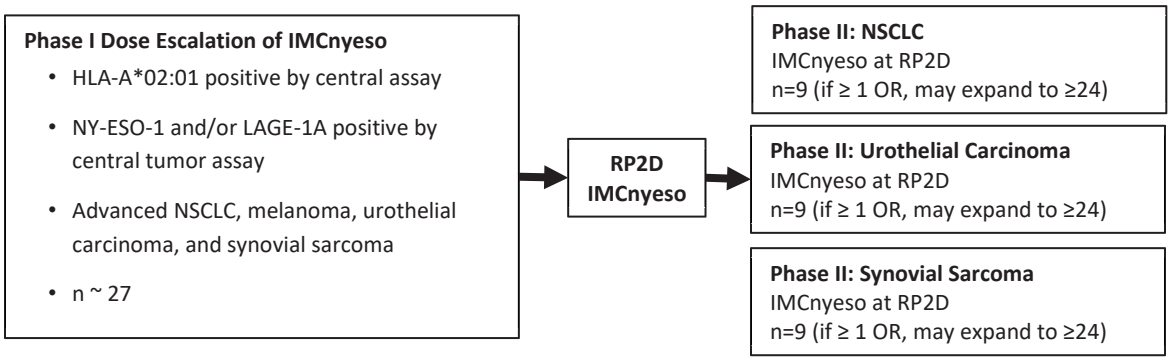

Figure 3-1: IMCnyeso-101 Study Design

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

3.1 Phase I Dose Escalation

Phase I dose escalation will enroll patients with advanced NSCLC, melanoma, urothelial carcinoma, or synovial sarcoma. The primary objective is to determine the MTD and/or RP2D of IMCnyeso as a monotherapy in these patients.

Cohorts will initially enroll 3–6 patients. If necessary and deemed appropriate by the SST, additional patients may be enrolled in a given cohort to make informed dosing decisions. Cohorts of 2 patients may be considered for the first 2 doses. If any ≥ Grade 2 toxicities suspected related to IMCnyeso are observed during the first 2 cohorts, the cohorts should then be expanded following a discussion among the SST. Dosing will start with 3 mcg, which is the MABEL, as determined by in vitro toxicology studies (see Section 6.9). Phase I is estimated to enroll approximately 27 patients (see Section 9.9.1).

The initial dosing of patients in dose-escalation will be staggered, with at least a 1-week interval between the first 2 patients treated at each dose level. The integrated response system (IRS) will be used to control patient allocation to treatment and ensure the dosing intervals and cohort recruitment complies with the protocol.

The key decisions of dose escalation or de-escalation and identification of the MTD and/or the RP2D will be made by the SST and guided by the BLRM, as discussed in Section 6.10.

3.2 Phase II Dose Expansion

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, as discussed in Section 9.9.2.

3.3 Patient Population

In Phase I, HLA-A*02:01-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*02:01 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. All patients meet all eligibility criteria (see Section 5).

3.4 Definition of Study Periods

The study is made up of 6 study periods: (1) Pre-screening, (2) Screening, (3) Treatment, (4) Safety Follow-Up, (5) Disease Progression Follow-Up, and (6) Survival Follow-Up. The individual study periods are described in Section 7.

3.5 End of Treatment

IMCnyeso will be administered according to the protocol-defined regimen until the patient meets criteria for treatment discontinuation described in Section 6.16.

3.6 Definition of End of Study

An individual patient may end participation in the study for reasons listed in Section 6.19.

The planned end of the study occurs when:

- A minimum of 80% of patients have completed the follow-up for disease progression or have discontinued the study for any reason,
- All patients have completed treatment and the Safety Follow-Up Period, and
- The endpoints of best overall response (BOR), OS, progression-free survival (PFS), and duration of response (DoR) have been adequately assessed in all subjects.

Please refer to Section 9 for details of timing of the primary analysis and final reporting of data.

3.7 Early Study Termination

The study can be terminated at any time, for any reason by the Sponsor. Should this be necessary, any ongoing patient should be seen as soon as possible for an End of Treatment (EOT) visit (see Section 7.3).

The Investigator may be informed of additional procedures to be followed to ensure that adequate consideration is given to the protection of the patient's interests. Under guidance of the Sponsor, the Investigator will be responsible for informing the Institutional Review Board (IRB) and Independent Ethics Committee (IEC) of the termination of the study.

3.8 Post-Study Access to Treatment

As IMCnyeso is an investigational medication and not currently licensed for sale in any region, the drug is not available to patients outside of the study protocol.

4 STUDY OBJECTIVES AND ENDPOINTS

Study objectives and corresponding endpoints are shown in Table 4-1.

Table 4-1: Study Objectives and Endpoints

Objectives	Endpoints
Primary - Phase I	
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	Incidence of dose-limiting toxicities Incidence and severity of AE and SAE Changes in laboratory parameters, vital signs, and ECGs Dose interruptions, reductions, and discontinuations
Primary – Phase II	
To assess the preliminary anti-tumor activity of IMCnyeso as monotherapy in advanced NSCLC, urothelial cancer, and synovial sarcoma	BOR as determined by RECIST v1.1
Secondary- Phase II	
To characterize the safety and tolerability of IMCnyeso	Incidence and severity of AE and SAE Changes in laboratory parameters, vital signs, and ECGs Dose interruptions, reductions, and discontinuations
Secondary- Phase I and Phase II	
To assess the preliminary anti-tumor activity of IMCnyeso as monotherapy	Phase I: BOR, PFS, and DoR by RECIST v1.1; OS Phase II: PFS, and DoR by RECIST v1.1; OS
To characterize the PK profile of IMCnyeso as monotherapy	Serum PK parameters (eg, AUC, C_{max}, T_{max}, $t_{1/2}$) after single and multiple doses
To evaluate the preliminary incidence of anti-IMCnyeso antibody formation following multiple infusions of IMCnyeso	Incidence of anti- IMCnyeso antibody formation and its impact on PK
Exploratory	
[redacted]	[redacted]

Objectives	Endpoints
[redacted]	[redacted]
[redacted]	[redacted]

AE = adverse event; AUC = area under the curve; BOR = best overall response; CD# = cluster of differentiation #; C_{max} = maximum observed concentration; [redacted]; DoR = duration of response; ECG =electrocardiogram; [redacted]; MTD = maximum tolerated dose; NSCLC = non-small cell lung cancer; [redacted]; PFS = progression-free survival; PK = pharmacokinetic; RECIST = Response Evaluation Criteria in Solid Tumors; [redacted]; RP2D = recommended Phase II dose; SAE = serious adverse event; $t_{1/}$ = terminal elimination half-life; [redacted]; T_{max} = time of maximum concentration; [redacted].

5 POPULATION SELECTION CRITERIA

5.1 Patient Population

To fulfill the study objectives, it is essential that appropriate patients are enrolled. The following eligibility criteria are designed to select patients for whom protocol treatment is considered appropriate. Patient eligibility should be reviewed and documented by an appropriate member of the site study team.

5.2 Inclusion Criteria

Patients must meet all the following inclusion criteria to be eligible for inclusion in the study:

General

1. Male or female patients age ≥ 18 years of age at the time of informed consent
2. Ability to understand and provide written informed consent prior to undergoing any study procedures
3. Life expectancy of > 3 months as estimated by the Investigator
4. Eastern Cooperative Oncology Group (ECOG) Performance Status of 0 or 1 at Screening
5. In the opinion of the Investigator, all other relevant medical conditions must be well-managed and stable for at least 28 days prior to first administration of study drug

HLA and Tumor Antigen Testing

6. HLA-A*02:01 positive as confirmed by the central laboratory
7. NY-ESO-1 and/or LAGE-1A positive tumor confirmed by the central laboratory

Phase I: Disease Under Study and Prior Anti-Cancer Treatment

8. Histologically confirmed diagnosis of advanced NSCLC, melanoma, urothelial carcinoma, or synovial sarcoma
9. Patients must be relapsed from, refractory to, or intolerant to all approved and available classes of therapy known to provide clinical benefit for their condition

Phase II: Disease Under Study and Prior Anti-Cancer Treatment

10. Histologically confirmed diagnosis of advanced NSCLC, urothelial carcinoma, or synovial sarcoma

11. Measurable disease per Response Evaluation Criteria in Solid Tumors (RECIST) v.1.1 criteria (Section 13.1)

12. A minimum of 10 patients enrolled in Phase II must have disease that is amenable to biopsy, and consent to provide biopsies during Screening and on treatment

13. Patients will have received the following previous therapies. These therapies must have been given for unresectable / metastatic disease or given in the adjuvant setting if disease progression occurred during or within 6 months of completing adjuvant therapy

    - NSCLC — PD-1/PD-L1 inhibitor. Patients with a genomic tumor aberration (eg, EGFR, ALK) that is targeted by Health Authority-approved agent(s) must be relapsed from, refractory to, or intolerant of relevant targeted agent(s)
    - Urothelial cancer — PD-1/PD-L1 inhibitor
    - Synovial sarcoma — at least 1 prior systemic chemotherapy regimen

Contraception

14. Female patients should either be of non-childbearing potential or must agree to use highly effective methods of contraception from Screening until 6 months following administration of the last dose of study drug (see Section 6.14)

15. Male patients must be surgically sterile or use double barrier contraception from enrollment through treatment and for 6 months following administration of the last dose of study drug

5.3 Exclusion Criteria

Patients with any of the following will not be included in the study:

Disease Under Study and Prior Anti-Cancer Treatment

1. Presence of symptomatic or untreated central nervous system (CNS) metastases, leptomeningeal disease, cord compression, or CNS metastases that require doses of corticosteroids within 3 weeks prior to the planned first administration of study drug. **NOTE**: Asymptomatic and adequately treated CNS metastases are not exclusionary provided the patient is neurologically stable

2. Systemic anti-cancer therapy for the disease under study within 2 weeks of the planned first administration of study treatment. For cytotoxic or immunotherapy agents that can present with major delayed toxicity (eg, anti-CTLA-4), a 4-week washout period is required

3. Radiotherapy within 2 weeks of the planned first administration of study drug. **NOTE**: palliative radiotherapy to a limited field, such as for the treatment of bone pain or a focally painful tumor mass, is not exclusionary

4. Presence of National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) ≥ Grade 2 toxicity due to prior cancer therapy (except Grade 2 alopecia, stable Grade 2 peripheral neuropathy, Grade 2 endocrine disorder [on stable replacement doses and without symptoms], Grade 2 hypophosphatemia [on appropriate replacement therapy] and Grade 2 ototoxicity)

Laboratory Parameters

5. Patient with any out-of-range laboratory values defined as shown below. Hematology evaluations must be performed ≥ 7 days after any blood or blood product transfusion and ≥ 14 days after any dose of hematologic growth factor.

   - Creatinine clearance (calculated using Cockcroft-Gault formula or measured) < 40 mL/min
   - Total bilirubin > 1.5 × upper limit of normal (ULN); **NOTE:** for patients with Gilbert's syndrome; exclude if total bilirubin > 3.0 × ULN or direct bilirubin > 1.5 × ULN)
   - Alanine aminotransferase (ALT) > 3 × ULN
   - Aspartate aminotransferase (AST) > 3 × ULN
   - Absolute neutrophil count (ANC) < 1.0×10^9/L
   - Absolute lymphocyte count < 0.5×10^9/L
   - Platelet count < 75×10^9/L
   - Hemoglobin < 8 g/dL

Medical History and Concomitant Medications

6. Any active manifestations of autoimmune disease of the skin, including psoriasis and scleroderma, or history of severe skin manifestation of graft versus host disease

7. Clinically significant cardiac disease or impaired cardiac function including any of the following:

   - Clinically significant and/or uncontrolled heart disease such as diagnosed congestive heart failure (New York Heart Association Class ≥ 2), uncontrolled hypertension, or clinically significant arrhythmia currently requiring medical treatment
   - Confirmed manually over-read QT interval corrected by Fredericia's method (QTcF) > 470 msec on Screening ECG or known history of congenital long QT syndrome
   - History of acute myocardial infarction or unstable angina pectoris < 6 months prior to planned first administration of study drug

8. Active infection requiring systemic antibiotic therapy. **NOTE:** Patients requiring systemic antibiotics for infection must have completed treatment with any IV antibiotics at least 14 days before the planned first administration of study drug and any oral antibiotics at least 7 days before the planned first administration of study drug

9. Known history of human immunodeficiency virus (HIV) infection. Testing for HIV status is not necessary unless clinically indicated

10. Active hepatitis B virus (HBV) or hepatitis C virus (HCV) infection as defined per institutional protocol. Testing for HBV or HCV status is not necessary unless clinically indicated or the patient has a history of HBV or HCV infection

11. Patients receiving systemic treatment with steroid therapy (ie, prednisone > 10 mg daily [QD] or the equivalent) or any other immunosuppressive medication at any dose level that could interfere with the action of the study drugs, in the opinion of the Principal Investigator

    - Treatment for well controlled and asymptomatic adrenal insufficiency is permitted provided the patient has no history of adrenal crisis and replacement dosing is limited to prednisone ≤ 10 mg QD or the equivalent
    - Local steroid therapies (eg, otic, ophthalmic, intra-articular, or inhaled medications) are acceptable

12. Malignant disease other than that being treated in this study, with the following exceptions:

    - Malignancies that were treated curatively and have not recurred within 2 years prior to study treatment

- Completely resected basal cell and squamous cell skin cancers
- Any malignancy considered to be indolent and that has never required therapy
- Completely resected carcinoma in situ of any type

13. Any medical condition that would, in the Investigator's judgment, prevent the patient's participation in the clinical study due to safety concerns, compliance with clinical study procedures, or interpretation of study results

14. Any major surgical procedure (as judged by the Principal Investigator) within 2 weeks of the planned first administration of study drug. **NOTE:** Minimally invasive procedures such as bronchoscopy, tumor biopsy, insertion of a central venous access device, and insertion of a feeding tube are not considered major surgery and are not exclusionary

15. Pregnant, likely to become pregnant, or lactating women (where pregnancy is defined as the state of a female after conception and until the termination of gestation)

6 STUDY TREATMENTS AND ADMINISTRATION

6.1 IMCnyeso Study Treatment

IMCnyeso will be supplied by the Sponsor, Immunocore.

Dose and treatment schedules are described in Table 6-1 below.

Table 6-1: Dose and Treatment Schedule

Study Treatments	Pharmaceutical Form and Route of Administration	Dose	Frequency and/or Regimen
IMCnyeso	Liquid in vial for intravenous infusion (single-use vials)	Dose determined by cohort level	Every week

IMCnyeso will be supplied as a sterile, frozen solution, in individual, single-use glass vials at a concentration of 0.5 mg/mL. Each vial is to be used for 1 dose / 1 patient.

The drug solution contains citrate (5.2 mM), phosphate (14.8 mM), trehalose 5% (weight/volume), mannitol 1% (weight/volume), and Tween-20 0.05% (weight/volume). The frozen solution appears clear, colorless, or pale yellow when thawed and has a pH 6.0.

6.2 Treatment Regimen and In-Patient Hospitalization

Patients enrolled in this study will receive treatment with single-agent IMCnyeso dosed weekly on Days 1, 8, 15, and 22 of each 4-week cycle. All dosages prescribed and dispensed to patients and all dose changes during the study must be recorded on the Dosage Administration Record and electronic case report form (eCRF).

For each administration of study medication, a physician must be present at the site or immediately available to respond to emergencies. Study sites will be instructed on the conservative management of symptoms associated with CRS (eg, hypotension), as described in Section 6.15. Fully functional resuscitation equipment and medications to handle acute infusion-related emergencies (eg, anaphylaxis, CRS) must be available at each study site.

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 1 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 has reviewed 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.

6.3 IMCnyeso Handling, Storage, and Preparation

IMCnyeso vials must be stored frozen below -60°C until ready for use.

When required, 1 vial per dose / 1 vial per patient should be thawed at room temperature or at 2°C–8°C. The pharmacy preparation involves the dilution of IMCnyeso using 50 mL or 100 mL 0.9% (weight/volume) sodium chloride infusion bags to which human serum albumin (HSA) has been added at a specified concentration. Due to the low IMCnyeso doses administered in this study, the dilution for administration may require the use of more than 1 infusion bag. Detailed instructions for preparation of doses and provision of dilution bags and HSA will be provided in the Pharmacy Handling Instruction document.

The start time for the expiry calculation is the time the container closure integrity is breached. The prepared IV bag containing IMCnyeso may be stored at room temperature for up to 4 hours or at 2°C–8°C for up to 24 hours. If refrigerated, 30 minutes should be allowed for equilibration to room temperature and total room temperature exposure, including equilibration and infusion must not exceed 4 hours.

6.4 Study Drug Administration

For each patient, the first dose will be infused over 2 hours (±15 minutes); for dose levels ≤ 30 mcg; the first dose may be infused over 1 hour (±10 minutes). If the first dose is well tolerated without ≥ 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.

The entire contents of the IV bag will be administered using an infusion pump. A further 30 mL of 0.9% sodium chloride should be used to flush the line after the IMCnyeso solution has been infused. The infusion rate should not be changed, unless necessary to manage acute reactions. If the line is not flushed, this must be documented.

The initial dosing of patients in the dose-escalation cohorts will be staggered, with at least a 1-week interval between the first 2 patients at each dose level. The IRS will be used to control

patient allocation to treatment and ensure the dosing intervals and cohort recruitment complies with the protocol.

Please refer to Section 6.12 for guidance regarding pre-medication and interruption of anti-hypertensive medications around the time of each dose.

6.5 Study Drug Compliance and Accountability

Study treatment will be administered to the patient at the study site by trained study staff.

Patient 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.

The Investigator or his/her designee must maintain accurate records of the receipt and dispensing of all study treatment according to local institutional drug accountability processes. Drug accountability documentation will be reviewed by the Study Medical Monitor during site visits and at the completion of the study.

6.6 Drug Supply, Storage, and Disposal

Study supplies must be received by designated personnel at the study site, handled and stored safely and kept in a secured location where only the Investigator and designated Site personnel have access.

Upon receipt, IMCnyeso vials should be recorded on the Drug Accountability documents and placed in a freezer below -60°C, as specified on the drug label. The freezer used for storage should be monitored, alarmed and the Sponsor informed of any temperature excursions. In the event of a temperature excursion any affected supplies should be quarantined, and the Sponsor contacted immediately.

All IMCnyeso supplies remaining at the end of the study (following appropriate drug accountability procedures) will be destroyed following approval from the Sponsor. This destruction will be performed per local institutional practice at the study site or at a third-party vendor, as appropriate. All destruction of study medications must be documented appropriately.

6.7 Patient Numbering and Treatment Assignment

Patients are identified in the study by a 5-digit number that is assigned by the IRS at the time the patient is first consented for the study. The 5-digits are made up of a 2-digit site identifier followed by a 3-digit sequential patient number suffix. This number is retained throughout the patient's participation in the study and ensures that each patient is numbered uniquely across the entire study database.

6.8 Dose-limiting Toxicities Observation Period

The DLT observation period is defined in Section 6.10.2

6.9 Starting Dose Rationale

The rationale for the QW dosing regimen in this study are based on the proof-of-concept clinical study of tebentafusp where manageable toxicity was observed with QW dosing of tebentafusp, as well as single-agent anti-tumor activity in both uveal and cutaneous melanoma.

IMCnyeso is a highly human-specific fusion protein. Neither the anti-CD3 nor the TCR portions cross react with any of the standard toxicology species, as discussed in Section 1.3. Therefore, there is no relevant toxicology species to enable the setting of a starting dose using the conventional no adverse effect level (NOAEL) method. In the absence of a relevant toxicology species, MABEL, with receptor occupancy calculations, was used to set a safe starting dose. Derivation of the first clinical dose using the MABEL is shown below.

In vitro pharmacology assays measuring the efficacy of IMCnyeso against cancer cell lines were used to define the MABEL. In these assays, human T cells were added to target cells with different concentrations of IMCnyeso to determine the effects of cytokine release and killing induced at the given concentrations of IMCnyeso. The target cells used were HLA-A*02:01 positive and NY-ESO-1 positive cancer cells, which in the presence of IMCnyeso, induce the CD3 positive effector T cells in the PBMC population to both release IFN-γ and kill the tumor cells. In general, IFN-γ release is observed at IMCnyeso concentrations that are lower than the concentrations required for the observation of target-cell killing. Based on the killing assays and IFN-γ release assays, the MABEL observed in the in vitro assays for IMCnyeso is 5 pM.

The acceptable starting dose in the Phase I dose-escalation study is defined as the IV dose of IMCnyeso with a predicted C_{max} of serum at the MABEL (5 pM) and a receptor occupancy between 10%–30% at C_{max}. The use of C_{max} as the PK determinant of the starting dose prediction is based on the observed toxicity profile of the first ImmTAC in the clinic, tebentafusp, where it was observed that the related and more severe toxicities are observed in the immediate hours following dosing, when the concentration of tebentafusp was maximal. These data suggest that toxicity is related to the maximal plasma concentration more than the overall exposure or the area under the curve (AUC).

Thus, the determination of the starting dose is as follows:

- Given the observation of immediate rash and hypotension following administration of tebentafusp in patients, the appropriate volume of distribution (V_D) of an ImmTAC would incorporate both the blood and tissue compartments. A total V_D of 8 L was

assumed for IMCnyeso based on the observed volume of distribution of tebentafusp in patients

- The molecular weight of the IMCnyeso is 77 kDa; therefore, the expected concentration of IMCnyeso in the serum where a minimal biological effect (ie, < 5 pM) would occur is approximately 400 pg/mL
- The PK data in C57BL/6 mice indicates that IMCnyeso displays linear kinetics upon IV bolus injection with a $t_{1/2}$ of 2–3 hours, in accordance with that observed for tebentafusp
- Assuming a V_D of 8 L and an 80-kg patient, the absolute dose to achieve a C_{max} of 400 pg/mL is 3 mcg
- With the K_D (equilibrium dissociation constant) of 41 pM, the receptor occupancy (Saber, 2016) is anticipated to be approximately 10%

6.10 Dose-Escalation Decision Making

Dosing will begin with the first cohort at the starting dose of 3 mcg QW (Table 6-2). 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 ≥ Grade 2 toxicity data, PK, and pharmacodynamic data from evaluable patients (as defined in Section 6.10.2). 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.

If toxicity resolves following appropriate management and provided treatment discontinuation criteria are not met (see Section 6.16), patients experiencing DLTs may continue treatment with IMCnyeso only after agreement with the Sponsor Medical Monitor. With each dose cohort in Phase I, determination of the next dose to be tested in the dose escalation will be guided by the BLRM. Decision making will be based on all evaluable patients in the dose-determining set (DDS) at each cohort level (see Section 6.10.1). 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 9). 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. 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. Further details of the BLRM including additional simulated escalation pathways are provided in Section 13.3.

The estimated dose levels to be tested in this study (in the scenario that no DLT are reported) are shown in Table 6-2. Actual doses will be determined using the BLRM and must be agreed upon by the SST.

Table 6-2: Example IMCnyeso Dose Levels for Phase I Dose Escalation

Dose Level	Estimated IMCnyeso Dose Level	Planned Enrollment
1 (starting dose)	3 mcg	2–6
2	10 mcg	2–6
3	30 mcg	3–6
4	100 mcg	3–6
5	190 mcg	3–6

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.

6.10.1 Intra-Patient Escalation

A recent FDA review concluded that incorporation of a step dose / IPE can result in better patient tolerance of higher doses of CD3 bispecific molecules (Saber, 2017) due to a phenomenon of induced tolerance or tachyphylaxis. IPE regimens are used for the related ImmTAC molecule tebentafusp as well as the approved CD3 bispecific blinatumomab.

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 1-step 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, as shown in Figure 6-1.

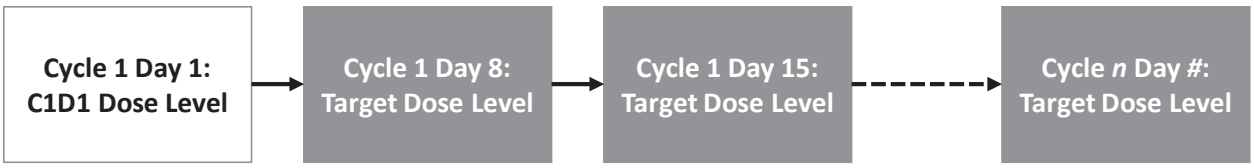

Figure 6-1**: Schematic Illustration of a 1-Step IPE Regimen**

Rules for the 1-step IPE regimen are as follows:

- The initial target dose level must be a permitted escalation step based on BLRM output and the consensus of the SST
- The initial target dose level must not exceed the fixed-dose MTD (if established)
- The C1D1 dose level must be at least one dose level below the initial target dose, and must be a dose level that has been evaluated in ≥ 3 patients using a fixed-dose regimen, with a decision to escalate based on the BLRM output and SST review of all available relevant data.
- Escalation of the target dose in subsequent cohorts may proceed as in the main dose escalation:
    - Separate MTD/RP2D may be identified using fixed-dose and 1-step IPE regimens
    - DLT will be attributed to the dose level of the most recently administered dose prior to onset of the DLT (eg, a DLT with onset on C1D4 would be attributed to the C1D1 dose level, while a DLT with onset on C1D10 would be associated to the C1D8 dose level)
- The dose level for C1D1 remains fixed for all subsequent cohorts
- Patients receiving IPE must receive the C1D1 dose prior to receiving the target dose
- If a 1-step IPE regimen is evaluated in Phase I, it may be selected for further evaluation in Phase II

Experience with other CD3 bispecific molecules (including tebentafusp and blinatumomab) indicates that multi-step IPE may mitigate the risk of a cytokine-mediated AE more effectively than a 1-step IPE or fixed-dose regimen. If further mitigation of cytokine-mediated events is desired, the SST may decide to evaluate a two-step IPE regimen, in which an intermediate dose is given on Cycle 1 Day 8, as shown in Figure 6-2.

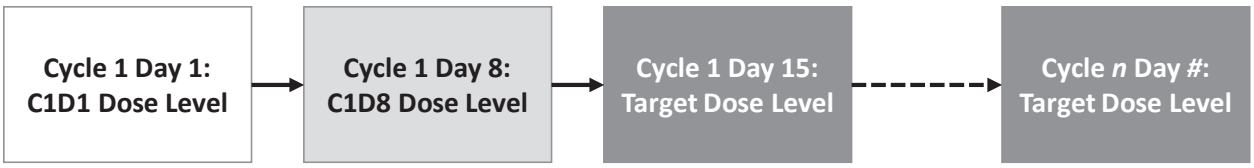

Figure 6-2: Schematic Illustration of a 2-Step IPE Regimen

Rules for the 2-step IPE regimen are as follows:

- The initial target dose level must be a permitted escalation step based on BLRM output and the consensus of the SST
- The initial target dose level must not exceed the 1-step dose-escalation MTD (if established)
- The C1D8 dose level must be at least one dose level below the initial target dose, and must be a dose level that has been evaluated in ≥ 3 patients using a fixed-dose or 1-step IPE regimen, with a decision to escalate based on the BLRM output and SST review of all available relevant data
- Escalation of the target dose in subsequent cohorts may proceed as in the main and 1-step dose escalation:
    - Separate MTD/RP2D may be identified using fixed-dose, 1-step IPE, and 2-step IPE regimens
    - DLT will be attributed to the dose level of the most recently administered dose prior to onset of the DLT (eg, a DLT with onset on C1D4 would be attributed to the C1D1 dose level, while a DLT with onset on C1D10 would be associated to the C1D8 dose level)
- The dose levels for C1D1 and C1D8 remain fixed for all subsequent cohorts
- Patients receiving 2-step IPE must receive the C1D1 and C1D8 doses prior to receiving the target dose
- If a 2-step IPE regimen is evaluated in Phase I, it may be selected for further evaluation in Phase II

An example of how IPE might be implemented is shown in Figure 6-3.

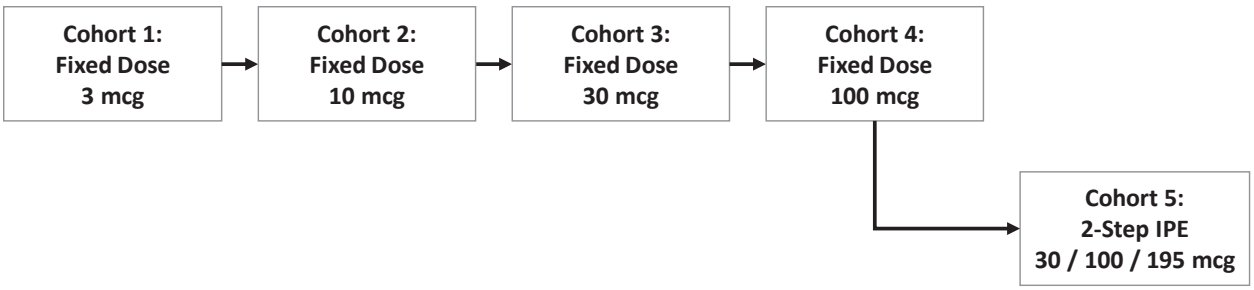

Figure 6-3: Representative Escalation Path Incorporating IPE

IPE = intra-patient escalation.

Actual dose levels will be determined using BLRM and must be approved by SST. In this scenario, after 3 patients were enrolled in Cohort 4 and completed DLT evaluation, the recommended next dose per BLRM was 195 mcg. The SST determined that the 195 mcg dose would be better tolerated using a 2-step escalation regimen, and so Cohort 5 was opened with a dose of 30 mcg on C1D1, 100 mcg on C1D8, and 195 mcg as the target dose (weekly starting on C1D15).

In addition, a patient who is enrolled in a lower dose cohort may move to a higher dose cohort once all the following criteria are met:

- The patient has completed at least 3 cycles of treatment
- The patient did not experience any DLT or any ≥ Grade 3 treatment-related toxicity
- The patient does not have any ongoing ≥ Grade 2 treatment-related toxicity
- The higher dose cohort has completed SST review with a decision to escalate or was determined to be the MTD/RP2D

6.10.2 Definition of DLT-Evaluable Patients for the Dose-Determining Set

Patients are considered as DLT-evaluable if they meet one of the following criteria:

- Experienced a DLT during the 28-day DLT evaluation period, **OR**
- Did not experience a DLT during the 28-day DLT evaluation period, received at least 3 of the 4 planned doses of IMCnyeso (including at least 2 doses at the target dose level), and were observed for ≥ 28 days following the first dose

6.11 Definition of Maximum Tolerated Dose and Recommended Phase II Dose

The MTD will be determined if the following conditions are met:

1. At least 6 patients have been treated at this dose and associated treatment regimen (ie, fixed-dose, 1-step IPE, or 2-step IPE).

2. The dose has the highest posterior probability that the true DLT rate is in the target interval for toxicity (16%–33%), as predicted by the BLRM. The interval boundaries of 16% and 33% are chosen to be consistent with the traditional 3+3 design toxicity boundary (ie, 1/6 and 1/3).

3. The dose satisfies the EWOC principle (the probability that the DLT rate lies within the excessive toxicity or the unacceptable toxicity window is less than 25%).

The RP2D will be defined as the dose and associated treatment regimen selected for further evaluation in Phase II by the SST. The RP2D will be determined from a synthesis of all data available, including safety, tolerability, PK, pharmacodynamics, and preliminary anti-tumor activity observations from Phase I. The RP2D must not exceed the MTD as determined by the BLRM. A minimum of 6 patients will be treated at the RP2D in Phase I and monitored through the DLT evaluation period before enrollment in Phase II may begin.

During Phase II, following enrollment of at least 12 subjects, if the observed rate of Grade 3 and/or Grade 4 toxicity considered related to IMCnyeso and meeting the definition of DLT is > 30%, a safety teleconference will be convened with the SST to determine if the cohorts should continue enrollment.

6.12 Definitions of Dose-Limiting Toxicity

A DLT is defined as an AE or abnormal laboratory value assessed as having a suspected relationship to study drug that occurs within the DLT evaluation period (Section 6.10.2), is unrelated to disease, disease progression, inter-current illness, or concomitant medications, and meets any of the criteria included in Table 6-3. Any death not clearly due to the underlying disease or extraneous causes will be considered a DLT. Other clinically significant toxicities, including a single event or multiple occurrences of the same event that lead to a dosing delay or interruption lasting > 7 days in Cycle 1, may be considered a DLT by the SST, even if not ≥ Grade 3. Events meeting DLT criteria but occurring outside the DLT evaluation period may also be considered DLT by the SST. In the absence of clinically significant signs or symptoms, abnormal laboratory values that potentially meet DLT criteria must be confirmed by re-testing at least 24 hours after the initial observation.

Cytokine release syndrome will be graded based on the ASTCT 2019 criteria in Section 13.1. NCI CTCAE version 4.03 will be used for all other grading. The Investigator must notify the Sponsor within 24 hours of any DLT (additional events requiring reporting within 24 hours are listed in Section 8.5).

Guidance for toxicity management is in Section 6.15.

Table 6-3: Criteria for Defining Dose-Limiting Toxicities

DLTs include ≥ Grade 3 AE occurring during the DLT evaluation period, with a suspected relationship to study drug, with the following modifications:	
Hematology	Grade 4 neutropenia persisting > 5 days after onset or associated with infection is a DLT ≥ Grade 3 febrile neutropenia is a DLT Grade 4 thrombocytopenia or ≥ Grade 3 thrombocytopenia associated with ≥ Grade 3 bleeding is a DLT Grade 4 anemia is a DLT ≥ Grade 3 lymphopenia in the presence of an infection indicating clinical significance is a DLT
Hepatic and pancreatic	Grade ≥ 2 elevated total bilirubin (> 2 × ULN) with concurrent Grade ≥ 2 elevated ALT and/or AST (> 3 × ULN), with no clear alternate etiology (eg, biliary obstruction with elevated alkaline phosphatase), is a DLT Grade 3 isolated ALT and/or AST (> 5-8 × ULN) elevation or Grade 3 isolated bilirubin elevation (> 3-5 × ULN) that does not resolve to ≤ Grade 1 within 14 days of onset is a DLT ≥ Grade 3 isolated ALT and/or AST (> 8 × ULN) elevation or ≥ Grade 3 isolated bilirubin (> 5 × ULN) elevation is a DLT ≥ Grade 3 amylase and/or lipase elevation, with associated clinical signs, symptoms, or radiographic evidence of pancreatitis, is a DLT
Gastrointestinal	Grade 3 nausea, vomiting or diarrhea persisting for > 3 days after onset, despite optimal therapy, is a DLT
Hypotension	Grade 3 hypotension that does not resolve to ≤ Grade 1 within 6 hours of onset, despite optimal therapy, is a DLT Grade 4 hypotension of any duration and with any management is a DLT
Hypertension	Grade 3 hypertension (systolic BP ≥ 160 mm Hg or diastolic BP ≥ 100 mm Hg) persisting > 2 days after onset, despite treatment, is a DLT Grade 4 hypertension of any duration is a DLT
Infection	Grade 3 infection or fever in the absence of neutropenia that persists > 7 days after onset is a DLT Grade 4 infection of any duration is a DLT

DLTs include ≥ Grade 3 AE occurring during the DLT evaluation period, with a suspected relationship to study drug, with the following modifications:	
Tumor Flare	Grade 3 inflammatory reaction at a tumor site associated with local anti-tumor immune response that does not resolve to ≤ Grade 2 within 7 days after onset is a DLT
Electrolyte Abnormalities	Grade 3 electrolyte abnormalities that do not resolve to ≤ Grade 1 within 3 days after onset, despite optimal medical management, are DLTs Grade 4 electrolyte abnormality of any duration is a DLT
Skin toxicity	Grade 3 rash and/or pruritis that persists > 7 days after onset, despite optimal medical management, is a DLT Grade 4 cutaneous toxicity of any duration is a DLT
Fatigue	≥ Grade 3 fatigue that persists > 4 days after onset is a DLT
Infusion-related reaction / hypersensitivity / anaphylaxis	Grade 3 infusion-related reaction that does not resolve to ≤ Grade 1 within 6 hours of onset, despite appropriate medical management, is a DLT Grade 4 infusion reaction is a DLT
Cytokine release syndrome	Grade 3 cytokine release syndrome that does not resolves to ≤ Grade 2 within 6 hours after onset, despite optimal medical management (eg, corticosteroid dosing), is a DLT Grade 4 cytokine release syndrome of any duration is a DLT

ALT = alanine aminotransferase; AST = aspartate aminotransferase; DLT = dose-limiting toxicity; SST = Study Safety Team; ULN = upper limit of normal.

6.13 Concomitant Therapy

6.13.1 Permitted Concomitant Therapy

In general, concomitant medications and therapies deemed necessary for the supportive care and safety of the patient are allowed. Examples include anti-diarrheal medications, anti-emetics, electrolyte supplementation, intravenous fluids, hematologic growth factors, or blood transfusions. However, hematologic growth factors and blood transfusions should only be administered starting with Cycle 2 to avoid confounding interpretation of potential drug-related toxicities during the DLT evaluation period.

Patients are required to notify the investigational site staff about any new medications, herbal remedies, or dietary supplements taken after the start of the study treatment, regardless of treatment duration. All concomitant medications and significant non-drug therapies (including physical therapy, herbal or natural medications and blood transfusions) administered during the study must be listed on the Concomitant Medications Log or the Surgical and Medical Procedures log in the eCRF.

IV hydration required to manage toxicity associated with the study medications (eg, hypotension) should be recorded in the Concomitant Medications Log in the eCRF.

Palliative radiation therapy to non-target lesions is permitted during the study after consultation with the Sponsor Medical Monitor and should be recorded in the eCRF as concomitant therapy.

6.13.2 Concomitant Therapy Requiring Caution

Anti-coagulant therapy is permitted. International normalized ratio should be monitored as clinically indicated per the Investigator's discretion. Ongoing anti-coagulant therapy should be temporarily discontinued to allow tumor biopsy according to institutional guidelines. Recent hospitalizations that required low dose heparin for deep vein thrombosis prophylaxis are not a contraindication.

Anti-hypertensive drugs are allowed as concomitant medications; however, because transient hypotension has occurred during infusions of monoclonal antibodies, anti-hypertensives should not be administered 24 hours before and 24 hours after IMCnyeso administration in the first 6 weeks of treatment. Thereafter, anti-hypertensives can be reintroduced at the discretion of the Principal Investigator. Appropriate management of patients with more severe hypertension, receiving medications that may cause rebound hypertension when abruptly discontinued, or on multiple blood pressure medications, should be discussed with the Sponsor Medical Monitor prior to making any adjustments during the first 6 weeks of treatment.

Non-live vaccines are allowed but are not to be administered within 14 days before, and 28 days after, the first dose of IMCnyeso. Following completion of the first treatment cycle, non-live vaccines should not be given within 24 hours before or after IMCnyeso administration.

6.13.3 Prohibited Concomitant Therapy

During study treatment, patients may not receive other investigational drugs, agents, devices, chemotherapy, or any other systemic therapies that may be active against the cancer under study.

Additionally, no other therapeutic monoclonal antibodies (excepting denosumab) and no immunosuppressive medication may be administered to patients in this study (except as noted in Exclusion Criterion 11 and Section 6.15).

While systemic corticosteroid therapy may interfere with the mechanism of action of the study medications, its use is permitted/recommended in the following settings:

- Pre-medication for known allergy to contrast reagents
- To manage toxicities (eg, infusion reactions, hypotension not resolving with fluid support) as noted in Section 6.15

- Replacement-dose steroids (ie, prednisone ≤ 10 mg QD or equivalent) in the setting of adrenal insufficiency (patients with a pre-existing history of adrenal crisis are excluded from study participation; see Exclusion Criterion 11)

- Based on the emerging safety profile of IMCnyeso, the SST may decide to recommend a standard pre-treatment regimen (which may include antihistamine, acetaminophen, and/or corticosteroid)

Any additional uses of systemic corticosteroid therapy during the study should be discussed with the Sponsor Medical Monitor.

Live or attenuated vaccines are prohibited from 28 days prior to the first dose of IMCnyeso until 30 days after the last dose of IMCnyeso.

6.14 Contraception

6.14.1 Contraception in Females

Women of childbearing potential, defined as all women physiologically capable of becoming pregnant, may be included in the study provided they are using highly effective methods of contraception during dosing and for 6 months after the last dose of IMCnyeso.

Highly effective contraception methods include the following:

- Total abstinence from sexual relations for the duration of the treatment when applicable to the lifestyle of the patient. Periodic abstinence (eg, calendar, ovulation, symptothermal and post-ovulation methods) and withdrawal are not acceptable methods of contraception.

- Female sterilization (surgical bilateral oophorectomy with or without hysterectomy) or tubal ligation at least 6 weeks before taking study treatment. In case of oophorectomy alone, this applies only when the reproductive status of the woman has been confirmed by follow-up hormone level assessment.

- Male sterilization (at least 6 months prior to Screening). For female patients on the study the vasectomized male partner should be the sole partner for that patient.

- Use of oral, injected, implanted, intravaginal, or transdermal hormonal methods of contraception (either estrogen and progestogen containing or progestogen-only) associated with inhibition of ovulation that have comparable efficacy (failure rate < 1%), for example hormone vaginal ring or transdermal hormone contraception.

- Placement of an intrauterine device (IUD) or intrauterine system (IUS).

When using oral contraception, women should have been stable and on the same oral contraceptive pill for a minimum of 3 months before the start of study treatment.

Women are considered post-menopausal and not of childbearing potential if they have had 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile (eg, age appropriate and history of vasomotor symptoms), or have had surgical bilateral oophorectomy (with or without hysterectomy) or have had tubal ligation at least 6 weeks prior to study treatment. In the case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow-up hormone level assessment is she considered not of childbearing potential.

6.14.2 Contraception in Males

Male patients must be surgically sterile or agree to use double barrier contraception from Screening to 6 months after the last dose of IMCnyeso.

6.15 Management of Adverse Reactions

Guidelines for management of AEs and dose modifications are presented in Table 6-4.

Grading of CRS is based on the American Society for Transplantation and Cellular Therapy (ASTCT) 2019 consensus grading system shown in Section 13.1. All other AE are graded per NCI CTCAE v4.03.

Appropriate clinical experts should be consulted as deemed necessary in the judgement of the Principal Investigator for any AEs observed during the trial.

6.15.1 IMCnyeso Dose Reductions

Recommended dose reductions of IMCnyeso for observed toxicity should be as follows:

- All dose modifications should be based on the worst preceding toxicity
- The dose will be reduced ≥ 1 dose level from the initial prescribed dose for any toxicity requiring dose reduction, as per toxicity management guidelines. **NOTE:** Following a single dose-reduction, if there is no recurrence of toxicity with subsequent doses of IMCnyeso, return to the initial prescribed dose is permitted following discussion with the Sponsor Medical Monitor
- If toxicity recurs, the dose may be reduced again, by an additional ≥ 1 dose level

- Patients who require more than 2 dose reductions of IMCnyeso should permanently discontinue treatment

6.15.2 IMCnyeso Dose Interruptions

One to two doses of IMCnyeso may be omitted to permit resolution of treatment-related toxicity. If a patient who misses more than 2 consecutive doses due to a treatment-related toxicity is experiencing clinical benefit, and in the opinion of the Investigator, the benefit/risk profile favors continued treatment, then treatment may be restarted after discussion with the Sponsor Medical Monitor. If more than 3 consecutive doses of IMCnyeso are not administered due to treatment-related toxicity or if a > 21-day treatment interruption occurs, the default position is that the patient must then permanently discontinue study treatment.

Patients whose treatment is interrupted or permanently discontinued due to an AE or clinically significant laboratory value must be followed up at least once a week (or more frequently if clinically indicated) for 4 weeks, and at approximately 4-week intervals thereafter, until resolution or stabilization of the event, whichever occurs first.

Table 6-4: Recommended Management and Dose Modifications by Toxicity Grade and Type

Grade	Recommended Toxicity Management	Dose Modifications
Cytokine Release Syndrome (occurring at least 1 hour after the start of infusion) - refer to modified grading system in Table 13-1		
Grade 1	If not already hospitalized, admit for close observation (eg, monitor vital signs hourly); implement supportive care per institutional standards. Provide anti-pyretics and analgesics as needed; monitor fluid balance (IV fluid support as indicated). Consider prophylactic electrolyte supplementation for patients receiving IV fluids with low-normal serum phosphorus or magnesium. Serum should be collected for central lab cytokine assessments (see Section 7.4.6.4).	**May continue dosing.**
Grade 2	**Notify the Sponsor within 24 hours of onset.** As above for Grade 1; additionally, monitor with continuous cardiac telemetry and pulse oximetry and follow organ function closely. If the patient experiences dyspnea, consider supportive measures such as supplemental oxygen. If the patient experiences hypotension, consider bolus IV fluids at a rate of approximately 1 L crystalloid per hour. If the patient is asymptomatic and non-orthostatic after infusion of 2 to 3 L administered over 2 to 3 hours, consider transition to maintenance IV fluids until resolved. If hypotension does not respond to fluids, consider systemic corticosteroids (eg, methylprednisolone 1 mg/kg IV twice daily).	**Do not administer next scheduled dose of IMCnyeso until CRS has resolved.** • Overnight hospitalization is required for the scheduled next dose of IMCnyeso

Grade	Recommended Toxicity Management	Dose Modifications
Grade 3	As above for Grade 2; additionally, systemic treatment with immunosuppressive agents (eg, methylprednisolone 2 mg/kg/day or equivalent and/or tocilizumab 8 mg/kg IV, not to exceed 800 mg/infusion) per institutional guidelines must be administered. Escalate level of care (eg, intensive care unit) as indicated. For persistent hypotension, treat with a single vasopressor (with or without vasopressin). For hypoxia, provide oxygen with a high-flow device.	**Do not administer next scheduled dose of IMCnyeso until CRS has resolved.** • Treatment may continue provided all the following conditions are met: o Overnight hospitalization is required for the next scheduled dose of IMCnyeso o Reduce the IMCnyeso dose by ≥ 1 dose level o Consider pre-medication (eg, methylprednisolone 1 mg/kg IV) < 60 min prior to the start of the next scheduled infusion o If the patient experiences ≤ Grade 1 CRS following the first reduced dose, then the next dose of IMCnyeso should be administered at the reduced dose without pre-medication, but must be hospitalized overnight for observation • Any patient that experiences recurrence of Grade 3 CRS following re-treatment should permanently discontinue study treatment unless the Investigator believes the overall benefit-risk favors continued treatment and following discussion and agreement with the Sponsor Medical Monitor
Grade 4	As above for Grade 3; additionally, consider treating hypotension with multiple vasopressors, for hypoxia provide oxygen using a positive-pressure device, and consider other immunosuppressive agents for persistent or recurrent signs and/or symptoms as indicated (eg, infliximab or mycophenolate mofetil).	**Study medication must be permanently discontinued.**

Grade	Recommended Toxicity Management	Dose Modifications
Rash and/or Pruritus		
Grade 1	If symptomatic, consider the systemic antihistamine regimen (see Grade 2 guidance below).	**May continue dosing.**
Grade 2	Treat according to institutional practice and/or implement guidance below. Use systemic management and/or local skin management as indicated by symptoms. With bullous formation or blistering rashes, consider dermatology consultation to rule out other causes (eg, bullous pemphigoid). Oral or topical corticosteroids can be used. If bullous formation or blistering recur, consult Sponsor Medical Monitor for guidance. <u>Systemic antihistamine (anti-pruritic) regimens:</u> Recommended as first-line management of pruritus. Use non-sedating, long-acting antihistamines (cetirizine, 10 mg oral or equivalent). If a sedating antihistamine is preferred (eg, evening dosing) consider diphenhydramine 25 mg oral or IV. The use of sedating antihistamines should be minimized in patients with co-morbid pulmonary pathology including pulmonary metastases or underlying inflammatory airway disease such as COPD or asthma. <u>Topical corticosteroid regimens;</u> When involved areas include face and/or intertriginous areas (including genitalia) recommend a low potency corticosteroid or antihistamine creams. For other body areas (ie, trunk and extremities), recommend a low to medium potency corticosteroid cream. Consider spray preparation for ease of application on trunk.	**May continue dosing.**

Grade	Recommended Toxicity Management	Dose Modifications
Grade 3	As above for Grade 2; additionally, oral corticosteroids can be considered in cases of symptomatic rash that do not respond to systemic antihistamine and topical corticosteroids. Prednisolone 20-40 mg/day (or equivalent) should be given for as short a duration as clinically feasible to facilitate symptom resolution while minimizing any potential detrimental effect on efficacy. In addition, montelukast 10 mg by mouth can be given to patients with pruritus refractory to antihistamine and local corticosteroid treatments. Patients with persistent, severe symptoms who fail to respond to the addition of montelukast can be treated with a single hydrocortisone 50 mg IV or prednisone 20 mg by mouth after discussion with the Sponsor Medical Monitor. Consider performing a skin punch biopsy (see Section 7.4.6.3).	**Do not administer IMCnyeso until rash / pruritus has improved to ≤ Grade 1.** • If Grade 3 rash / pruritus resolves to ≤ Grade 1 in < 7 days, treatment may continue at same dose level. • If Grade 3 rash / pruritus resolves to ≤ Grade ≤ 1 in 7–21 days, restart with ≥ 1 dose-level reduction in IMCnyeso. • **If the Grade 3 rash / pruritus does not resolve within 21 days, study medication must be permanently discontinued.**
Grade 4	As above for Grade 3; additionally, consultation with a dermatologist is recommended.	**Study medication must be permanently discontinued.**
Infusion-related Reactions (occurring within 1 hour of starting the infusion) / Anaphylaxis		
All grades	Acute allergic reactions should be treated as needed using institutional guidelines. In the event of anaphylactic / anaphylactoid reactions, any therapy needed to restore normal cardiopulmonary status should be implemented immediately.	
Grade 1	Monitor vital signs at least approximately every 15 minutes through EOI.	**May continue the infusion**

Grade	Recommended Toxicity Management	Dose Modifications
Grade 2	Treat according to institutional practice. Provide all supportive measures as indicated. Provide supplemental oxygen and fluids, as needed. Monitor vital signs (eg, blood pressure, pulse, and temperature), pulse oximetry, and continuous cardiac telemetry (if clinically indicated) until resolution. Administer medications, supplemental oxygen, and/or IV fluids for symptomatic relief as needed. Antihistamines, acetaminophen (paracetamol), bronchodilator therapy, or corticosteroids (eg, methylprednisolone 1 mg/kg IV or equivalent) may be administered as needed, at the discretion of the Investigator.	**Stop infusion and keep IV line open.** • If a Grade 2 IRR resolves within 4 hours of onset with medical management, may restart the infusion provided all the following conditions are met: o Oral pre-medications (eg, 1000 mg of acetaminophen [paracetamol], 50–100 mg diphenhydramine hydrochloride or alternative antihistamine) are administered within 60 minutes prior to re-starting the infusion, and prior to the next scheduled dose of IMCnyeso o The restarted infusion rate does not exceed 50% of previous rate o Vital signs are monitored at least approximately every 15 minutes until the infusion is completed • If Grade 2 IRR resolves > 4 hours after onset, or if Grade 2 IRR recurs after re-starting the infusion at a reduced rate and despite oral pre-medication, do not resume infusion. Treatment may continue at the next scheduled dose. Consider oral pre-medications for subsequent IMCnyeso doses (eg, 1000 mg of acetaminophen [paracetamol] and 50–100 mg diphenhydramine hydrochloride or alternative antihistamine within 60 minutes prior to the start of infusion).

Grade	Recommended Toxicity Management	Dose Modifications
Grade 3	As above for Grade 2; additionally, consider systemic immunosuppressive agents (eg, methylprednisolone 1 mg/kg IV twice daily) and high-dose or multiple vasopressors as clinically indicated per institutional standards.	**Discontinue infusion immediately.** • If a Grade 3 IRR improves to ≤ Grade 1 within 6 hours of onset with medical management, treatment may continue with the next scheduled dose of IMCnyeso; if resolution requires > 6 hours, treatment may continue with a ≥ 1 dose-level reduction • The next scheduled dose is to be delivered using a rate of infusion not to exceed 50% of rate used when the IRR occurred • Oral pre-medications (eg, 1000 mg of acetaminophen [paracetamol], 50–100 mg diphenhydramine hydrochloride or alternative antihistamine) are to be given within 60 minutes prior to the next scheduled dose of IMCnyeso • If Grade 3 IRR recurs after re-starting IMCnyeso treatment, dosing should be permanently discontinued unless the Investigator believes the overall benefit-risk favors continued treatment and following discussion and agreement with the Sponsor Medical Monitor
Grade 4	Treat as above for Grade 3 infusion-related reaction.	**Permanently discontinue study treatment**
Hepatic Function Abnormalities		
Grade 2	Regular monitoring of liver function tests until improving or resolved. Evaluate concurrent medications for agents that may prolong or exacerbate laboratory abnormalities. Consider IV corticosteroid therapy (eg, hydrocortisone 100 mg or the equivalent) if not improving within 72 hours.	**May continue dosing.**

Grade	Recommended Toxicity Management	Dose Modifications
Grade 3	**Notify the Sponsor within 24 hours.** As above for Grade 2; additionally, consider further testing to assess liver synthetic function and consider hepatology consult to advise on management and additional workup. Consider IV corticosteroid therapy (eg, hydrocortisone 100 mg or equivalent) per institutional guidelines if not resolving within 48 to 72 hours.	**Do not administer IMCnyeso until LFTs have improved to ≤ Grade 1 and following discussion and agreement with the Sponsor Medical Monitor.** • For isolated ALT and/or AST elevation (>5-8 × ULN) or isolated total bilirubin elevation (>3-5 × ULN) that resolves to Grade ≤1 within 7 days, dosing at the current dose level may resume • For isolated ALT and/or AST elevation (>5-8 × ULN) or isolated total bilirubin elevation (>3-5 × ULN) that requires > 7 days to resolve, dosing may resume with ≥ 1 dose-level reduction in IMCnyeso • For isolated ALT and/or AST elevation (>8 × ULN) or isolated total bilirubin elevation (>5 × ULN) that resolves to Grade ≤1, dosing should be permanently discontinued unless the Investigator believes the overall benefit-risk favors continued treatment, in which case dosing may resume with ≥ 1 dose-level reduction in IMCnyeso
Grade 4	As above for Grade 3; additionally, promptly consider IV corticosteroid therapy (eg, hydrocortisone 100 mg or equivalent) per institutional guidelines if not resolving within 24 hours. Perform supplementary testing to assess liver synthetic function and obtain hepatology consult to advise on management and additional workup.	**Study medication must be permanently discontinued.**

Grade	Recommended Toxicity Management	Dose Modifications
Vomiting		
Grade 2	Anti-emetic therapy as per institutional standard. IV fluids, electrolyte supplementation, and other supportive measures for additional adverse events as needed.	**May continue dosing.**
Grade 3	Anti-emetic therapy as per institutional standard. IV fluid support and other supportive measures for additional adverse events.	**If Grade 3 vomiting persists > 3 days, do not administer IMCnyeso until vomiting has improved to ≤ Grade 1.** • If Grade 3 vomiting resolves to ≤ Grade 1 within 3 days of onset, dosing at the current dose level may continue at the next scheduled dose • If Grade 3 vomiting requires > 3 days to resolve to ≤ Grade 1, a ≥ 1 dose-level reduction is required for the next scheduled dose of IMCnyeso
Grade 4	As above for Grade 3.	**Do not administer IMCnyeso until vomiting has improved to ≤ Grade 1.** A ≥ 1 dose-level reduction is required for the next scheduled dose of IMCnyeso
Other Adverse Events		
Grade 1 or 2	Manage according to institutional practice. Monitor as clinically indicated for potential worsening and assess whether more intense medical intervention is indicated.	**May continue dosing.**
Grade 3 or 4	Treat according to institutional practice. For immune-related AE, consider treatment with corticosteroids. Consult Sponsor Medical Monitor for further guidance as needed.	**Consider not administering IMCnyeso until toxicity has improved to ≤ Grade 1.**

COPD = chronic obstructive pulmonary disease; CRS = cytokine release syndrome; CTCAE = Common Terminology Criteria for Adverse Events; IRR = infusion-related reaction; IV = intravenous; LFT = liver function test; NCI = National Cancer Institute.

6.16 Treatment Discontinuation

Reasons for discontinuation of study treatment will include:

- Disease progression (Note: Patients may receive treatment after initial disease progression per RECIST v1.1 based on criteria in Section 6.18)
- Initiation of alternative anti-cancer therapy including another investigational agent
- Unacceptable toxicity as defined in Table 6-3 or any AE that, in the opinion of the Investigator or the Sponsor, contraindicates further dosing
- Withdrawal of consent for further treatment
- Lost to follow-up
- Patient is determined to have met 1 or more of the exclusion criteria or failed to meet all inclusion criteria AND continuing to receive IMCnyeso might constitute a safety risk. Patients who fall into this category and for whom continuation of treatment is not thought by the Investigator to pose a safety risk may, after discussion with the Sponsor Medical Monitor, continue to receive study treatment
- Pregnancy or intent to become pregnant

Information about the EOT visit and follow-up periods is provided in Section 7.3.

6.17 Replacement of Patients

During Phase I, any patient deemed not DLT-evaluable (see Section 6.10.2) may be replaced according to the guidelines for Phase I dose escalation, to achieve the minimum number of DLT-evaluable patients.

6.18 Treatment Past Disease Progression

Clinical evidence suggests that a minority of patients treated with immunotherapies will derive clinical benefit after an initial assessment of PD. For patients in this study, if initial PD based on RECIST v.1.1 occurs, treatment may continue according to the protocol-specified regimen provided all of the following criteria are met:

- Absence of signs or symptoms indicating clinically significant disease progression
- No decline in ECOG performance status

- No associated impending threat to vital organ function (eg, cord compression, liver function) or indication for immediate palliative therapy (eg, radiation for cord compression)

Patients continuing treatment beyond the initial protocol-specified RECIST v.1.1 progression must provide separate consent to continue IMCnyeso treatment. Disease assessments will continue to be performed according to the schedule in Table 7-2. The size of any new, measurable lesions is to be reported in the eCRF.

Patients treated beyond initial disease progression who experience further progression, defined as an additional ≥ 5 mm increase in tumor burden (sum of diameters of both target and new lesions) and/or identification of additional new lesions, at least 4 weeks after the initial PD assessment (Seymour, 2017), must permanently discontinue study treatment.

6.19 Study Discontinuation

The reasons for discontinuing individual patients from further participation the study include:

- Patient death
- Patient lost to follow-up
- Patient withdraws consent for any further participation in the study including further participation in Survival Follow-Up
- End of the study is reached (see Section 3.6)

6.20 Overdose

No antidote is known for IMCnyeso nor has it been defined what constitutes an overdose. However, inadvertent incorrect dosing, such as administration of a higher dose than stated in the protocol, should be rigorously monitored for potential (serious) adverse reactions. Patients experiencing toxicity upon incorrect dosing or overdosing must receive adequate, supportive care as indicated by the symptoms observed, which will generally include IV corticosteroid therapy, at the discretion of the treating physician. Patients must be followed until full recovery or confirmed stabilization of the event.

7 STUDY SCHEDULE AND ASSESSMENTS

7.1 Pre-Screening and Screening Period Schedule

All patients will be given both a written and verbal description of the study and allowed adequate time to ask questions and decide whether they want to participate. The Investigator (or an appropriate delegate at the Investigator Site) will obtain written consent from each patient prior to commencing any study-related activities or assessments.

Pre-Screening activities may begin once a patient has signed the study IRB/IEC-approved Pre-Screening ICF. During Pre-Screening the patient's HLA-A*02:01, NY-ESO-1, and LAGE-1A status will be determined to establish patient eligibility. Once confirmed HLA-A*02:01-positive **and** NY-ESO-1- and/or LAGE-1A-positive, the patient will be invited to take part in the full study and provided with the main study information sheet.

There is no window for completion of the Pre-Screening activities. Pre-Screening may be performed while the patient is still on another anti-cancer treatment, prior to experiencing disease progression.

Screening must be completed within 21 days of C1D1; baseline radiological evaluations must be performed within 28 days prior to C1D1. Laboratory and radiological assessments performed as part of standard of care prior to signing the ICF may be used if performed within the Screening window. Screening assessments must be repeated if performed outside of the specified Screening window. Patients may re-screen after abnormal labs or symptoms are corrected or treated, but these should first be discussed and agreed with the Sponsor.

The schedule of assessments for Pre-Screening and Screening is shown in Table 7-1.

Table 7-1: Schedule of Pre-Screening and Screening Assessments

Procedure	Pre-Screening	Screening
Days (relative to first dose)		**-21 to -1**
Informed consent	X	X
HLA-A*02:01 testing	X	
NY-ESO-1 / LAGE-1A testing (archival or new biopsy)	X	
Demography		X
Inclusion/exclusion criteria		X
Medical history and cancer history		X
Prior anti-cancer therapy		X
Prior/concomitant medications		X
Adverse events		X
Safety Assessments		
Complete physical examination		X
Height and weight		
ECOG performance status		X
Vital signs (body temperature, pulse, respiratory rate, blood pressure, and oxygen saturation)		X
12-lead ECG (triplicate)		X
Hematology panel		X
Chemistry panel		X
Coagulation		X
Urinalysis		X
Thyroid function		X
Serum pregnancy test (women of childbearing potential)		X
Serum FSH test (if required to confirm non-childbearing potential)		X
CT/MRI scans for tumor evaluation		X
[redacted]		
Tumor biopsy (required for ≥ 10 patients in Phase II, optional for all other patients)		X
[redacted]		X

CT = computed tomography; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; FSH = follicle-stimulating hormone; HLA = human leukocyte antigen; LAGE-1A = L antigen family member-1 isoform A; MRI = magnetic resonance imaging; NY-ESO-1 = New York esophageal squamous cell carcinoma-1.

Pre-Screen Failures: Any patient who signed the Pre-Screen ICF but failed to sign the Main Study ICF and proceeded with Screening for any reason, will be considered a Pre-Screen failure. The histologic diagnosis, HLA-A*02:01 result and tumor antigen screening (NY-ESO-1 and LAGE-1A) results will be collected for all Pre-Screen failure patients. No other data will be entered in the eCRF.

Screen Failures: Any patient who signed the Main Study ICF, but failed to start treatment for any reason, will be considered a screen failure. The demographic information and reason for screen fail must be completed for screen failure patients. No other data will be entered into the eCRF unless the patient experienced any AEs during Screening, which would be reported in the usual manner via eCRF AE page (see Section 8).

7.2 Treatment Period Schedule

The treatment period starts with Day 1 of Cycle 1 (C1D1). A treatment cycle is defined as 28 days for the purposes of scheduling procedures and evaluations.

Any assessments required on C1D1 that are also performed as part of Screening do not need to be repeated on C1D1 if the data were obtained 72 hours prior to the first dose of study treatment. For subsequent visits, pregnancy testing may be performed up to 72 hours prior to dosing and other safety assessments may be performed up to 24 hours prior to dosing.

During the study visits, all tests and/or procedures should occur on schedule whenever possible. A visit window of ±7 days (with a minimum of 7 days between doses of IMCnyeso) is allowed unless otherwise indicated in the protocol. If study drug infusions are delayed, the assessments associated with those infusions should be rescheduled accordingly. However, the timing of protocol-specified radiological assessments should be calculated in weeks using C1D1 as reference and should not be adjusted because of delays in treatment.

Assessments required during the treatment period are presented by visit inTable 7-2. For patients receiving IPE, follow the alternate Cycle 1 schedule provided in Section 13.4. Assessments marked “X” should be performed prior to dosing. Assessments that are to be performed at multiple timepoints are marked with the number of timepoints (including optional timepoints, if applicable) for the visit (eg, 2× is twice) and details of the timepoints are provided in the footnote. Additional details regarding the assessments are provided in Section 7.4. Please refer to Section 6 for dosing details. Patients will continue treatment until they meet criteria for discontinuation, as described in Section 6.16.

Table 7-2: Schedule of Treatment Period Assessments

Procedure	Cycle 1						Cycle 2				Cycle 3				Later Cycles
Day of Cycle	**1**	**2**	**8**	**9**	**15**	**22**	**1**	**8**	**15**	**22**	**1**	**8**	**15**	**22**	**Visits on Days 1, 8, 15, and 22**
Adverse events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Safety Assessments															
Complete physical examination	X														
Abbreviated physical examination			X		X	X	X	X	X	X	X	X	X	X	D1 of each cycle
Weight	X						X				X				D1 of each cycle
Vital signs	~14×		~14×		3×	3×	3×	3×	3×	3×	3×	3×	3×	3×	3× each dosing day
12-lead ECG (single)	2×						2×				2×				2× on C4D1, C5D1, and C6D1
ECOG performance status	X										X				D1 of each cycle
Hematology panel	X	X	X	X	X	X	X	X	X	X	X		X		D1 of each cycle
Chemistry panel	X		X		X	X	X	X	X	X	X		X		D1 of each cycle
Thyroid function	X						X				X				
Urine pregnancy test (women of childbearing potential)	X						X				X				D1 of each cycle
PK and Immunogenicity															
Pharmacokinetic sampling	8×	3×	8×	X	4×	4×	2×		2×		2×		2×		2× on D1 of odd-numbered cycles
Immunogenicity sampling	X		X		X		X				X				D1 of odd-numbered cycles
Disease Assessment															
CT/MRI scans and disease assessment											X				Q8W to W40 (C3, C5, C7, C9, C11), then Q12W (C14, C17, etc)
[redacted]															
Tumor biopsy	Between C1D9 and C1D16 (required for ≥ 10 patients in Phase II, optional for all other patients) Optional for all patients at time of progression														
[redacted]															

[redacted]															
IMCnyeso administration	X		X		X	X	X	X	X	X	X	X	X	X	D1, D8, D15, and D22 of each cycle

AE = adverse event; C#D# = Cycle # Day #; [redacted]; CT = computerized tomography; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; EOI = end of infusion; hr = hour(s); min = minutes; MRI = magnetic resonance imaging; [redacted]; PK = pharmacokinetics; Q#W = every # weeks; [redacted]; W = week.

ECG assessments are to be done pre-dose and within 1 hour of EOI on indicated days.

Vital signs (body temperature, pulse, respiratory rate, and blood pressure; in addition, oxygen saturation should be collected for ≥ first 3 cycles of treatment) are to be assessed at the following timepoints:

- C1D1/C1D2 and C1D8/C1D9: pre-dose (within 2 hours), EOI (within 15 min), every 2 hours (± 15 min) through 12-hour post-EOI, every 4 hours (± 30 min) until discharge
- All other doses: pre-dose (within 2 hours), EOI (within 15 min), and 1-hour post-EOI (± 15 min)

Pharmacokinetics samples are to be collected at the following timepoints:

- C1D1 and C1D8: pre-dose (within 2 hours), EOI (within 15 min), 1-hour post-EOI (± 15 min), 2-hour post-EOI (± 15 min), 4-hour post-EOI (± 15 min), 6-hour post-EOI (± 30 min), 8-hour post-EOI (± 1 hr), and 12-hour post-EOI (± 3 hr)
- C1D2: 24-hour post-EOI (± 4 hr), 36-hour post-EOI (optional, ± 4 hr), and 48-hour post-EOI (optional, ± 4 hr)
- C1D9: 24-hour post-EOI (± 4 hr)
- C1D15 and C1D22: pre-dose (within 2 hours), EOI (within 15 min), 8-hour post dose (± 1 hr), and 12-hour post-EOI (optional, ± 3 hr)
- C2D1, C2D15, C3D1, C3D15, and D1 of subsequent odd-numbered cycles: pre-dose (within 2 hours), EOI (within 15 min)
- An unscheduled PK sample should be collected just after an ECG performed due to any unexpected cardiac signal

Central lab cytokine testing samples are to be collected at the following timepoints:

- C1D1 and C1D8: pre-dose (within 2 hours), 4-hour post-EOI (± 15 min), 8-hour post-EOI (± 1 hr), and 12-hour post-EOI (± 3 hr)
- C1D2 and C1D9: 24-hour post-EOI (± 4 hr)
- C1D15, C1D22, C2D1, and C3D1: pre-dose (within 2 hours) and 4-hour post-EOI (± 15 min)
- Additional samples may be collected if a patient has suspected CRS. Recommended timepoints are < 5 hours and 1 week after occurrence of the AE

[redacted]

7.3 Safety, Disease Progression, and Survival Follow-Up Period Schedule

Patients may voluntarily discontinue study treatment for any reason at any time. If a patient decides to discontinue study treatment, the Investigator should make every effort to determine the primary reason for this decision and record this information in the patient's chart and on the appropriate eCRF pages. Reasons for discontinuation of study treatment are outlined in Section 6.16.

At the time a patient discontinues study treatment, a visit should be scheduled as soon as possible, within 14 days of the last dose of study drug or within 14 days of the decision to permanently discontinue study treatment. If the decision to withdraw the patient occurs at a regularly scheduled visit, that visit may become the EOT visit.

Safety Follow-Up Period: Information related to all AEs (including concomitant medication taken for ongoing AEs) and SAEs will be collected for 30 days after the last dose of study drug. All AEs suspected to be related to study treatment and all SAEs should be followed up QW or as clinically indicated until resolution or stabilization. If a patient initiates subsequent systemic anti-cancer therapy, the patient will transition from Safety Follow-Up to Survival Follow-Up. Treatment-related SAEs should be reported, even if Safety Follow-Up has been completed.

Disease Progression Follow-Up Period: Patients who discontinue study treatment for any reason other than death, unequivocal disease progression, lost to follow-up, withdrawal of consent, start of new cancer therapy or study termination, should continue tumor evaluation assessments until progression of disease per RECIST v.1.1. If patients refuse to return for these visits or are unable to do so, every effort should be made to contact them, or a knowledgeable informant, by telephone to determine if the patient had disease progression. If a patient starts a new anti-cancer therapy during this period, Disease Progression Follow-Up will cease.

Survival Follow-Up Period: Patients will be followed for survival every 3 months (may be done by telephone call) until death or until the end of the study is reached, unless they withdraw consent or are lost to follow-up. For patients whose status is unclear because they fail to appear for study visits without stating an intention to withdraw consent, the Investigator should show "due diligence" by contacting the patient, family, or family physician as agreed in the informed consent. The Investigator should record in the source documents the steps taken to contact the patient, eg, dates of telephone calls, registered letters, etc. A patient should not be considered lost to follow-up until due diligence has been completed. Patients lost to follow-up should be recorded as such on the appropriate Patient Disposition eCRF.

Assessments required as part of the study are presented by visit in Table 7-3. A visit window of ±14 days is allowed during follow-up.

Table 7-3: Schedule of Follow-Up Assessments

Procedure	EOT	30 days post last dose	90 days post last dose then Q3M
All Patients			
Survival contact		X	X
Subsequent anti-cancer treatment	X	X	X
Patients in Safety Follow-Up			
Adverse events	X	X	
Concomitant medications	X	X	
Abbreviated physical examination	X	X	
Weight	X	X	
Vital signs	X	X	
12-lead ECG (single)	X	Only if abnormal at EOT	
ECOG performance status	X	X	
Hematology panel	X	X	
Chemistry panel	X	X	
Coagulation	X	Only if abnormal at EOT	
Urinalysis	X	Only if abnormal at EOT	
Thyroid function	X	Only if abnormal at EOT	
Pregnancy test (serum or urine, women of childbearing potential)	X	X	
Immunogenicity	X		
Patients in Disease Progression Follow-Up			
CT/MRI scans and disease assessment	Q8W to Week 40 (post C1D1) then Q12W		
Tumor biopsy (optional)	Recommended at time of progression		

CT = computed tomography; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; EOT = End of Treatment; MRI = magnetic resonance imaging; PK = pharmacokinetics; Q3M = every 3 months.

7.4 Details of Assessments

Details for the collection, processing, storage and shipment of all samples are provided in the laboratory manual along with the order of prioritization for sampling, where sampling time points are scheduled to occur at the same time. Blood samples scheduled at the same time point should be taken after the ECGs have been completed. Any remaining [redacted] samples may be kept for up to 15 years after the end of the study for additional testing to understand the cancer, the drug response, or to validate diagnostic/[redacted] assays.

7.4.1 HLA-A*02:01 and NY-ESO-1 / LAGE-1A Testing

A 2 mL blood sample will be taken and sent to the central laboratory for DNA extraction and determination of HLA-A*02:01 status using a sequence-based assay for HLA-A*02:01. Any remaining DNA sample will be kept up to 15 years in case additional testing is required.

If the patient is already known to be HLA-A*02:01 positive, the HLA sample and tumor sample can be submitted in parallel, otherwise patients must have HLA-A*02:01 tested centrally and be confirmed as positive prior to tumor samples being sent for NY-ESO-1 and LAGE-1A expression testing.

Patients confirmed as HLA-A*02:01 positive will submit a tumor sample for NY-ESO-1 and LAGE-1A expression testing. This can be an archival or fresh sample. NY-ESO-1 and LAGE-1A antigen positivity will be confirmed using a quantitative, real-time, reverse transcription polymerase chain reaction (qRT-PCR) assay that tests in parallel for NY-ESO-1 and LAGE-1A expression levels.

Further background regarding the NY-ESO-1 / LAGE-1A screening strategy is provided in Section 1.5.

7.4.2 Patient Demographics and Other Baseline Characteristics

Data to be collected will include general patient demographics, relevant medical history and current medical conditions, diagnosis and extent of cancer, details of prior anti-cancer treatments (including systemic therapy, radiotherapy, and surgery), prior/concomitant medications, prior procedures, significant non-drug therapies and any other assessments done for determining eligibility for inclusion in the study.

7.4.3 Efficacy Assessments

Tumor response will be determined locally according to (RECIST) v.1.1. Further details about RECIST v1.1 are in Section 13.1. Patients may receive treatment after disease progression per RECIST v1.1 based on criteria in Section 6.18.

During the study, Immunocore may decide to have a central review of the radiological assessments performed. In such case, the Investigator's staff will be instructed on how to send data from these radiological assessments to the Contract Research Organization (CRO) for central review when needed.

The Sponsor reserves the right to request additional scans obtained within 6 months of the screening assessment to evaluate tumor growth kinetics prior to and following treatment with IMCnyeso.

See Table 7-4 for details regarding disease assessments. If a patient is intolerant of iodine-based contrast agents, CT may be performed without contrast. Visible skin lesions and easily palpable subcutaneous tumors may be measured by physical examination using a ruler or calipers. Ultrasound should not be used to measure sites of disease.

Table 7-4: Disease Assessment Collection Plan

Procedure	Screening/Baseline	During Treatment / Follow-up
CT or MRI with contrast enhancement (chest and abdomen; also, pelvis as appropriate based on indication and extent of disease)	Mandatory	Mandatory The same imaging modality should be used throughout the study (CT or MRI)
Brain MRI with contrast	Required only if clinical suspicion of brain metastasis at Screening	If disease was detected at Baseline or if clinically indicated

CT = computed tomography scan; MRI = magnetic resonance imaging.

7.4.4 Safety and Tolerability Assessments

Safety will be monitored by performing physical examination, and evaluating vital signs, ECG, weight, performance status, hematology, chemistry, coagulation, urinalysis, thyroid function, cytokine testing, and collection of AEs. Significant findings present at Screening must be included in the Medical History eCRF page. Significant new findings that begin or worsen after the start of Screening must be recorded as AEs in eCRF.

A complete physical examination will include the examination of general appearance, skin, neck (including thyroid), eyes, ears, nose, throat, lungs, heart, abdomen, back, lymph nodes, extremities, and neurological system. If indicated based on medical history and/or symptoms, rectal, external genitalia, breast, and pelvic exams will be performed. An abbreviated physical examination will include the examination of general appearance and body sites as directed by signs and symptoms.

Vital signs include body temperature, pulse, respiratory rate, and blood pressure. Additionally, blood oxygen saturation should be included in vital sign assessments at Screening and for at least the first 3 treatment cycles. Vital signs should be assessed on the scheduled day, even if study treatment is being withheld. More frequent examinations may be performed, at the discretion of the Investigator, if medically indicated and should be recorded as unscheduled assessments in the eCRF.

Height will be measured in cm and body weight to the nearest 0.1 kg in indoor clothing.

A standard 12-lead ECG will be performed (in triplicate at Screening and once at other timepoints). To ensure the safety of the patients, a qualified individual at the Investigator Site will review the ECG measurements. New or worsening clinically significant ECG findings occurring after informed consent should be confirmed by performing at least 2 additional ECG reads within approximately 30 minutes and taking the average of at least 3 manually over-read measurements. Confirmed new or worsening clinically significant ECG abnormalities must be reported as AEs in the eCRF.

Eastern Cooperative Oncology Group (ECOG) performance status is determined as indicated in Table 7-5.

Table 7-5: ECOG Performance Status

Grade	Eastern Cooperative Oncology Group Status
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (eg, light housework, office work)
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
3	Capable of only limited self-care. Confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair
5	Death

Laboratory parameters assessed for safety purposes, shown in Table 7-6 will be evaluated locally. Normal ranges and accreditation documentation must be provided for all local laboratories. More frequent evaluations may be performed if medically indicated; results should be recorded as unscheduled laboratory assessments in the eCRF.

Table 7-6: Local Clinical Laboratory Parameters Collection Plan

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 = triiodothyroxine; 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, 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.

7.4.5 Pharmacokinetics and Immunogenicity Assessments

Blood samples (2 mL) will be taken for IMCnyeso PK analysis. At C1D1 and C1D8, a full PK profile sampling schedule is specified, assuming hospitalization of the patient for these doses and "out-patient" sampling at doses 3 and 4 (C1D15 and C1D22). To generate C_{min} data only, subsequent sampling is limited to pre-dose and EOT. It is essential that the actual time and date of sample collection is recorded on the patient's eCRF.

A 2-mL blood sample will also be taken to measure IMCnyeso anti-drug antibody (ADA) levels.

[redacted]

7.4.6.3 Skin Punch Biopsy

An OPTIONAL skin punch biopsy (3 mm or 5 mm, depending on the size of the area affected) is to be taken in patients experiencing ≥ Grade 3 rash, to characterize immune activation status in the skin and potentially identify the mechanisms of skin toxicity. [redacted]

8 ADVERSE EVENTS AND SAFETY REPORTING

8.1 Assessment of Safety

Timely, accurate and complete reporting and analysis of safety information from clinical studies are crucial for the protection of patients and is mandated by regulatory agencies worldwide. The Sponsor and CRO have established standard operating procedures in conformity with regulatory requirements worldwide to ensure appropriate reporting of all safety information. All clinical studies conducted by the Sponsor or its affiliates will be conducted in accordance with those procedures.

Individual AEs should be evaluated by the Investigator and should be reported to the CRO/Sponsor for evaluation. This includes the evaluation of the event's seriousness and the causality between the study drug and/or concomitant therapy and the AE. The CRO/Sponsor is required to maintain detailed records of all AEs reported by the Investigator(s) and to perform an evaluation with respect to seriousness, causality, and expectedness. On request of a competent authority in whose territory the clinical trial is being conducted, the Sponsor should submit detailed records of all AEs that are reported by the relevant Investigators. Case report processing includes evaluation of data in individual cases, identification of individual cases requiring specific handling, recognition and processing of alerts, and any other data processing of aggregated cases.

8.2 Definitions

Definitions of AEs, adverse drug reactions, SAEs, serious, unexpected adverse drug reactions (SUSARs), and AEs of special interest (AESI) are presented below.

AE: An AE is defined as the appearance of (or worsening of pre-existing) an undesirable sign, symptom, or medical condition that occurs after patient's signed ICF has been obtained. Abnormal laboratory values or test results occurring after informed consent constitute AEs only if they induce clinical signs or symptoms, are considered clinically significant, require therapy (eg, hematologic abnormality that requires transfusion or hematological stem cell support), or require changes in study medication.

Adverse drug reaction: An adverse drug reaction is an unwanted or harmful reaction that occurs after administration of a drug or drugs and is suspected or known to be due to the drug. Adverse drug reactions have traditionally been categorized as pharmacologic (predicted based on the pharmacology of the drug) or idiosyncratic (not predicted based on pharmacology).

SAE: A SAE is any AE that meets any of the following criteria:

- Is fatal or life-threatening
- Results in persistent or significant disability or incapacity
- Constitutes a congenital anomaly/birth defect
- Is medically significant, ie, defined as an event that jeopardizes the patient or may require medical or surgical intervention to prevent the outcomes listed above
- Requires in-patient hospitalization or prolongation of existing hospitalization, unless hospitalization is for the following:
    - Routine treatment or monitoring of the studied indication not associated with any deterioration in condition
    - Elective or pre-planned treatment for a pre-existing condition that is unrelated to the indication under study and has not worsened since signing the informed consent
    - Treatment on an emergency out-patient basis for an event not fulfilling any of the definitions of a SAE given above and not resulting in hospital admission
    - Social reasons and respite care in the absence of any deterioration in the patient's general condition

Unexpected adverse drug reaction: An adverse drug reaction that is not consistent with applicable product information or characteristics of the study drug.

Suspected, unexpected, serious adverse reaction (SUSAR): A SUSAR is an adverse reaction meeting serious criteria (above), the nature or severity of which is not consistent with the reference safety information for the investigational drug(s).

Adverse events of special interest (AESI): An AESI (serious or non-serious) is an AE with scientific and/or medical concern specific to the Sponsor's program, for which ongoing monitoring and rapid communication by the Investigator to the Sponsor can be appropriate. CRS is considered as an AESI for IMCnyeso. Refer to the IMCnyeso Investigator's Brochure for details on the AESI for IMCnyeso.

8.3 Criteria for Expectedness

The concept of expectedness refers to events that may or may not have previously been observed and documented and not necessarily the known pharmacological properties of the medicine. An AE will be unexpected for purposes of regulatory reporting unless it is mentioned in the

appropriate reference safety information within the current Investigator's Brochure for the investigational drug, even if it is a medical occurrence expected for the disease being treated.

8.4 Assessment of Causality

The Investigator decides whether he or she interprets the observed AE as either related to disease, to the study medication, study procedure, or other concomitant treatment or pathologies. To assess the relationship of the AE to the study drug, the following terms are defined:

- **Related**: A direct cause and effect relationship between the study treatment and the AE is likely
- **Possibly related**: A cause and effect relationship between the study treatment and the AE has not been demonstrated at this time and is not probable, but is also not impossible
- **Not related**: Without question, the AE is definitely not associated with the study treatment

All "related" and "possibly related" AEs and SAEs will be defined as related to study drug.

8.5 Adverse Event Reporting

The Investigator must notify the Sponsor within 24 hours of any SAE, DLT, ≥ Grade 2 CRS, or ≥ Grade 3 hepatic function abnormality.

8.5.1 Expedited Reporting

Cases of adverse drug reactions from all sources that are assessed as serious are subject to expedited reporting. Expedited reporting of cases will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRB/IEC and Investigators. Additionally, any safety information from other observations that could change the benefit-risk evaluation of the product will be communicated in an expedited manner to the regulatory authorities and all Investigators by the Sponsor.

The CRO will be responsible for the processing and reporting of SAEs. AEs will be coded by using International Conference on Harmonisation (ICH) Medical Dictionary for Regulatory Activities.

Minimum criteria for a valid adverse drug reaction case have been established by ICH and individual regulatory agencies and are listed as the following:

- An identifiable reporter

- An identifiable patient
- A reaction/event
- A suspected medicinal product
- Other safety issues that also qualify for expedited reporting by the Sponsor are those that would materially alter the current benefit-risk assessment of the investigational product (sufficient to consider changes in the administration or in the overall conduct of the trial). Although these events will not be reported as SUSARs, they might require other action, such as putting in place urgent safety measures, the generation of substantial amendments, or early termination of the trial. The Sponsor will inform the regulatory authorities and all IEC of safety issues that might materially alter the benefit-risk assessment of the investigational agents.

8.5.2 Standards for Expedited Reporting

Cases of adverse drug reactions from all sources that are assessed as suspected, unexpected and serious (SUSAR) are subject to expedited reporting. Additionally, any safety information from other observations that could change the benefit-risk evaluation of the product should be promptly communicated to the regulatory authorities. Any other SUSARs associated with the investigational product should be reported as soon as the Sponsor becomes aware of them. This includes SUSARs that occur in another trial conducted by the same Sponsor, are identified by spontaneous reports or a publication, or are transmitted to the Sponsor by another regulatory authority.

8.5.3 Reporting of Out-of-Range Laboratory Test Results as Adverse Events

Out-of-range laboratory test results should be reported as AEs if, in the opinion of the Principal Investigator, they are clinically significant. Abnormal laboratory results that are not considered to be clinically significant will not be reported as AEs. Significance of abnormal laboratory results should be documented in the study records.

When an abnormal laboratory value is recorded as an AE, the diagnosis (eg, anemia) should be recorded as the event term, not the abnormality (eg, low hemoglobin or hemoglobin decreased).

8.5.4 Reporting Events Associated with Disease Progression

Clinically significant signs or symptoms that occur due to disease progression should be reported as AE/SAE. However, to avoid inconsistencies in the clinical database, neither the term “disease progression” nor identification of a new lesion should be reported as an AE/SAE. Instead, information about disease progression, including any new lesions, is to be reported on the disease assessment pages. Similarly, death due to progression of the malignancy under study should not

be reported as a fatal SAE, and information about the cause of death is to be reported on the death eCRF page.

8.5.5 Reporting Guidelines for Other Observations

Other safety issues that qualify for expedited reporting where they might materially alter the current benefit-risk assessment of the investigational product (sufficient to consider changes in the administration or in the overall conduct of the trial) include:

- An increase in the rate of occurrence of an expected serious adverse reaction, which is judged to be clinically important
- A post-study SUSAR that occurs after the patient has completed a clinical trial and is reported by the Investigator to the Sponsor

Events that occur during the trial and are relevant in terms of patient safety, but do not fall within the definition of SUSAR (therefore are not subject to the reporting requirements for SUSARs) are:

- A SAE that could be associated with the trial procedures and could modify the conduct of the trial
- A significant hazard to the patient population (eg, lack of efficacy of an investigational medicinal product)
- A major safety finding from a newly completed animal study (eg, carcinogenicity)
- A temporary halt of a trial for safety reasons if the trial is conducted with the same investigational medicinal product in another country by the same Sponsor
- Safety recommendations of the SST

Although these events/observations will not be reported as SUSARs, they might require other action, such as putting in place urgent safety measures, the generation of substantial amendments, or early termination of the trial. The Sponsor will inform the regulatory authorities and the IEC of safety issues that might materially alter the benefit-risk assessment of the investigational medicinal product.

Expedited reporting is not usually required for reactions that are serious but expected or for non-serious adverse reactions whether expected or not. It is also usually inappropriate to report events that are considered unrelated to the investigational medicinal product.

8.5.6 Pregnancy Reporting

Pregnancy will be reported through the Pregnancy Reporting Form (paper) and in the eCRF. The Pregnancy Reporting Form (paper) should be completed and reported as indicated to the CRO pharmacovigilance team within 24 hours of being made aware of the event. Women who become pregnant during the study will be withdrawn from treatment at the earliest opportunity. The CRO will then notify the Sponsor within 1-business day of being informed of the event. Following permanent discontinuation of study treatment, every attempt will be made to follow the patient and any resulting offspring for up to 6-weeks postpartum, unless otherwise medically indicated. Abortion, stillbirth, or any malformation/disease in the offspring must be reported as a SAE.

For men participating in the study who report the pregnancy of a partner, the Investigator will ask to collect information about the results of the pregnancy/birth using the Pregnant Partner Form. The partner may be asked to sign a consent form giving permission for information to be collected. This health information will become part of the research study records. It will be shared with the Sponsor.

8.6 Investigator's Responsibilities

The Investigator is responsible for the collection of AE data. All AEs must be recorded in the eCRF.

The Investigator must report all SAEs within 24 hours of being made aware of the event to pharmacovigilance via the clinical database by completing as much information about the AE as possible in the eCRF and checking "Yes" on the "Serious?" checkbox. The initial reporting can be supplemented by written reports using the SAE report form provided.

If the eCRF is unavailable, or paper reports are to be submitted, forms should be faxed to the CRO pharmacovigilance team using the safety hotline number:

- Safety Hotline (Fax): [redacted] (US and Canada), [redacted] (UK)

The following minimum information is required for the SAE report:

- Patient identification (patient number and age)
- Trial number
- Study therapy (dose, route, form, regime, start date, and end date)
- Concomitant medication (including dose, route, form, regimen, and start date where available)

- Nature of SAE (overall diagnosis where available or signs and symptoms)
- Date and time of occurrence
- Any associated factors (concomitant disease or medication)
- Proposed relationship to study therapy
- Outcome
- Identification of the reporter
- Action in relation to study (withdrawn from treatment, suspended, or none)

Investigators may be asked for additional information for any reported SAE, such as laboratory or diagnostic reports or the outcome of the event. A SAE follow-up report with attached documents (if necessary) should be forwarded to CRO pharmacovigilance as soon as the additional information is available by email. The study number IMCnyeso-101 must be in the title of any email for study identification purposes and the unique patient identification number must be referenced.

8.7 Sponsor and Clinical Research Organization's Responsibilities

The Sponsor is responsible for the ongoing safety evaluation of the investigational drugs being studied. The Sponsor and CRO are responsible for ensuring that expedited reports are made to all concerned Investigators, to the IEC where required, and to all regulatory authorities of all adverse drug reactions that are both serious and unexpected, findings that could adversely affect the health of patients, impact the conduct of the trial, or alter the competent authority's authorization to continue the trial in accordance with local applicable regulations.

9 STATISTICAL METHODS AND DATA ANALYSES

9.1 General Principles

Categorical data will be presented as frequencies and percentages. For continuous data, the mean, standard deviation, median, minimum and the maximum will be presented.

The Phase I study data will be analyzed and reported based on all patient data from the dose escalation up to the time when all Phase I patients have completed at least 6 cycles of treatment or have discontinued study treatment. Data will be listed, summarized, and analyzed by treatment group. Data for the Phase II expansion cohorts will be reported separately, with a data cut off at the point where at least 80% of patients have completed the follow up for disease progression or discontinued the study for any reason. Additional details of data reporting will be outlined in the statistical analysis plan (SAP).

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 listings
- Baseline is defined as the last assessment prior to the first dose of treatment received (ie, C1D1 pre-dose)
- For Phase I, all summaries, listings, figures and analyses will be performed by treatment group
- For Phase II, all summaries, listings and figures for primary efficacy analyses and safety analyses will be presented by disease group (NSCLC, urothelial carcinoma, or synovial sarcoma)

Patients from the dose escalation and dose expansion may be pooled for the RP2D. Additional analyses not described here will also be detailed in the SAP.

Unless otherwise stated, missing data will simply be noted as missing on appropriate tables/listings.

Compliance with the protocol will be assessed by the number and proportion of patients with protocol deviations. Protocol deviations will be identified prior to database lock and will be listed and summarized.

9.2 Analysis Sets

9.2.1 Full Analysis Set

The full analysis set (FAS) comprises all patients who received at least 1 full dose or partial dose of IMCnyeso. Patients will be analyzed according to the planned treatment. The FAS will be used for all listings of raw data, demography and baseline characteristics. Unless otherwise specified, the FAS will be the default analysis set used for analyses.

9.2.2 Safety Analysis Set

The safety analysis set 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. The safety analysis set will be used for the safety summary of the study. If the safety analysis set and the FAS are identical, then analyses described by the safety analysis set will not be performed.

9.2.3 Per-Protocol Analysis Set

The per-protocol set (PPS) consists of a subset of FAS patients who meet these 4 criteria:

- Presence of measurable disease according to RECIST v1.1
- At least 1 post-baseline tumor assessment or discontinued prior to the first tumor assessment
- Received at least 1 dose of planned treatment at the RP2D
- No violation of key inclusion or exclusion criteria (to be defined in the SAP)

Patients in the PPS will be classified according to planned treatment. If the PPS and the FAS are identical, then analyses described by the PPS will not be performed.

9.2.4 Dose-Determining Analysis Set

The DDS consists of all patients from the safety analysis set in Phase I who meet the criteria described in Section 6.10.2.

9.2.5 Pharmacokinetic Analysis Set

The PK analysis set consists of all patients who have at least 1 blood sample providing evaluable PK data. The PK analysis set will be used for all PK analyses.

Note: 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.

9.3 Patient Demographics and Other Baseline Characteristics

Demographic data, baseline disease characteristics, and other baseline data will be listed in detail. Qualitative data (eg, performance status) and quantitative data (eg, weight) will be summarized by descriptive statistics.

9.4 Treatment Data

Actual dose and duration in days of treatment for IMCnyeso, as well as the dose intensity (actual dose received/actual duration) and relative dose intensity (the ratio of dose intensity to planned dose/planned duration) will be summarized by descriptive statistics by treatment group.

Concomitant medications and significant non-drug therapies prior to and after the start of the study treatment will be listed by patient and summarized by anatomical therapeutic chemical term and treatment group.

The reason for discontinuation from treatment will be summarized and listed, along with dates of first and last doses, duration of exposure to each study drug, and date of discontinuation for each patient.

9.5 Primary Analysis Variables

9.5.1 Phase I: DLT

In Phase I, the primary variable is the occurrence of 1 or more DLTs. An adaptive BLRM guided by the EWOC principle will be used to guide dose recommendations and estimate the MTD, as described in Section 6.10 and Section 13.3.

Patients in Phase I who are ineligible for the DDS will be excluded from the primary analysis, although their data will be used for all remaining analyses.

As a supportive analysis in the Phase I dose escalation part of the study, a dose-exposure relationship may be estimated for IMCnyeso via a BLRM to further guide the dose recommendation to targeted exposure of IMCnyeso. From the estimation of the dose-exposure model, the following posterior summaries will be derived for each dose:

- Mean, median, standard deviation, and 95%-credible interval for the exposure
- The probability that the true AUC after first dose of treatment achieves the target exposure

9.5.2 Phase II: Efficacy

In Phase II, the primary endpoint is the best overall response (BOR). The primary summary measure is ORR, defined as the proportion of patients with a BOR of complete response (CR) or partial response (PR) based on local Investigator assessment, as defined in RECIST v.1.1. ORR will be analyzed separately for the Phase II cohorts. Confirmation of response is required for declaring a PR or CR as the BOR. A confirmed response is defined as a CR or PR followed by a CR or PR at least 4 weeks later. ORR will be summarized with accompanying 95% confidence interval.

9.6 Secondary Analysis Variables

9.6.1 Efficacy

Analysis of efficacy endpoints will be performed using the FAS unless otherwise noted. For all efficacy parameters, data will be listed, summarized, or analyzed by treatment group for the Phase I dose escalation and separately for the Phase II expansion cohorts.

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. Best overall change in tumor size for individual patients will be shown in waterfall plots.

PFS and OS will be listed by patient. PFS will be presented graphically using Kaplan-Meier plots including all patients treated at the MTD or RP2D and by disease group. 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. Similarly, OS will be presented graphically using Kaplan-Meier plots including all patients treated at the MTD or RP2D and by disease group. Median OS time and the proportion of patients who are alive at 3, 6, 9, and 12 months will be estimated.

DoR and time-to-response for patients who experience a CR or PR at any time on study will be listed by patient. If a large proportion of patients achieve a response (eg, 5/10), Kaplan-Meier plots for DoR will also be produced, and the median DoR will be estimated.

9.6.2 Safety

For all safety analyses, the safety analysis set will be used. All listings and tables will be presented by treatment group.

9.6.2.1 Adverse Events

The AE summary tables include only AEs that are new or worsened during the on-treatment period (treatment-emergent AEs). 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 treatment-emergent AEs will be summarized by system organ class and/or preferred term, severity (based on NCI CTCAE v.4.03 grades), type of AE, and relation to study treatment by treatment group. Deaths reportable as SAEs and non-fatal SAEs will be listed by patient and tabulated by type of AE and treatment group.

Definitions of notably abnormal vital signs results (eg, hypotension) will be specified in the SAP and a shift table of Baseline to worst on-treatment result will be produced by the Phase I dose escalation and the Phase II expansion groups.

9.6.2.2 Laboratory Abnormalities

For laboratory tests covered by the NCI CTCAE version 4.03, the study team will grade laboratory data accordingly. 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.

The following by-treatment summaries will be generated separately for hematology, biochemistry, and other laboratory data:

- Frequency table for newly occurring on-treatment Grade 3 or 4 and all grades
- Shift tables of laboratory and ECG data using CTCAE grades to compare Baseline to the worst on-treatment value
- Listing of all clinically relevant laboratory data and relevant ECG data with values flagged to show the corresponding CTCAE grades and the classifications relative to the laboratory normal ranges

Other exploratory analyses, eg, figures plotting time course of raw or change in laboratory tests over time or box plots, may be specified in the SAP.

9.6.2.3 Other Safety Variables

- Vital signs, absolute values and changes from Baseline will be summarized. Normal ranges will be specified in the SAP and shift tables of Baseline to worst on-treatment results will be produced
- ECG data: QTcF interval absolute values and changes from Baseline will be summarized. Abnormalities will be classified according to NCI CTCAE grades and shift tables of Baseline to worst on-treatment results will be presented

9.6.2.4 Tolerability

Tolerability of study treatment will be assessed by summarizing the number of treatment dose interruptions and dose reductions. Reasons for dose interruptions and dose reductions will be listed by patient and summarized.

9.6.3 Pharmacokinetics and Immunogenicity

The PK parameters that will be assessed are presented in Table 9-1.

Table 9-1: Pharmacokinetic Parameters to be Analyzed

Parameter	Definition
AUC_{last}	The area under the curve (AUC) from time 0 to the last measurable concentration sampling time (t_{last}) (mass × time × volume^{-1})
AUC_{inf}	The AUC from time 0 to infinity (mass × time × volume^{-1})
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
CL	The total body clearance of drug from the plasma (volume × time^{-1})
Vz	The apparent volume of distribution during terminal phase (associated with λz) (volume)
AR	Accumulation ratio = maximum observed concentration (C_{max} [multiple dose]/C_{max} [single dose])

The safety analysis set will be used in all PK data analysis and PK summary statistics.

Descriptive statistics of all PK parameters for IMCnyeso will include arithmetic and geometric mean, median, standard deviation and coefficient of variation, geometric coefficient of variation and minimum and maximum. Zero concentrations will not be included in the geometric mean calculation. Since T_{max} is generally evaluated by a non-parametric method, median values and ranges will be given for this parameter. Missing concentration values will be reported as is in data listings. Concentration values below lower limit of quantitation will be handled as 0 in summary statistics and reported as is in data listings. Any missing PK parameter data will not be imputed.

The PK data will be displayed graphically. Displays will include individual patient plasma concentration profiles (on the linear and log-scale) versus time and geometric mean plasma concentration (± standard deviation) versus time, stratified by dose.

Scatter plots of PK parameters versus dose, or log-dose will also be considered to assess dose proportionality. In a preliminary assessment of dose proportionality, log-transformed AUC and C_{max} parameter estimates will be examined using the Power Model:

$$\text{parameter} = e^{a} (\text{dose})^{b}$$

ie, $\log(\text{parameter}) = a + (b * \log(\text{dose}))$

where a is the intercept, depending on patients, and b is the slope, measuring the extent of dose proportionality. Dose proportionality implies that the slope of the regression line b = 1 and will be assessed by estimating b along with its confidence interval.

Further analyses may be conducted using population PK approaches. In addition, a model-based approach may be used to explore the potential relationship between efficacy, safety, and/or [redacted] endpoints and IMCnyeso concentration and/or exposure metrics. All analyses will be reported either in the clinical study report or a stand-alone report.

The safety analysis set will be used in all immunogenicity analyses. The frequency of ADA at baseline and following treatment will be summarized. All analyses will be reported either in the clinical study report or a stand-alone report.

9.7 Exploratory Analyses

[redacted]

9.8 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 (Section 6.10).

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 (Section 9.9.2).

9.9 Sample Size Calculation

9.9.1 Phase I Escalation Cohorts

Dose decisions will be guided by the BLRM. Among the simulations that were conducted (see Section 13.3), the mean sample size was 27 patients, and the sample size was less than 33 patients in over 80% of simulations.

9.9.2 Phase II Expansion Cohorts

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).

10 DATA HANDLING AND MANAGEMENT

All data collected during this study, including clinical and [redacted] data, may be pooled with data from other studies using the same study drug or a different study drug with a similar mechanism (eg, ImmTAC) in order to advance our understanding about study drug safety, [redacted] correlation with a variety of outcomes, or other study endpoints in order inform future development provided the patient provides consent to permit such pooling of data.

10.1 Data Confidentiality

Information about study patients will be kept confidential and managed under the applicable laws and regulations. Those regulations require a signed patient authorization informing the patient of the protected health information that will be collected and the use or disclosure of that information. If the patient revokes authorization to collect or use this information, the Investigator, by regulation, retains the ability to use all information collected prior to the revocation of patient authorization. To protect the health information of study patients, access to the data collection system will be controlled by a sequence of individual user identification codes and passwords that are made available only to authorized trained personnel.

10.2 Site Monitoring

Before study initiation at trial sites, Sponsor and/or CRO study team members will review the protocol and eCRFs with the Investigators and the site study staff. During the study, the field monitor will visit the site regularly to check the completeness of patient records, the accuracy of entries on the eCRFs, the adherence of the protocol to Good Clinical Practice, the progress of enrollment, and to ensure that study treatments are being stored, dispensed, and accounted for according to specifications. Key study personnel must be available to assist the field monitor during these visits. The Investigator must assure that the site monitor is allowed access to all study files, including all site medical records, case and visit notes and laboratory reports.

10.3 Data Collection

The Investigator is required to maintain source documents for each study patient, consisting of case and visit notes (site medical records), containing demographic and medical information, laboratory data, ECGs, and the results of any other tests or assessments. All information recorded in the eCRF must be traceable to source documents in the patient's file. The Investigator must also keep an original signed ICF and provide an original signed copy to the patient.

This study will use an electronic data capture (EDC) system and the Principal Investigator and site study staff will enter the data required by the protocol into the eCRF. The eCRF will use fully validated, secure web-enabled software that conforms to 21 CFR Part 11 requirements. The

Principal Investigator and all identified site staff will not be given access to the EDC system until they have been trained. The Principal Investigator is responsible for assuring that the data entered into the eCRF are complete, accurate, and that entry and updates are performed in a timely manner. Field monitors will review the eCRF data entries and assist site personnel with any required corrections or additions.

Tissue samples obtained during the study (eg, tumor, blood for PK, or other analyses) will be collected from the Investigator Sites and analyzed in laboratories contracted by the Sponsor and/or companies employed by the Sponsor (eg, CROs). Radiological scans will be reviewed locally but may be sent for independent central review if deemed necessary. Field monitors will review the eCRF and laboratory paper requisition forms for accuracy and completeness and instruct site personnel to make any required corrections or additions. One copy of the requisition form will be forwarded to each analytical laboratory with the respective sample by the site staff and 1 copy will be retained at the investigational site.

10.4 Database Management

Sponsor clinical study personnel and trial field monitors will review the eCRF data entries and assist site personnel with any required corrections or additions. Electronic data queries stating the nature of the problem and requesting clarification will be created for discrepancies and missing values and sent to the investigational site via the EDC system.

Concomitant treatment and prior medication data in the database will be coded using the World Health Organization (WHO) Drug Reference List, based on the Anatomical Therapeutic Chemical classification. Medical history, current medical conditions and AEs in the database will be coded using the Medical Dictionary for Regulatory Activities terminology. After database lock, the Investigator will receive a CD-ROM of the patient data for archiving at the investigational site.

11 ETHICAL CONSIDERATIONS AND ADMINISTRATIVE PROCEDURES

11.1 Regulatory and Ethical Compliance

This clinical study was designed, shall be implemented and reported in accordance with the ICH Harmonised Tripartite Guidelines for Good Clinical Practice, with applicable local regulations (including European Directive 2001/20/EC and Unites States Code of Federal Regulations, CFR Title 21), and with the ethical principles laid down in the Declaration of Helsinki (2013).

11.2 Responsibilities of the Investigator and Institutional Review Board/Independent Ethics Committee/Research Ethics Board

Before the start of the study the study protocol and/or other relevant documents (eg, ICFs) will be reviewed and approved by the competent authority and an appropriately constituted IRB or IEC, in accordance with local legal requirements. The Sponsor must ensure that all ethical and legal requirements have been met before the first patient is enrolled in the study.

Prior to study start, the Investigator is required to sign a protocol signature page confirming his/her agreement to conduct the study according to the protocol and to give access to all relevant data and records to the Sponsor and/or designated agents of Sponsor (eg, monitors and auditors), the IRB or IEC, the research ethics board (REB) and regulatory authorities as required.

11.3 Informed Consent Procedures

Eligible patients may only be included in the study after providing written (witnessed, where required by law or regulation), IRB/IEC/REB-approved informed consent or, if incapable of doing so, after such consent has been provided by a legally acceptable representative of the patient. In cases where the patient's representative gives consent, the patient should be informed about the study to the extent possible given his/her understanding. If the patient is capable of doing so, he or she should indicate assent by personally signing and dating the written informed consent document or a separate assent form.

Informed consent must be obtained before conducting any study-specific procedures. The only exception is where laboratory and radiologic assessments are performed as part of standard care and have been conducted within the screening window (28 days for radiological assessments, 21 days for all other assessments). The process of obtaining informed consent should be documented in the patient source documents. The date when a patient's informed consent was actually obtained will be captured in the eCRF.

11.4 Discontinuation of the Study

The Sponsor reserves the right to discontinue this study under the conditions specified in the clinical study agreement. Specific conditions for terminating the study are outlined in Section 3.7.

11.5 Publication of Study Protocol and Results

The Sponsor will publish the key design elements of this protocol in a publicly accessible database (clinicaltrials.gov). At the time of study and clinical study report completion, the results of this study will be either submitted for publication and/or posted in a publicly accessible database.

11.6 Study Documentation, Record Keeping, and Retention of Documents

Each participating site will maintain appropriate medical and research records for this study, in compliance with Section 4.9 of the ICH E6 Good Clinical Practice, and regulatory and institutional requirements for the protection of confidentiality of patients. Each site will permit authorized representatives of the Sponsor and regulatory agencies to examine any clinical records for the purposes of quality assurance reviews, audits and evaluation of the study safety and progress. Source data are all information, original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial.

Data collection is the responsibility of the clinical trial staff at the site under the supervision of the Site Principal Investigator. The study eCRF is the primary data collection instrument for the study. The Investigator should ensure the accuracy, completeness, legibility, and timeliness of the data reported in the eCRFs and all other required reports. Data reported on the eCRF, that are derived from source documents, should be consistent with the source documents or the discrepancies should be explained. All data requested on the eCRF must be recorded.

The Investigator should maintain the trial documents as specified in Essential Documents for the Conduct of a Clinical Trial (ICH E6 Section 8) and as required by applicable regulations and guidelines. The Investigator should take measures to prevent accidental or premature destruction of these documents. Essential documents should be retained for a period of not less than 15 years from the completion of the clinical trial unless the Sponsor provides written permission to dispose of them or requires their retention for an additional period of time because of applicable laws, regulations and guidelines.

11.7 Confidentiality of Study Documents and Patient Records

The Investigator must ensure anonymity of the patients; patients must not be identified by name in any documents submitted to the Sponsor and/or designated agents of Sponsor. Signed ICFs

and a patient enrollment log must be maintained in confidence by the Investigator. Patients will be identified on eCRFs and other documents submitted to the Sponsor by study number.

11.8 Audits and Inspections

Source data and all trial documents must be available to inspections by the Sponsor or designee, the CRO and/or Health Authorities.

11.9 Financial Disclosures

Financial disclosures should be provided by study personnel who are directly involved in the treatment or evaluation of patients at the site, prior to study start.

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13 APPENDICES

13.1 Cytokine Release Syndrome Definitions and Grading

Events of CRS should be assessed in accordance with the ASTCT Consensus Guidelines (Lee, 2019).

13.1.1 Definition of CRS

For this study, CRS is defined as a supra-physiological response following IMCnyeso treatment that results in the activation or engagement of endogenous T cells. Symptoms can be progressive, must include fever at the onset, and may include hypotension, capillary leak (hypoxia), and end organ dysfunction. A reasonable temporal relationship to IMCnyeso treatment must be present. Investigators should exclude other causes of fever, hypotension, hemodynamic instability, and/or respiratory distress such as an overwhelming infection.

13.1.2 CRS Grading Criteria

Events of CRS are to be graded based on presence of fever and treatment provided for hypotension and/or hypoxia, as shown in Table 13-1. Associated constitutional symptoms and/or organ toxicities do not influence CRS grading (and are to be graded individually per CTCAE v4.03, consistent with AE grading for this study). In patients who have CRS and then receive treatment with anti-pyretics or anti-cytokine therapy (eg, tocilizumab or steroids), fever is no longer required to grade subsequent CRS severity. In patients experiencing hypotension and hypoxia, grading is to be assigned based on the more severe event.

Table 13-1: ASTCT CRS Grading Criteria

Grade	Fever	with Hypotension	and/or Hypoxia
1	≥ 38.0 °C	None	None
2	≥ 38.0 °C	Not requiring vasopressors	Requiring oxygen delivered by low-flow nasal cannula (≤ 6 L/min) or blow-by
3	≥ 38.0 °C	Requiring a vasopressor with or without vasopressin	Requiring oxygen delivered by high-flow nasal cannula (>6L/min), facemask, nonrebreather mask, or Venturi mask
4	≥ 38.0 °C	Requiring multiple vasopressors (excluding vasopressin)	Requiring oxygen delivered by positive pressure (eg, CPAP, BiPAP, intubation and mechanical ventilation)

BiPAP = bilevel positive airway pressure; CPAP = continuous positive airway pressure; min = minute.

Grade 5 CRS is defined as death due to CRS in which another cause is not the principle factor leading to this outcome.

13.1.3 Resolution of CRS

For purposes of this study, CRS is considered as resolved when fever, hypotension, and hypoxia have all resolved (unless there are alternative causes for the fever, hypoxia, and/or hypotension). The duration of associated constitutional symptoms and/or organ toxicity should be reported independently.

13.1.4 Immune Effector Cell-Associated Neurotoxicity Syndrome

Neurotoxicity (eg, delirium, encephalopathy, aphasia, lethargy, difficulty concentrating, agitation, tremors, seizures, and, rarely, cerebral edema) has been observed with autologous T cell therapies. Under the ASTCT 2019 guidelines, these events are treated as distinct entity from CRS, called immune effector cell-associated neurotoxicity syndrome (ICANS) due to its distinct timing and response to intervention.

Neurologic symptoms may occur during or more commonly after CRS symptoms. The earliest manifestations of ICANS are tremor, dysphagia, mild difficulty with expressive speech (especially in naming objects), impaired attention, apraxia, and mild lethargy. Expressive aphasia appears to be the most characteristic feature of ICANS.

No events of ICANS have been reported following ImmTAC treatment. However, the ASTCT 2019 guidelines notes that bispecific antibodies that engage immune effector cells may have similar neurological side effects. Patients experiencing CRS should be carefully monitored for evidence of neurological toxicity.

13.2 Guidelines for Implementation of RECIST Criteria

These guidelines are based on the original RECIST for tumor responses (Therasse, 2000), and the revised RECIST v1.1 guidelines (Eisenhauer, 2009). The efficacy assessments and definitions of best response and PD for the purposes of the primary endpoint of BOR described in this study are based on the RECIST v1.1 criteria (Table 13-2).

13.2.1 Efficacy Assessments

Tumor evaluations for the purposes of the primary endpoint are made based on RECIST criteria (Therasse, 2000), New Guidelines to Evaluate the Response to Treatment in Solid Tumors, *Journal of National Cancer Institute*, Volume 92; pages 205–216 and revised RECIST guidelines (version 1.1) (Eisenhauer, 2009).

13.2.2 Definitions of Measurable and Non-Measurable Disease

Measurable disease represents the presence of at least 1 measurable nodal or non-nodal lesion. If the measurable disease is restricted to a solitary lesion, its neoplastic nature should be confirmed by cytology/histology.

Measurable lesions (both nodal and non-nodal): The minimum size of a measurable, non-nodal target lesion at Baseline should be no less than double the slice thickness or 10 mm, whichever is greater, eg, the minimum non-nodal lesion size for CT/MRI with 5 mm cuts will be 10 mm).

Lytic bone lesions or mixed lesions with identifiable soft tissue components that can be evaluated by CT/MRI can be considered as measurable lesions, if the soft tissue component meets the definition of measurability. Measurable nodal lesions (ie, lymph nodes), lymph nodes ≥ 15 mm in short axis can be considered for selection as target lesions. Lymph nodes measuring ≥ 10 mm and < 15 mm are considered non-measurable. Lymph nodes smaller than 10 mm in short axis at Baseline, regardless of the slice thickness, are normal and not considered indicative of disease.

Cystic lesions thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. Simple cysts with non-enhancing walls and low CT density are not considered malignant lesions unless proven by biopsy.

Non-measurable lesions: All other lesions are considered non-measurable, including small lesions (eg, longest diameter < 10 mm with CT/MRI or pathological lymph nodes with ≥ 10 to < 15 mm short axis), as well as truly non-measurable lesions eg, blastic bone lesions, ascites, pleural/pericardial effusion and inflammatory breast disease.

13.2.3 Methods of Tumor Measurement

All measurements should be taken and recorded in metric notation (mm), using a ruler or calipers. All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 4 weeks before the beginning of the treatment. Imaging-based evaluation is preferred to evaluation by clinical examination when both methods have been used to assess the anti-tumor effect of a treatment. For optimal evaluation of patients, the same methods of assessment and technique should be used to assess each reported lesion at Baseline and during Follow-up. Contrast-enhanced CT of chest, abdomen, and pelvis should preferably be performed using a 5-mm slice thickness. If a patient is known to have a medical contraindication to CT contrast or develops a contraindication during the trial, the following change in imaging modality will be accepted for follow-up: a non-contrast CT of chest (MRI not recommended due to respiratory artifacts) plus contrast-enhanced MRI of abdomen and pelvis.

13.2.3.1 Other Tumor Response Considerations

Fluorodeoxyglucose-positron emission tomography, endoscopy, and laparoscopy: The utilization of positron emission tomography imaging, endoscopy, and laparoscopy for objective tumor evaluation has not yet been fully and widely validated. The utilization of such techniques for objective tumor response should be restricted to validation purposes in specialized centers; however, such techniques can be useful in confirming complete pathological response when biopsies are obtained.

Cytology and histology: Cytology and histology can be used to differentiate between partial response (PR) and complete response (CR) in rare cases (ie, after treatment to differentiate between residual benign lesions and residual malignant lesions in tumor types such as germ cell tumors).

Clinical examination: Clinical lesions will only be considered measurable when they are superficial (ie, skin nodules and palpable lymph nodes). Documentation by color photography is recommended for the case of skin lesions, including a ruler to estimate the size of the lesion. Clinical disease progression is acceptable and wherever possible, should be confirmed by imaging studies.

13.2.4 Definitions of Target and Non-Target Lesions

For the evaluation of lesions at Baseline and throughout the study, the lesions are classified at Baseline as either target or non-target lesions.

Target Lesions: All measurable lesions (nodal and non-nodal) up to a maximum of 5 lesions in total (and a maximum of 2 lesions per organ), representative of all involved organs, should be identified as target lesions and recorded and measured at Baseline. Target lesions should be

selected based on their size (lesions with the longest diameter) and their suitability for accurate repeated measurements (either by imaging techniques or clinically).

Each target lesion must be uniquely and sequentially numbered on the eCRF (even if it resides in the same organ). A sum of diameters (long axis for non-nodal lesions, short axis for nodal) for all target lesions will be calculated and reported as the baseline sum of diameters. The baseline sum of diameters will be used as reference by which to characterize the objective tumor response. Each target lesion identified at Baseline must be followed at each subsequent evaluation and documented on eCRF.

Non-Target Lesions: All other lesions are considered non-target lesions, ie, lesions not fulfilling the criteria for target lesions at Baseline. Presence or absence or worsening of non-target lesions should be assessed throughout the study; measurements of these lesions are not required. Multiple non-target lesions involved in the same organ can be assessed as a group and recorded as a single item (ie, multiple liver metastases). Each non-target lesion identified at Baseline must be followed at each subsequent evaluation and documented on eCRF.

13.2.5 Determination of Target Lesion Response

Table 13-2: Response Criteria for Target Lesions

Response Criteria	Evaluation of Target Lesions
Complete response	Disappearance of all non-nodal target lesions. In addition, any pathological lymph nodes assigned as target lesions must have a reduction in short axis to < 10 mm[a]
Partial response	At least a 30% decrease in the sum of diameter of all target lesions, taking as reference the baseline sum of diameters
Progressive disease	At least a 20% increase in the sum of diameter of all measured target lesions, taking as reference the smallest sum of diameter of all target lesions recorded at or after Baseline. In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm[b]
Stable disease	Neither sufficient shrinkage to qualify for partial response or complete response nor an increase in lesions which would qualify for progressive disease

a. Sum of diameters for complete response may not be 0 when nodal lesions are part of target lesions.
b. Following an initial complete response, progressive disease cannot be assigned if all non-nodal target lesions are still not present and all nodal lesions are < 10 mm in size. In this case, the target lesion response is complete response.

Notes on Target Lesion Response

Lesions split: In some circumstances, disease that is measurable as a target lesion at Baseline and appears to be 1 mass can split to become 2 or more smaller sub-lesions. When this occurs, the diameters (long axis — non-nodal lesion, short axis - nodal lesions) of the 2 split lesions should be added together and the sum recorded in the diameter field on the electronic case report form under the original lesion number. This value will be included in the sum of diameters when deriving target lesion response. The individual split lesions will not be considered as new lesions, and will not automatically trigger a PD designation

Lesions coalesced: Conversely, it is also possible that 2 or more lesions, which were distinctly separate at Baseline, become confluent at subsequent visits. When this occurs, a plane between the original lesions may be maintained that would aid in obtaining diameter measurements of each individual lesion. If the lesions have truly coalesced such that they are no longer separable, the maximal diameters (long axis — non-nodal lesion, short axis - nodal lesions) of the "merged lesion" should be used when calculating the sum of diameters for target lesions. On the electronic case report form, the diameter of the "merged lesion" should be recorded for the size of 1 of the original lesions while a size of "0" mm should be entered for the remaining lesion numbers which have coalesced.

13.2.6 Determination of Non-Target Lesion Response

Table 13-3: Response Criteria for Non-Target Lesions

Response Criteria	Evaluation of Non-Target Lesions
Complete Response	Disappearance of all non-target lesions. In addition, all lymph nodes assigned a non-target lesion must be non-pathological in size (< 10 mm short axis)
Progressive Disease	Unequivocal progression of existing non-target lesions[a]
Non-complete response / Non-progressive disease	Neither complete response nor progressive disease

a. Although a clear progression of non-target lesions only is exceptional, in such circumstances, the opinion of the treating physician does prevail, and the progression status should be confirmed later on by the central review.

Non-Target Lesion Response

The response for non-target lesions is CR only if all non-target, non-nodal lesions that were evaluated at Baseline are now all absent and all non-target nodal lesions returned to normal size

(ie, < 10 mm). If any of the non-target lesions are still present, or there are any abnormal nodal lesions (ie, ≥ 10 mm), the response can only be "Non-CR/Non-PD."

Unequivocal progression: To achieve "unequivocal progression" on the basis of non-target disease there must be an overall level of substantial worsening in non-target disease such that, even in presence of CR, PR, or SD in target disease, the overall tumor burden has increased sufficiently to merit discontinuation of therapy. In order for a PD to be assigned on the basis of non-target lesions, the increase in the extent of the disease must be substantial even in cases where there is no measurable disease at Baseline

New Lesions

The appearance of a new lesion is always associated with PD and has to be recorded as a new lesion in the eCRF.

- If a new lesion is equivocal, for example because of its small size, continued therapy and follow-up evaluation will clarify if it represents truly new disease. If repeat scans confirm there is definitely a new lesion, then progression should be declared using the date of the first observation of the lesion
- If new disease is observed in a region which was not scanned at Baseline or where the particular baseline scan is not available for some reason, then this should be considered PD
- A lymph node is considered as a "new lesion" and therefore, indicative of PD if the short axis increases in size to ≥ 10 mm for the first time in the study plus 5 mm absolute increase

13.2.7 Evaluation of Overall Lesion Response

The evaluation of overall lesion response at each assessment is a composite of the target lesion response, non-target lesion response, and presence of new lesions as shown below in Table 13-4.

Table 13-4: Overall Lesion Response at Each Assessment (RECIST v1.1)

Target Lesions	Non-target Lesions	New Lesions	Overall Lesion Response
CR	CR	No	CR[a]
CR	Non-CR/Non-PD	No	PR
PR	Non-PD	No	PR[a]
SD	Non-PD	No	SD[a,b]

Target Lesions	Non-target Lesions	New Lesions	Overall Lesion Response
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

CR = complete response; PD = progressive disease; PR = partial response; RECIST = Response Evaluation Criteria in Solid Tumors; SD = stable disease.

a. This overall lesion response also applies when there are no non-target lesions identified at Baseline.
b. Once confirmed PR was achieved, all these assessments are considered PR.

13.3 Bayesian Logistic Regression Model

This section (along with Section 6.10) describes the Bayesian Logistic Regression Model (BLRM) used to make dose recommendations during Phase I.

13.3.1 Specification

See Section 6.12 for DLT definitions and Section 6.10.2 for definitions of DLT-evaluable patients for inclusion in the DDS.

After each cohort of patients, the posterior distributions for the probabilities of DLT rates at different dose levels will be obtained. Dose recommendation will be based on the probability that the true DLT rate for each dose lies in 1 of the following categories in Table 13-5.

Table 13-5: Toxicity Categories

Name	Lower Limit	Upper Limit
Under dosing	0%	< 16%
Target toxicity	16%	< 33%
Excessive toxicity	33%	100%

The N-CRM model will predict rates of toxicity for doses between 1 mcg and 200 mcg. This is the limit that has been identified for the purposes of the simulations. For ease of presentation, summaries of the state of the N-CRM model will collapse these 1 mcg dose increments into bands as follows:

- Between 1 mcg and 9 mcg: no collapsing
- Between 10 mcg and 18 mcg: in increments of 2 mcg
- Between 20 mcg and 200 mcg: in increments of 5 mcg

Note: If IPE proceeds to a target dose of >150 mcg according to BLRM output and treatment at this dose level is well-tolerated, then an additional BLRM that allows for a maximum target dose of up to 350 mcg will be constructed. This model will be specific to the dose-toxicity relationship of target doses following IPE. The prior distribution for this new model and pseudo-patient information will consider posterior distributions from the existing BLRM(s). Operating characteristics will be assessed from a series of simulations to be summarized in a simulation report.

In case of changes in dosing schedule during dose escalation, a BLRM of the same functional form will be used to estimate the dose-DLT relationship for each schedule based on a newly derived "Bayesian prior" incorporating the historical trial data and the on-study data from previous schedule. Each time the model is updated, all available information on the dose-DLT relationship from all explored dosing schedules will be used. To account for between schedule variability in the assessment of a given dosing schedule, the DLT data obtained from other explored dosing schedules will be down-weighted.

Escalation Rule

Let d* be the highest dose at which the DLT status of at least 3 patients is known. A dose is cleared if the ratio between it and d* is less than or equal to 3.34. A dose is eligible if it is both cleared and the current posterior estimate of the probability that it lies in the excessive toxicity band is less than 0.25 [the EWOC rule]. The dose recommended by the N-CRM will be the eligible dose currently with the highest posterior probability of being in the target toxicity band.

Futility Rule

There will be no futility rule. Phase I cohorts will continue to enroll until either the MTD (or RP2D) is identified or the Sponsor terminates the study for other reasons.

Success Rule

The N-CRM model will recommend that enrollment to Phase I cohorts should stop once either (a) at least 6 evaluable patients have been treated in the dose range in which the MTD is currently thought to lie or (b) no dose is eligible for dosing because of the EWOC rule. The Sponsor reserves the right to continue enrollment in the Phase I cohorts beyond this time if it is considered clinically useful so to do.

Enrollment Limit

There will be no enrollment limit. Enrollment will be open.

Dose-toxicity Model

<u>X-hats</u>:

Let d_i = i mcg, i=1, …, 200. Let $\hat{x}_i$ denote the nominal dose used in the dose-toxicity model that corresponds to d_i. Let d_{ref} = 0 mcg. Then $\hat{x}_i = d_i - d_{ref} = d_i$.

Functional Form:

Let Y_j be a Bernoulli random variable indicating whether the j^{th} patient experiences a DLT (Y_j=1) or not (Y_j=0). Let $\hat{x}_{ij}$ denote the nominal dose received by the j^{th} patient. The BLRM will model the probability that the j^{th} patient experiences a DLT as

$$p\left(Y_j = 1 \left| \hat{x}_{ij}, \alpha, \beta, \{(\hat{x}_{ik}, y_k); k = 1, \dots, j-1\}\right.\right) = \frac{e^{\alpha+\beta\hat{x}_{ij}}}{1+e^{\alpha+\beta\hat{x}_{ij}}}$$

The Prior:

The dose-toxicity model is a logistic model and takes the form:

$$logit\,(p) = \alpha + \beta\hat{x}$$

It is assumed that toxicity increases with increasing dose and thus the slope, β, must be greater than 0. This assumption is implemented in the model by estimating γ where $\gamma = \ln(\beta)$. The prior for α and γ takes the form

$$[\alpha] \sim MVN\left(\begin{bmatrix}\mu_\alpha\\ \mu_\gamma\end{bmatrix}, \begin{bmatrix}\sigma_\alpha \times \sigma_\alpha & \rho \times \sigma_\alpha \times \sigma_\gamma\\ \rho \times \sigma_\alpha \times \sigma_\gamma & \sigma_\gamma \times \sigma_\gamma\end{bmatrix}\right)$$

Initial values for μ_α, μ_β, σ_α, σ_β and ρ were based on the results of simulation study (on file at PPD) and are given in Table 13-6.

Table 13-6: Initial Values for BLRM Simulation

Parameter	Initial Value
μ_α	-2.95
μ_β	-5
σ_α	2.75
σ_β	2.75
ρ	0

BLRM = Bayesian Logistic Regression Model.

Bayes' Theorem will be used to update the values of μ_α, μ_β, σ_α, σ_β and ρ (and hence the probabilities of toxicity and toxicity band membership for each dose) after the results of each cohort of patients are known.

The pseudo-patient information in Table 13-7 was also included as prior information.

Table 13-7: Pseudo-Patient Information

Dose	Number of Patients	Number of DLTs
3	1	0.1
10	1	0.125
30	1	0.15
100	1	0.3
135	1	0.4
200	1	0.5

DLT = dose-limiting toxicity.

This prior gives rise to the probabilities of toxicity and band membership for selected doses as shown in Table 13-8.

Table 13-8: Prior Probabilities

Dose	p(Toxicity)	Probability that Dose is in Toxicity Band:		
		Under Dosing	Target Toxicity	Excess Toxicity
3 mcg	0.109	0.765	0.156	0.079
10 mcg	0.118	0.742	0.169	0.089
20 mcg	0.136	0.697	0.184	0.119
40 mcg	0.186	0.620	0.187	0.193
80 mcg	0.268	0.539	0.170	0.290
100 mcg	0.297	0.512	0.165	0.323
140 mcg	0.343	0.471	0.157	0.372
180 mcg	0.378	0.441	0.148	0.412

The dose recommended by the N-CRM model will be subject to clinical review. The SST may select the recommended dose or a lower dose.

13.3.2 Operating Characteristics

Information in this section is based on a simulation study, the results of which are on file at PPD.

When 3 mcg and all higher doses are unsafe, the model described above has an average sample of 9.2 patients.

When all doses are safe, the model will recommend stopping after an average of 24.5 patients (80th centile 33 patients).

The simulation study also investigated a range of dose-toxicity scenarios with the true MTD located at the low end of the dose range, at the high end of the dose range and in the middle of the dose range. Relatively steep and relatively gentle slopes were considered. The average sample size was only slightly affected by the gradient of the dose-toxicity curve and ranged from 26.9 (80th centile 27) when the true MTD was at the lower end of the dose-toxicity curve to 27.8 (80th centile 33) when the true MTD was at the upper end.

The chance that the model identified as the MTD a dose which truly was in the target toxicity band ranged from 64% to 42% depending on whether the true MTD was at the lower or upper end of the dose range.

13.3.3 Sample Paths

The tables in this section (Table 13-9, Table 13-10, Table 13-11, and Table 13-12) illustrate various possible paths of dose recommendation and state of the N-CRM model given various response patterns that might be observed in the study.

Table 13-9: Scenario 1, No DLT Reported at Any Dose

Dose (mcg)	Number of DLTs / Number of Patients Treated	Estimated MTD	Recommended Next Dose
3	0 / 3	38	10
10	0 / 3	67	30
30	0 / 3	185	100
100	0 / 3	198	195
195	0 / 3	>200	200

DLT = dose-limiting toxicity; MTD = maximum tolerated dose.

Table 13-10: Scenario 2, One DLT Reported at 30 mcg Dose

Dose (mcg)	Number of DLTs / Number of Patients Treated	Estimated MTD	Recommended Next Dose
3	0 / 3	38	10
10	0 / 3	67	30
30	1 / 3	185	100
25	0 / 3	35	35
35	0 / 3	77	75
75	0 / 3	148	145
145	0 / 3	>200	200
200	0 / 3	>200	200
200	0 / 3	>200	Stop

DLT = dose-limiting toxicity; MTD = maximum tolerated dose.

Table 13-11: Scenario 3, Two DLTs Reported at 100 mcg Dose

Dose	Number of DLTs / Number of Patients Treated	Estimated MTD	Recommended Next Dose
3	0 / 3	38	10
10	0 / 3	67	30
30	0 / 3	185	100
100	2 / 3	61	60
60	0 / 3	70	70
70	0 / 3	78	75
75	0 / 3	87	85
85	0 / 3	100	100
100	2 / 3	83	80
80	0 / 3	87	85
85	0 / 3	91	90
90	0 / 3	97	Stop

DLT = dose-limiting toxicity; MTD = maximum tolerated dose.

Table 13-12: Scenario 4, One DLT at 30 mcg, 2 DLTs at 145 mcg and 2 DLTs at 100 mcg Dose

Dose	Number of DLTs / Number of Patients Treated	Estimated MTD	Recommended Next Dose
3	0 / 3	38	10
10	0 / 3	67	30
30	0 / 3	28	25
25	1 / 3	35	35
35	0 / 3	77	75
75	0/ 3	148	145
145	2 / 3	87	85
85	0 / 3	99	95
95	0 / 3	109	105
105	2 / 3	93	90
90	0 / 3	99	Stop

DLT = dose-limiting toxicity; MTD = maximum tolerated dose.

13.4 Schedule of Cycle 1 Assessments, Intra-Patient Escalation Regimen

Patients who receive IPE should follow the schedule below during Cycle 1, and the main schedule at all other times, including Pre-Screening, Screening, Cycle 2 and subsequent treatment cycles, and Follow-up.

The Cycle 1 schedule is provided in Table 13-13. Assessments marked "X" should be performed prior to dosing. Assessments that are to be performed at multiple timepoints are marked with the number of timepoints (including optional timepoints, if applicable) for the visit (eg, 2× is twice) and details of the timepoints are provided in the footnote. Additional details regarding the assessments are provided in Section 7.4.

Table 13-13: Schedule of Cycle 1 Assessments, IPE Regimen

Procedure	**Cycle 1**						
Day of Cycle	**1**	**2**	**8**	**9**	**15**	**16**	**22**
Adverse events	X	X	X	X	X	X	X
Concomitant medications	X	X	X	X	X	X	X
Safety Assessments							
Complete physical examination	X						
Abbreviated physical examination			X		X		X
Weight	X						
Vital signs	~14×		~14×		~14×		3×
12-lead ECG (single)	2×						
ECOG performance status	X						
Hematology panel	X	X	X	X	X		X
Chemistry panel	X		X		X		X
Thyroid function	X						
Urine pregnancy test (women of childbearing potential)	X						
PK and Immunogenicity Assessments							
Pharmacokinetic sampling	3×	X	8×	X	8×	X	3×
Immunogenicity sampling	X		X		X		
[redacted]							
Tumor biopsy	Between C1D9 and C1D16 (required for ≥ 10 patients in Phase II, optional for all other patients)						
[redacted]							

Procedure	Cycle 1						
[redacted]							
IMCnyeso Administration							
One-step IPE	C1D1 dose level		Target dose level		Target dose level		Target dose level
Two-step IPE	C1D1 dose level		C1D8 level		Target dose level		Target dose level

AE = adverse event; C#D# = Cycle # Day #; CRS = cytokine release syndrome; [redacted]; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; EOI = end of infusion; hr = hour(s); min = minutes; [redacted] PK = pharmacokinetics; [redacted]

ECG assessments are to be done pre-dose and within 1 hour of EOI on indicated days.

Vitals (body temperature, pulse, respiratory rate, blood pressure; oxygen saturation should also be assessed for ≥ first 3 cycles of treatment), are to be assessed at the following timepoints:

- C1D1/C1D2, C1D8/C1D9, and C1D15/C1D16: pre-dose (within 2 hours), EOI (within 15 min), every 2 hours (± 15 min) through 8-hour post-EOI, then every 4 hours (± 30 min) until discharge
- C1D22: pre-dose (within 2 hours), EOI (within 15 min), and 1-hour post-EOI (± 15 min)

Pharmacokinetics samples are to be collected at the following timepoints:

- C1D1: pre-dose (within 2 hours), EOI (within 15 min), 8-hour post-EOI (± 1 hr)
- C1D8 and C1D15: pre-dose (within 2 hours), EOI (within 15 min), 1-hour post-EOI (± 15 min), 2-hour post-EOI (± 15 min), 4-hour post-EOI (± 15 min), 6-hour post-EOI (± 30 min), 8-hour post-EOI (± 1 hr), and 12-hour post-EOI (optional, ± 3 hr)
- C1D2, C1D9, and C1D16: 24-hour post-EOI (± 4 hr)
- C1D22: pre-dose (within 2 hours), EOI (within 15 min), 8-hour post dose (± 1 hr)

Central lab cytokine testing samples are to be collected at the following timepoints:

- C1D1: pre-dose (within 2 hours) and 4-hour post-EOI (± 15 min)
- C1D8 and C1D15: pre-dose (within 2 hours), 4-hour post-EOI (± 15 min), 8-hour post-EOI (± 1 hr), and 12-hour post-EOI (optional, ± 3 hr)
- C1D2, C1D9, and C1D16: 24-hour post-EOI (± 4 hr)
- C1D22: pre-dose (within 2 hours) and 4-hour post-EOI (± 15 min)
- Additional samples may be collected if a patient has suspected CRS. Recommended timepoints are within 5 hours and 1 week after onset of CRS.

[redacted]

13.5 Detailed Description and Rationale for Changes

13.5.1 Amendment 3

Section	Change	Rationale
Multiple	The generic name "tebentafusp" is used throughout for IMCgp100	To use current nomenclature
Synopsis	The synopsis was updated as needed to reflect the changes below	To ensure consistency
Section 1.4	Added clinical experience in ongoing study as of 22Jan2020	To provide current enrollment and safety information for the study
Section 5.3	The exclusion criterion for minimum creatinine clearance was decreased from 50 mL/min to 40 mL/min	Especially in urothelial carcinoma, patients with advanced cancers may have decreased renal function but are not anticipated to be at elevated risk for treatment-related toxicities
Section 5.3	The exclusion criterion for congestive heart failure was updated to add the word "diagnosed": Clinically significant and/or uncontrolled heart disease such as diagnosed congestive heart failure (New York Heart Association Class ≥ 2)	To clarify that the exclusion is for diagnosed congestive heart failure rather than signs and symptoms that could be confused with Class 2 congestive heart failure (mild symptoms [mild shortness of breath and/or angina] and slight limitation during ordinary activity) but are due to other causes
Section 5.3	The exclusion criterion for ongoing ≥ Grade 2 toxicity due to prior cancer therapy was updated so that any Grade 2 endocrine disorder [on stable replacement doses and without symptoms] is an exception; previously this exception was limited to hypothyroidism	Other Grade 2 endocrine disorders may occur due to prior cancer therapy and are not anticipated to be associated with an elevated risk for treatment-related toxicities if asymptomatic and clinical stable on replacement therapy

Section	Change	Rationale
Section 5.3	In the exclusion criterion for antibiotic use, the washout period for oral antibiotics was reduced from 14 days to 7 days prior to the first dose of study drug (note: there was no change to the washout period for IV antibiotics).	Patients who responded to oral antibiotics, completed treatment at least 7 days before the first dose of study drug, and meet all other eligibility criteria are not anticipated to be at an elevated risk for treatment-related toxicities
Section 6.2	Added that after Phase I is completed and the SST has reviewed all available relevant data for at least 6 patients at the RP2D, the SST may decide to reduce the minimum required monitoring time to no less than 8 hours post-end of infusion on C1D1, C1D8, and/or C1D15 (with longer hospitalization if indicated) during the Phase II portion of the study.	Based on the observation that all signs/symptoms of CRS, to date, have occurred rapidly (within a few hours) following administration of IMCnyeso, and provided the initial assessment of safety at the RP2D supports the dose as being well-tolerated and any signs/symptoms suggestive of CRS occur within 2-4 hours post-end of infusion, then monitoring for 8 hours post-end of infusion provides an adequate safety margin
Section 6.4	If the Cycle 1 Day 1 dose is ≤ 30 mcg, the infusion may be given over 1 hour rather than 2 hours	Based on emerging safety data, an initial dose of ≤ 30 mcg infused over 1hour is anticipated to be tolerable and would simplify study conduct
Section 6.10.1	For any allowed dose escalation step, an option was added to switch from a fixed-dose regimen to a 1-step or 2-step IPE regimen (or from a 1-step to a 2-step IPE regimen as applicable). Figure 6-3, which shows representative escalation paths with IPE options, was updated accordingly.	Initial assessment of a new higher dose level is anticipated to present less risk when IPE regimen is used instead of a fixed-dose regimen
Section 6.10.1 and 6.10.2	The DLT observation period is 28 days for all regimens (previously the DLT observation period was extended for intrapatient escalation regimens)	The DLT observation period is designed to allow detection of acute treatment-related toxicities, which are anticipated to occur within the first 28 days of treatment, regardless of regimen

Section	Change	Rationale
Section 6.10.1	Added an option for patients who were enrolled in a lower dose cohort to move to a higher dose level after the higher dose level has successfully completed SST review, if the patient has completed at least 3 cycles of treatment, and has tolerated treatment well	To allow patients to receive a dose level that may provide more therapeutic benefit, with appropriate safeguards for safety
Section 6.13	Added that non-live vaccines are not to be administered within 14 days before and 28 days after the first dose of IMCnyeso treatment, and thereafter not within 24 hours before or after IMCnyeso treatment, and live or attenuated vaccines are prohibited from 28 days prior to the first dose of IMCnyeso until 30 days after the last dose of IMCnyeso	Vaccine-related adverse events may be exacerbated by immune activation associated with IMCnyeso treatment
Section 7	Schedule of Assessments Tables 7-1 and 7-2 were updated to reflect changes in Section 7.4.4 shown below	To ensure consistency between the Schedule of Assessments tables and the body of the protocol
Section 7	In the Schedule of Treatment Period Assessments table (Table 7-2), inconsistencies between the main table and footnote were resolved	Correction of typographical errors
Section 7	The sample collection for pharmacokinetics at the Cycle 1 Day 2 36-hour post-EOI timepoint is optional rather than mandatory	To aid in protocol compliance
Section 7.4.4	Follicle-stimulating hormone is to be done only if required to confirm non-childbearing potential, rather than required for all post-menopausal women	It is not necessary to test FSH in all post-menopausal women
Section 7.4.4	Added that blood oxygen saturation should be assessed at Screening and for at least the first 3 treatment cycles	Monitoring oxygen saturation may aid in detection and management of cytokine release syndrome

Section	Change	Rationale
Section 13.1.1	Added that if dose escalation proceeds to a dose of >150 mcg according to the BLRM and treatment at this dose level is well-tolerated, additional BLRM simulations may be performed to predict rates of toxicity for higher dose levels	To enable consideration of higher doses if supported by emerging safety data
Section 13.4	The sample collection for pharmacokinetic and central lab cytokine assessments at 12 hours post end of infusion are optional rather than mandatory	To aid in protocol compliance

13.5.2 Amendment 2

Section in Amendment 1	Change	Rationale
Cover page	Updated sponsor contact information	The study has a new Medical Monitor
Synopsis	The synopsis was updated as needed to reflect the changes below	To ensure consistency
Synopsis	Inclusion / exclusion criteria, study objectives, and rationale for selection of the starting dose were removed from the synopsis	To simplify the synopsis and prevent potential inconsistencies
Synopsis	Updated to "Based on the available IMCnyeso preclinical data and clinical safety information from the related ImmTAC molecule IMCgp100, IMCnyeso may induce rash, tumor flare/pain, lymphopenia (associated with lymphocyte trafficking), and cytokine release syndrome. Conservative monitoring and management guidelines as well as definitions of DLT have been implemented"	To provide more current and comprehensive summary of risk information rather than focusing primarily on potential for skin toxicity
Section 1.1	IMCnyeso is a "bispecific protein therapeutic" rather than "bispecific biologics"	To clarify that IMCnyeso is a protein

Section in Amendment 1	Change	Rationale
Section 1.2	Simplified language describing mechanism of action	To clarify the mechanism of action of IMCnyeso
Section 1.2	Updated mechanism of action statement to add sentence: "In addition, IMCnyeso-mediated tumor lysis may prime an endogenous anti-tumor immune response"	To add a description of a second potential mechanism of action based on emerging data from other ImmTAC clinical trials
Section 1.2	Information about NY-ESO-1 / LAGE-1A testing removed from this section and consolidated in Section 1.5 (screening strategy) and Section 7.4.1 (description of assessments)	Removed redundant information
Section 1.3	Consolidated description of species specificity of IMCnyeso at the start of Section 1.3 and removed this information from the following sub-sections	Removed redundant information
Section 1.4	Added clinical experience in ongoing study as of 26Apr2019	To provide current enrollment and safety information for the study
Section 1.4	Cytokine release syndrome (CRS) section updated to add: Release of pro-inflammatory cytokines (eg, IL-6, IFN-γ, TNF-α) is a predicted pharmacodynamic effect of IMCnyeso. Based on experience with IMCgp100, symptoms such as pyrexia, chills, nausea, hypotension, and edema were observed in most patients, typically 4-24 hours after the first 2-3 doses. As of August 2018, 2% of patients in the IMCgp100-102 study experienced severe (Grade 3) CRS with IMCgp100	To provide more current and comprehensive risk information
Section 1.4	Added that IMCnyeso may cause inflammation within the tumor microenvironment. Depending on the location of the tumors, various AEs may occur, including hepatic events and pulmonary events	To provide more current and comprehensive risk information

Section in Amendment 1	Change	Rationale
Section 1.5	Added that target expression frequencies are significantly lower in uveal melanoma and NSCLC adenocarcinoma	To provide additional information regarding target antigen expression
Section 1.6.4	A reference was added regarding treatment options for patients with synovial sarcoma	To provide a more current reference
Section 2.1, Section 6.4	The Study Safety Team will include Study Investigators, Sponsor Medical Monitor, and a statistician (role of independent medical oncologist removed)	For operational simplicity and to align with standard practice for FIH studies
Section 2.2	Description of measures taken to minimize risks for patients in the study updated to include "eligibility criteria designed to exclude patients at potentially high risk for experiencing treatment-related toxicity"	To correct an omission
Section 3, Section 9	A substantial amount of redundant information was removed; hyperlinks were added to the relevant sections where information is located	To remove redundant information
Section 3, Section 9.9.1	The estimated number of patients in Phase I is 27. In 80% of simulations conducted, the sample size was < 33 patients	Estimated patient numbers were updated to reflect results of the new BLRM simulations
Section 3, Section 9.9.2	Simon 2-stage design incorporated for Phase II with initial enrollment of 9 patients and option to enroll 15 additional patients if there is at least one response. A formal interim analysis was added to Phase II	To enable more robust assessment of efficacy and provide justification for the Phase II sample size
Section 3.4	Redundant information regarding study periods was deleted from Section 3.4 and assessment details moved to Section 7	To remove redundant information and improve organization
Section 3.4, Section 7.3, and others	Safety follow-up changed to 30 days (from 90 days)	30-day safety follow-up is appropriate based on the <24-hour half-life of ImmTAC

Section in Amendment 1	Change	Rationale
Section 3.5	Substantially shortened. Criteria for treatment discontinuation consolidated in Section 6.16	To remove redundant information and improve organization
Section 3.6	Clarified requirements for planned End of Study, including requiring that secondary endpoints of objective response, overall survival, progression-free survival, and duration of response have been adequately assessed in all subjects	To ensure that study objectives and endpoints are adequately assessed before End of Study
Section 4	Redundant body text was removed; objectives and corresponding endpoints are shown in table format only	Removed redundant information and improve organization
Section 2.1, Section 3.1, Section 4	The primary objective for Phase II was changed from "to further explore the safety and tolerability of the identified RP2D" to preliminary efficacy (BOR per RECIST v.1.1). Safety and tolerability is a secondary objective for Phase II.	To align with the goals of the Phase II portion of the study
Section 4	A secondary efficacy objective (based on RECIST v1.1) was added for Phase I	Efficacy is evaluated in Phase I but previously was not associated with a study objective
Section 4, Section 7	Response will no longer be evaluated per modified irRECIST	To simplify study conduct and align with current standards in the field
Section 4	The secondary PK endpoint was clarified to indicate that serum PK parameters would be determined after single and multiple doses	To clarify scope of planned analysis
Section 4	The secondary ADA endpoint was updated to include the impact of ADA on PK	To clarify scope of planned analysis
Section 4	[redacted]	[redacted]

Section in Amendment 1	Change	Rationale
Section 4	[redacted]	[redacted]
Section 4	[redacted]	[redacted]
Section 5.1	Shortened description of patient population	To remove redundant information
Section 5.2, Section 5.3	Organized eligibility criteria by topic and simplified	To aid in protocol compliance
Section 5.2	Clarified prior treatment requirements for Phase I to "Patients must be relapsed from, refractory to, or intolerant to all approved and available classes of therapy known to provide clinical benefit for their condition"	To clarify study inclusion criteria
Section 5.2	Clarified prior treatment requirements for Phase II to note that required therapies may have been given in the adjuvant setting if disease progression occurred during or within 6 months of completing adjuvant therapy, and patients with NSCLC with a genomic tumor aberration (eg, EGFR, ALK) that is targeted by Health Authority-approved agent(s) must be relapsed from, refractory to, or intolerant of relevant targeted agent(s).	To align with standard of care
Section 5.3	Allow patients with Grade 2 hypophosphatemia [if receiving appropriate replacement therapy] or hypothyroidism [if on stable replacement doses] due to prior cancer therapy to enroll	Hypophosphatemia due to prior ifosfamide and hypothyroidism due to prior checkpoint inhibitors are relatively common in the eligible patient population and are not expected to be exacerbated by IMCnyeso treatment

Section in Amendment 1	Change	Rationale
Section 5.3	Patients with leptomeningeal disease or cord compression are not eligible for study participation	To ensure adequate baseline health status of enrolled patients
Section 5.3	Clarify that hematology evaluations used to determine study eligibility must be performed ≥ 7 days from any blood or blood product transfusion and ≥ 14 days from any dose of hematologic growth factor; removed exclusion criteria regarding use of hematopoietic growth factors and erythroid stimulating agents	To ensure that enrolled patients have adequate hematologic function and simplify the protocol
Section 5.3	Eligibility criteria for renal function will be based only on creatinine clearance, rather than creatinine concentration and/or creatinine clearance	To reduce ambiguity in eligibility criteria
Section 5.3	Added for patients with Gilbert's syndrome exclude if total bilirubin > 3.0 × ULN or direct bilirubin > 1.5 × ULN	Slightly elevated bilirubin in patients with Gilbert's syndrome is not a safety concern for IMCnyeso
Section 5.3	Reduced minimum absolute lymphocyte count needed for eligibility to $<0.5 \times 10^9$/L (previously 1.0×10^9/L)	Grade 2 lymphopenia is a relatively common finding in patients with advanced cancers and is not expected to impact the safety or efficacy of IMCnyeso
Section 5.3	Removed electrolyte lab abnormalities from exclusion criteria	Electrolyte abnormalities can be appropriately managed and should not be exclusionary
Section 5.3	Removed exclusion criterion for prior hypersensitivity to other biologic drugs or monoclonal antibodies	Prior hypersensitivity to another biologic drug does not necessarily indicate elevated risk of hypersensitivity to IMCnyeso
Section 5.3	Systemic antibiotics must be completed at least 14 days prior to the first dose of study drug (rather than prior to screening)	To improve operational feasibility while maintaining appropriate safeguards

Section in Amendment 1	Change	Rationale
Section 6.1	Deleted "The term investigational drug (study medication) in this FIH Phase I/II study refers to IMCnyeso"	To simplify protocol language
Section 6.1	Clarified "Fully functional resuscitation equipment and medications to handle acute infusion-related emergencies (eg, anaphylaxis, cytokine release syndrome) must be available at each study site"; Previously "Fully functional resuscitation facilities must be available at each study site"	To clarify facility requirements for investigational sites
Section 6.1.1	Clarified that each vial is used for "1 dose /1 patient" (previously "1 patient")	To reinforce that drug product vials are for single use
Section 6.2	The first three patients at each dose level will be hospitalized for 2 nights after the first dose of IMCnyeso. After reviewing safety, PK, and cytokine data from at least 3 patients enrolled at a given dose level, the SST may decide that 1 night of hospitalization is adequate after the first dose for subsequent patients with longer hospitalization if indicated	ImmTACs have short (<24 hour) serum half-life and rapid pharmacodynamic effects; based on studies for the related ImmTAC molecule, IMCgp100, when treatment-related AE occur, the onset is anticipated to be rapid (<24 hours post dose) and no instances of rapid re-admission due to treatment-related AE occurred after discharge following one night of hospitalization after dosing. Per-protocol patients in the current study will be monitored for ≥36 hours (±4 hours) following the C1D1 dose.
Section 6.3	Clarified that storage times for prepared doses is determined starting at time of vial breach rather than time when dose preparation is complete	To correct an inconsistency
Section 6.3	Updated drug product storage and infusion windows	To incorporate new refrigerator stability data (2°C-8°C for up to 24 hours)

Section in Amendment 1	Change	Rationale
Section 6.4	Updated duration of infusion to "the first dose will be infused over 2 hours (±15 minutes). If the first dose is well tolerated without ≥ 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"	To support patient safety and simplify protocol compliance (by giving the first infusion over 2 hours for all patients and by having the same reduction in duration of infusion for all cohorts at subsequent doses)
Section 6.4	Redundant information regarding concomitant medications was removed and hyperlinks added to relevant sections	To remove redundant information and improve overall organization
Section 6.10, Section 13.3	The prior assumptions for the Bayesian Logistical Regression Model (BLRM) were updated. Higher dose levels were included in the model. The operating characteristics, example dose levels, and potential escalation schemes were updated accordingly	To emphasize emerging clinical data rather than preclinical assumptions of MTD in guiding dose-escalation increments
Section 6.10	If the emerging safety profile indicates that treatment-related AEs (eg, cytokine release) are more severe following initial doses and less severe after later doses, the Study Safety Team may initiate a 1-step or 2-step intra-patient escalation regimen. A longer DLT evaluation period and adjusted Cycle 1 schedule were added for patients receiving intra-patient escalation	Intra-patient dose-escalation approaches have proven beneficial in mitigating acute safety events for other CD3 bispecifics, including blinatumomab and the related ImmTAC molecule IMCgp100 (Saber, 2017)
Section 6.11	Separated criteria for MTD and RP2D	For clarity in study execution
Section 6.12	Added "In the absence of clinically significant signs or symptoms, abnormal laboratory values that potentially meet DLT criteria must be confirmed by re-testing at least 24 hours after the initial observation."	To ensure that isolated abnormal laboratory values are not considered as DLT unless clinically significant and/or confirmed by re-testing
Section 6.12	Redundant information in the DLT criteria table removed	To remove redundant information and provide clarity for study execution

Section in Amendment 1	Change	Rationale
Section 6.12	Grade 4 neutropenia persisting > 5 days after onset or associated with infection is a DLT	Transient laboratory findings of Grade 4 neutropenia in the absence of fever or infection do not indicate DLT
Section 6.12	≥ Grade 3 lymphopenia in the presence of an infection indicating clinical significance is a DLT	Laboratory findings of lymphopenia, in absence of infection, do not indicate DLT
Section 6.12	Grade 3 thrombocytopenia associated with bleeding is a DLT if bleeding is ≥ Grade 3	Low-grade bleeding does not indicate DLT
Section 6.12	DLT criterion for concurrent elevations in ALT/AST and bilirubin were updated to align with Potential Hy's Law criteria	To align with standards in the field including FDA guidance regarding the case definition of Hy's Law
Section 6.12	Grade 3 ALT/AST were adjusted to apply stricter criteria for elevations > 8 × ULN (DLT) than for more modest Grade 3 elevations (DLT if not resolved to Grade ≤ 1 within 14 days); previously any Grade 3 ALT/AST elevation was not a DLT if resolved to Grade ≤ 1 within 72 hours); similar adjustments were also made for bilirubin (> 5 × ULN is a DLT regardless of duration; more modest Grade 3 elevations are DLT if not resolved to Grade ≤ 1 within 14 days)	To provide more stringent DLT criteria for more severe Grade 3 isolated transaminase or isolated total bilirubin increase and to align with FDA guidance regarding when to discontinue study medication in the setting of potential drug-induced liver injury
Section 6.12	DLT criterion regarding amylase / lipase increase were added	To ensure only clinically significant findings meet DLT criteria
Section 6.12	DLT criterion for hypotension updated to remove "Any event of hypotension requiring pharmacologic blood pressure support … of any duration is a DLT"	To align with grading and DLT criteria for cytokine release syndrome
Section 6.12	Hypertension DLT criteria based on Grade 3 numeric criteria from CTCAE	To clarify which portions of the CTCAE definition are applicable

Section in Amendment 1	Change	Rationale
Section 6.12	Clarified "The Investigator must notify the Sponsor within 24 hours of any SAE, DLT, ≥ Grade 2 CRS, or ≥ Grade 3 hepatic function abnormality." rather than "The Investigator must notify the Sponsor immediately of any unexpected NCI CTCAE Grade ≥ 3 AEs or laboratory abnormalities."	To ensure rapid communication of the most important safety events and to aid in protocol compliance
Section 6.12	Grade 3 skin toxicity is not a DLT if resolved within 7 days (previously 4 days)	Based on experience with IMCgp100, a single event of Grade 3 skin toxicity is not dose-limiting, but may require slightly longer resolution time
Section 6.13	Updated guidance on anti-coagulant therapy to state: Anti-coagulant therapy is permitted. International normalized ratio should be monitored as clinically indicated per the Investigator's discretion. Ongoing anti-coagulant therapy should be temporarily discontinued to allow tumor biopsy according to institutional guidelines. Recent hospitalizations that required low dose heparin for deep vein thrombosis prophylaxis are not a contraindication	To provide a broader guidance regarding anti-coagulant therapy that covers newer anticoagulants as well as warfarin and heparin
Section 6.13	Added: Appropriate management of patients with more severe hypertension, receiving medications that may cause rebound hypertension when abruptly discontinued, or on multiple blood pressure medications, should be discussed with the Sponsor Medical Monitor	To ensure patient safety, in cases where withholding anti-hypertensive medications may be contraindicated
Section 6.13	Allow treatment with denosumab (previously no monoclonal antibodies were allowed)	To allow a standard supportive care agent for patients with bone metastasis
Section 6.13	Clarify that prohibition of anti-cancer therapies refers to systemic therapies for the cancer under study	To allow anti-cancer therapies for secondary malignancies that would not provide therapeutic benefit for the disease under study (eg, adjuvant

Section in Amendment 1	Change	Rationale
		tamoxifen for prior breast cancer would not be prohibited)
Section 6.13	Added: Based on the emerging safety profile of IMCnyeso, the SST may decide to recommend a standard pre-treatment regimen (which may include antihistamine, acetaminophen, and/or corticosteroid)	Pre-medications are commonly used for other anti-CD3 bispecific molecules and may improve benefit/risk based on emerging safety profile from other ImmTAC programs
Section 6.13	Allow corticosteroids for known allergy to contrast reagents	To allow exception to prohibition of steroid therapy for standard management of patients with contrast reagent allergy
Section 6.15	CRS is to be graded based on the ASTCT 2019 guidelines (Lee; 2019). The definition of CRS, grading criteria, and definition of resolution of CRS were added in Appendix 1	To align with the most current standards and provide further clarification regarding standards for reporting, resolution, and data collection of CRS events
Section 6.15	In addition to recommended toxicity management, a new column was added for dose-modification requirements, and guidance was added for each toxicity and grade if not already present	To provide clear guidance regarding when study treatment should be interrupted, dose-reduced, or permanently discontinued
Section 6.15	AE grading criteria for specific toxicities was removed from toxicity management guideline table	To remove redundant information
Section 6.15	Information provided both in table and text removed from table	To remove redundant information
Section 6.15	Information regarding management and dose modifications for hypotension were incorporated into the CRS guidance rather than a stand-alone category	Based on experience with related molecules, potential events of hypotension may occur in the context of CRS rather than as an isolated event
Section 6.15	CRS defined as occurring at least 1 hour after the start of infusion; IRR defined as occurring within 1 hour of starting the infusion	To clarify when CRS guidance vs. IRR guidance should be followed and how to systematically

Section in Amendment 1	Change	Rationale
		classify events for the purposes of AE data collection
Section 6.15	Guideline for Grade 1 CRS updated to remove "assess for potential infection", "treat … neutropenia" and "strongly consider early, high-dose corticosteroid therapy with changes in vital signs". Added reminder to collect serum for central lab cytokine assessments	To incorporate the most up-to-date management approaches, align with other ImmTAC protocols, and aid in protocol compliance
Section 6.15	Guideline for Grade 2 CRS updated to add "If patient experiences dyspnea, consider supportive measures such as supplemental oxygen". Require overnight hospitalization following the next scheduled dose	To align with ASTCT 2019 guidelines
Section 6.15	Guideline for Grade 3 CRS updated to provide recommended dosing for corticosteroids and tocilizumab. Added "for persistent hypotension treat with a single vasopressor (with or without vasopressin)" and "for hypoxia provide oxygen with a high-flow device" Added requirements for dose reduction, pre-medication, and overnight hospitalization if re-treatment is given. Added discontinuation criteria for recurrent Grade 3 CRS	To incorporate the most up-to-date management approaches, align with ASTCT 2019 guidelines, and align with other ImmTAC protocols
Section 6.15	Guideline for Grade 4 CRS updated to provide and add "treat hypotension with multiple vasopressors, for hypoxia provide oxygen using a positive-pressure device, and consider other immunosuppressive agents as indicated (eg, infliximab and mycophenolate mofetil)"	To incorporate the most up-to-date management approaches, align with ASTCT 2019 guidelines, and align with other ImmTAC protocols
Section 6.15	Management and dose-modification guidelines for rash and pruritus were consolidated into a single section	To remove redundant information and to aid in protocol compliance
Section 6.15	Guidance for Grade 2 rash and Grade 2 pruritis updated to allow dosing to continue (previously required return to ≤ Grade 1)	To incorporate the most up-to-date management approaches and align with other ImmTAC protocols

Section in Amendment 1	Change	Rationale
Section 6.15	Guidance for Grade 3 rash updated to require treatment discontinuation if Grade 3 rash does to not resolve to Grade 1 or better within 21 days	To provide guidance for a scenario not discussed in the prior version
Section 6.15	Guidance for Grade 3 pruritis updated to consider montelukast 10 mg by mouth for patients who are refractory to antihistamine and local corticosteroid treatments	To incorporate the most up-to-date management approaches and align with other ImmTAC protocols
Section 6.15	Guidance for Grade 1 IRR updated to add a requirement for more frequent monitoring of vital signs while removing treatment and infusion interruption	To align with CTCAE v4.03 definition of Grade 1 infusion-related reaction (infusion interruption not indicated; intervention not indicated)
Section 6.15	Guidance for Grade 2 IRR updated to monitor pulse oximetry and continuous cardiac telemetry (if clinically indicated). If IRR resolves in < 4 hours, the infusion may continue upon resolution without the previous requirement for an additional 1-hour monitoring period before resuming infusion. Added guidance for the scenario of IRR that requires > 4 hours to resolve	To ensure patient safety and provide guidance for scenarios not included in the prior version
Section 6.15	Guidance for Grade 3 IRR updated to allow treatment to continue only at the next scheduled dose (rather than re-starting the interrupted infusion on the same day), with mandatory pre-medication and a reduced rate of infusion	To provide more extensive mitigation for re-treatment following Grade 3 IRR and guidance for scenarios not included in the prior version
Section 6.15	Guidance for Grade 4 infusion-related reaction updated to require permanent discontinuation of study drug	To provide clear discontinuation criteria
Section 6.15	Guidance for Grade 3 hepatic function abnormality updated to include dose-modification guidelines including threshold for treatment discontinuation	To provide more extensive risk mitigation in the setting of re-treatment and clear guidelines for when treatment should be permanently discontinued

Section in Amendment 1	Change	Rationale
Section 6.15	Require permanent treatment discontinuation for Grade 4 hepatic function abnormalities	To provide clear discontinuation criteria
Section 6.15	Require treatment interruption for Grade 3 or Grade 4 vomiting and require dose reduction for prolonged (>3 days) Grade 3 or any duration Grade 4 vomiting	To provide more stringent dose modification for severe vomiting
Section 6.16	Reasons for treatment discontinuation were consolidated into a single section, with hyperlinks from other protocol sections	To aid in protocol compliance, remove inconsistencies and redundancies, and improve overall organization
Section 6.16	Updated reason for discontinuation of study treatment to "Disease progression (Note: Patients may receive treatment after initial disease progression per RECIST v1.1 based on criteria in Section 6.18)", previously unequivocal, confirmed disease progression based on the modified irRECIST criteria and/or RECIST v1.1 criteria	To ensure reason treatment is discontinued is reported accurately for all patients who discontinue treatment due to PD (including initial PD based on single assessment per RECIST v1.1, confirmed PD based on at least 2 assessments, or symptomatic / clinical deterioration consistent with disease progression)
Section 6.16	Information about the EOT visit consolidated in Section 7.3	To aid in protocol compliance
Section 6.18	Treatment discontinuation will be required when unequivocal disease progression is confirmed (defined as an additional ≥ 5 mm increase in tumor burden [sum of diameters of both target and new lesions] and/or identification of additional new lesions, at least 4 weeks after the initial PD assessment)	To align with more current iRECIST standards (Seymour 2017)
Section 7	Schedule tables were reformatted to have all schedule information for each study period within a single table. Schedule information was removed from other protocol sections including the Synopsis	To aid in compliance and reduce inconsistency and redundancy

Section in Amendment 1	Change	Rationale
Section 7	[redacted]	[redacted]
Section 7.1, Section 7.2.2	Moved HLA-A*02:01 testing, NY-ESO-1 / LAGE-1A testing, and patient demographics and other baseline characteristics to Section 7.4	To improve protocol organization
Section 7.1	If the patient is already known to be HLA-A*02:01 positive, the HLA sample and tumor sample can be submitted in parallel	To improve operational logistics
Section 7.2	Acceptable time windows were added if not previously included and adjusted in some cases	To improve operational feasibility and minimize protocol deviations
Section 7.2	Added that after C1D1 pregnancy testing may be performed up to 72 hours prior to dosing and other safety assessments may be performed up to 24 hours prior to dosing	To improve operational feasibility and improve protocol compliance
Section 7.2	Scheduled chemistry and hematology evaluations reduced to Q2W in Cycle 3 and Q4W for Cycle 4 and beyond	To reduce testing during later cycles, when risk of new treatment-related AE is lower
Section 7.2	The visit window during the treatment period is ±7 days; added that there must be a minimum of 7 days between doses of IMCnyeso	To ensure an adequate interval between doses of study drug, for patient safety
Section 7.3	Added safety assessments at the 30-day post last-dose visit	To allow evaluation of resolution of any abnormal findings or laboratory values at End of Treatment
Section 7.4	Clarified that patients who initiate subsequent anti-cancer treatment will proceed directly to Survival Follow-up. Any treatment-related SAE must be reported even if safety follow-up has completed	To minimize confounding effects of subsequent anti-cancer therapies when evaluating safety of IMCnyeso
Section 5.1, Section 7	All patients may use archival tumor for Pre-Screening	NY-ESO-1 / LAGE-1A expression is not expected to decrease following other treatments. Given the

Section in Amendment 1	Change	Rationale
		rates of antigen positivity, it is not appropriate to require biopsy procedures during Pre-Screening
Section 5.1, Section 7	On-study paired biopsies for exploratory biomarker evaluations are required for ≥10 patients (previously all patients) in Phase II	To ensure an adequate number of biopsies to meet study objectives while allowing enrollment of patients who cannot safely undergo multiple on-study biopsies
Section 7.4	Clarified that additional CT/MRI scans (beyond the main schedule) are not required at EOT or to confirm response	To correct an inconsistency
Section 7.4	Added: The Sponsor reserves the right to request additional scans obtained within 6 months of the screening assessment	To evaluate tumor growth kinetics prior to and following treatment with IMCnyeso
Section 7.4	Removed requirement for hepatic MRI at each disease assessment	To align with standard of care for the indications under study
Section 7.4	Clarified that pelvis scans are to be done as appropriate based on indication and extent of disease	To align with standard of care for the indications under study
Section 7.9	Hematocrit removed from required hematology panel	Hemoglobin testing is sufficient for safety monitoring given hematocrit is derived value
Section 7.9	Monocytes, eosinophils, and basophils removed from required hematology panel	These tests are not required for safety monitoring
Section 7.9	Thyroid function test panel adjusted to include free T3 as a reflex assay. Total T3 testing was removed	Total T3 is less informative and harder to interpret; Free T3 may help to interpret thyroid function test abnormalities
Section 7.9	Removed specification that urinalysis be performed using dipstick	Non-dipstick urinalysis methods are also acceptable

Section in Amendment 1	Change	Rationale
Section 7.9	Clarified that "blood and glucose" will be evaluated in urine rather than "blood glucose"	To clarify the scope of urinalysis assessments
Section 7.9	Clarified that any patient who becomes pregnant should be withdrawn from treatment rather than withdrawn from study	To ensure that the outcome of any pregnancy that occurs during the study is assessed
Section 7.9	Serum collected during potential events of CRS will be evaluated by a central laboratory rather than local laboratories	To improve operational feasibility (many local laboratories do not perform cytokine testing) and consistency of measured values
Section 7.9	Added that new or worsening clinically significant ECG findings should be confirmed by performing at least 2 additional ECG reads within approximately 30 minutes	To ensure accuracy of ECG findings
Section 7.9	Frequency of ECG adjusted to add assessment on Cycle 4 Day 1. Last planned start-of-cycle ECG assessment is on Cycle 6 (previously Cycle 12 in Phase I and Cycle 5 in Phase II)	To reduce testing during later cycles, when risk of new treatment-related AE is lower
Section 7.9	ECG assessments marked to indicate whether single read or triplicate is needed	To clarify the required assessment
Section 7.9	PK timepoint added at 36 hours after the first dose. An optional timepoint was added at 48 hours after first dose	Sampling schedule adjusted based on emerging PK data
Section 7.9	PK timepoints in Cycle 3 and beyond simplified to assess pre-dose and EOI on Day 1 of odd cycles only (previously Day 1 and Day 15 of odd cycles)	To limit PK testing to what is required to assess study endpoints
Section 7.9	Moved skin punch biopsy to [redacted] section	To align with described purpose and clarify that sample retention is aligned with other [redacted] specimens

Section in Amendment 1	Change	Rationale
Section 7.10	[redacted]	[redacted]
Section 7.10	Reduced Cycle 1 Day 22 timepoints for the multiplex cytokine and chemokine panel	To improve operational feasibility
Section 7.10	The optimal timing for the on-treatment biopsy sample is between Cycle 1 Day 9 and Cycle 1 Day 16 (previously during Cycles 1 and/or 3, 1-3 days following dosing)	To provide more consistent biopsy timing that is aligned with emerging experience from other ImmTAC programs
Section 7.10	Added biopsied lesions may not be followed as target lesions for disease assessments per RECIST v1.1 unless the lesion is > 2 cm and, in the opinion of the Investigator, the biopsy will not appreciably impact the dimensions of the lesion	To ensure that biopsy does not compromise ability to assess response per RECIST v1.1
Section 8.2	Clarified that disease progression, including identification of new lesions (or worsening of existing lesions) or death due to progression of the disease under study should not be reported as AE / SAE. Information regarding new lesions (or worsening of existing lesions) should be reported in the eCRF New Lesion and disease assessment pages, information regarding cause of death on Death page, and any signs or symptoms that occur as a result of PD and meet the definition of AE should be reported on the AE page	To ensure consistent reporting of patient disposition, adverse events, and disease progression
Section 8.2	CRS is considered as an AESI for IMCnyeso	To facilitate additional data collection and reporting to the Sponsor
Section 8.6	Age rather than date of birth is to be included on any SAE report	To protect patient information
Section 8.6	Updated technical details of the SAE reporting process	For accuracy

Section in Amendment 1	Change	Rationale
Section 9	Statistical analysis plans were revised to report 95% confidence interval for ORR (rather than 90%)	To align with standard practice
Section 9.5	Phase II BOR included in primary analysis section	For consistency with updates in objectives / endpoints
Section 9.6.2	Safety periods updated	To align with changes in safety follow-up
Section 9.6.2	Statistical analysis plans were revised to remove listings for physical examination data	Findings from physical exams are reported as AE and will be included in AE listings
Section 9.6.3	Added immunogenicity analyses in secondary analysis section	To correct an omission
Section 10	Added: All data collected during this study, including clinical and [redacted] data, may be pooled with data from other studies using the same study drug or a different study drug with a similar mechanism (eg, ImmTAC) in order to advance our understanding about study drug safety, [redacted] correlation with a variety of outcomes, or other study endpoints in order inform future development provided the patient provides consent to permit such pooling of data	To provide transparency regarding potential uses of study data
Section 13.1	Appendix regarding modified irRECIST was removed	irRECIST is no longer being used in this study
Section 13.3	BLRM dose range was updated to increase the maximum dose from 120 mcg to 200 mcg	To ensure that the maximum dose used in BLRM simulations exceeds the expected maximum dose in dose-escalation
Section 13.4	Appendix with detailed description of changes and rationale added	To provide transparency regarding changes in Amendment 2