CLINICAL TRIAL PROTOCOL

Trial Title:	A Phase 1, Open-Label, Multicenter Trial Investigating the Safety, Tolerability, and Preliminary Antineoplastic Activity of Sym023 (Anti-TIM-3) in Patients with Advanced Solid Tumor Malignancies or Lymphomas
Short Title:	Sym023 in Patients with Advanced Solid Tumor Malignancies or Lymphomas
Sponsor:	Symphogen A/S Pederstrupvej 93 DK-2750 Ballerup Denmark
Sponsor's Medical Expert:	[redacted]
Coordinating Investigator:	
Trial ID:	Sym023-01
Trial Phase:	Phase 1
EudraCT number:	Not Applicable
IND Number:	137066
Protocol Version/Date:	5.0 / 02-May-2019 (Amendment 4)
Previous Protocol Versions/Dates:	4.0 / 18-Mar-2019 (Amendment 3) 3.0 / 02-Aug-2018 (Amendment 2) 2.0 / 04-Apr-2018 (Amendment 1) 1.0 / 20-Feb-2018

Sponsor Declarations

The trial will be conducted in compliance with this clinical trial protocol, International Council for Harmonisation (ICH) of Technical Requirements for Pharmaceuticals for Human Use E6(R2): Guideline for Good Clinical Practice (GCP) (EMA/CHMP/ICH/135/1995), the Declaration of Helsinki, and applicable regulations.

The Sponsor has appointed a Coordinating Investigator for the trial. This Coordinating Investigator will provide input to the trial design and act as overall coordinator for Investigators across all sites. The Coordinating Investigator will furthermore sign off the Clinical Trial Report on behalf of all Investigators.

Lists of Investigators responsible for conducting the trial, medically qualified physicians responsible for all site-related medical decisions (if other than the Investigators), monitors, clinical laboratories, and other medical and/or technical departments and/or institutions involved in the trial are provided as separate documents.

Principal Investigator Signature Page

I, the undersigned, am responsible for the conduct of the trial at this site and agree:

- To assume responsibility for the proper conduct of the clinical trial at this Investigational Site
- Not to implement any changes to the clinical trial protocol without agreement from the Sponsor and prior review and written approval from the appropriate Health Authority (as indicated) and the Institutional Review Board/ Ethics Committee, except where necessary to eliminate an immediate hazard to the patients
- That I am aware of, and will comply with "Good Clinical Practice" (ICH E6(R2) GCP) (EMA/CHMP/ICH/135/1995), the Declaration of Helsinki, and all applicable regulatory requirements
- That all site staff to which I have delegated tasks for this clinical trial, are appropriately selected and adequately informed about the investigational product(s) and of their trial-related duties and functions as described in the clinical trial protocol

_____ _____
Signature Date of Signature

Name: _____

Academic Degree: _____

Function: _____

Institution: _____

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LIST OF ABBREVIATIONS AND EXPANDED TERMS

Abbreviation	Expanded Term
1M FUP	1-Month Follow-up
Ab	Antibody
ADA	Anti-Drug Antibody
ADCC	Antibody-Dependent Cellular Cytotoxicity
AE	Adverse Event
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase
ANC	Absolute Neutrophil Count
aPTT	Activated Partial Thromboplastin Time
ARDS	Acute Respiratory Distress Syndrome
AST	Aspartate Aminotransferase
AUC	Area Under the Concentration-Time Curve
AUC_{τ}	Area Under the Concentration-Time Curve in a dosing interval
AUC_{inf}	Area Under the Concentration-Time Curve from start of infusion to infinity
$AUC_{norm, \tau}$	Dose-Normalized Area Under the Concentration-Time Curve in a dosing interval
β-hCG	Beta-Human Chorionic Gonadotropin
BM	Bone Marrow
BNP	Brain Natriuretic Peptide
BP	Blood Pressure
BPM	Beats Per Minute
BUN	Blood Urea Nitrogen
Bx	Biopsy
C	Centigrade, Celsius
C#/D#	Cycle #/Day #
Ca	Calcium
CBC	Complete Blood Count
CDC	Complement-Dependent Cytotoxicity
CEACAM1	Carcinoembryonic Antigen Related Cell Adhesion Molecule 1
C_{EOI}	Concentration at the End of Infusion
CFR	Code of Federal Regulations
CHF	Congestive Heart Failure
CIOMS	Council for International Organizations of Medical Sciences

Abbreviation	Expanded Term
CK	Creatine Kinase
Cl	Chloride
CL	Clearance
C_{max}	Maximum Concentration
CPD	Confirmed Progressive Disease
C_{trough}	Trough Concentration
CNS	Central Nervous System
CR	Complete Response
CRF	Case Report Form
CS	Clinically Significant
CT	Computed Tomography
CTC	Common Toxicity Criteria
CTCAE v5.0	Common Terminology Criteria for Adverse Events (Version 5.0)
ctDNA	Circulating Tumor Deoxyribonucleic Acid
CTLA-4	Cytotoxic T-Lymphocyte-Associated Protein 4
CV	Curriculum Vitae
D, d	Day
dL	Deciliter
DL_{CO}	Diffusing Capacity of Carbon Monoxide
DLT	Dose-Limiting Toxicity
DMP	Data Management Plan
DNA	Deoxyribonucleic Acid
DRF	Dose-Range-Finding
DSUR	Development Safety Update Report
DVT	Deep Vein Thrombosis
EC	Ethics Committee
ECG	Electrocardiogram
ECHO	Echocardiogram
ECOG	Eastern Cooperative Oncology Group
EDC	Electronic Data Capture
EOC#	End of Cycle #
EOI	End of Infusion
EOS	End of Study

Abbreviation	Expanded Term
EOT	End of Treatment
F	Fahrenheit
FAS	Full Analysis Set
FDG	Fluorodeoxyglucose
FEV_1	Forced Expiratory Volume in 1 Second
FFPE	Formalin-Fixed, Paraffin-Embedded
FRC	Functional Residual Capacity
FSH	Follicle-Stimulating Hormone
fT3	Free Triiodothyronine
fT4	Free Thyroxine
FUP	Follow-up
FVC	Forced Vital Capacity
GCP	Good Clinical Practice
GI	Gastrointestinal
GLP	Good Laboratory Practice
H, h	Hour
HAVCR2	Hepatitis A Virus Cellular Receptor 2
HBV	Hepatitis B Virus
hCG	Human Chorionic Gonadotropin
HCV	Hepatitis C Virus
HIPAA	Health Insurance Portability and Accountability Act
HIV	Human Immunodeficiency Virus
HMGB1	High Mobility Group Box 1
HPF	High Power Field
HR	Heart Rate
HRT	Hormone Replacement Therapy
HSCT	Hematopoietic Stem Cell Transplantation
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use
ICMJE	International Committee of Medical Journal Editors
Ig	Immunoglobulin

Abbreviation	Expanded Term
IHC	Immunohistochemistry
IL-2	Interleukin-2
ILD	Interstitial Lung Disease
IMP	Investigational Medicinal Product
IND	Investigational New Drug
INR	International Normalized Ratio
IRB	Institutional Review Board
iRECIST	Immunotherapeutics Response Evaluation Criteria in Solid Tumors
IRR	Infusion-Related Reaction
IU	International Units
IV	Intravenous
K	Potassium
KD	Dissociation Constant
KLH	Keyhole Limpet Hemocyanin
kg	Kilogram
LSECtin	Liver Sinusoidal Endothelial Cell Lectin
LLN	Lower Limit of Normal
LVEF	Left Ventricular Ejection Fraction
M, m	Month, Molar, Meter
mAb	Monoclonal Antibody
MABEL	Minimal Anticipated Biological Effect Level
MAD	Maximum Administered Dose
MedDRA	Medical Dictionary for Regulatory Activities
Mg	Magnesium
mg	Milligram
MHC	Major Histocompatibility Complex
MI	Myocardial Infarction
min	Minute
mL	Milliliter
MLR	Mixed Lymphocyte Reaction
mm	Millimeter
MRI	Magnetic Resonance Imaging
MRSD	Maximum Recommended Starting Dose

Abbreviation	Expanded Term
msec	Millisecond
MTD	Maximum Tolerated Dose
MUGA	Multi-Gated Acquisition
Na	Sodium
NaCl	Sodium Chloride
NCS	Not Clinically Significant
NE	Not Evaluable
NK	Natural Killer (cell)
NL	New Lesion
NLNT	New Lesion-Non-Target
NLT	New Lesion-Target
NOAEL	No Observed Adverse Effect Level
NT	Non-Target
NYHA	New York Heart Association
OR	Objective Response
PBMC	Peripheral Blood Mononuclear Cell
PD	Progressive Disease, Disease Progression
PDF	Portable Document Format
PD-1	Programmed Cell Death Protein 1
PD-L1	Programmed Death-Ligand 1
PE	Pulmonary Embolism
PET	Positron Emission Tomography
PFT	Pulmonary Function Test
PK	Pharmacokinetic
PO	Per Os (orally, by mouth)
PR	Partial Response
PR Interval	ECG interval between beginning of the P-wave to beginning of the QRS complex
PS	Performance Status
PSA	Prostate Specific Antigen
PSPD	Pseudoprogression
PT	Prothrombin Time
PtdS	Phosphatidylserine
PTT	Partial Thromboplastin Time

Abbreviation	Expanded Term
Q2M	Every 2 Months
Q2W	Every 2 Weeks
QT Interval	ECG interval between onset of QRS complex to end of the T-wave
QTc Interval	Heart Rate-corrected QT interval
RBC	Red Blood Cell
RECIL 2017	Response Evaluation Criteria in Lymphoma (2017)
RECIST v1.1	Response Evaluation Criteria in Solid Tumors (Version 1.1)
RNA	Ribonucleic Acid
RNA-seq	Ribonucleic Acid Sequencing
RSI	Reference Safety Information
RP2D	Recommended Phase 2 Dose
RV	Residual Volume
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAR	Suspected Adverse Reaction
SAS	Statistical Analysis System
SD	Stable Disease
SEB	Staphylococcal Enterotoxin B
SOC	System Organ Class
SOI	Start of Infusion
SOM	Sum of Measurements
SOP	Standard Operating Procedure
SSA	Somatostatin Analog
SUSAR	Suspected Unexpected Serious Adverse Reaction
T	Target
$T_{1/2}$	Terminal Elimination Half-life
TBD	To Be Determined
TCR	T-cell Receptor
TDAR	T-cell Dependent Antibody Response
TEAE	Treatment Emergent Adverse Event
TIM-3	T-cell Immunoglobulin and Mucin-Domain Containing-3
TK	Toxicokinetic
TLC	Total Lung Capacity

Abbreviation	Expanded Term
T_{max}	Time to Maximum Concentration
TP	Timepoint
TRAE	Treatment Related Adverse Event
TSH	Thyroid Stimulating Hormone
TTP	Time to Progression
ULN	Upper Limit of Normal
µg	Microgram
µM	Micromolar
UPD	Unconfirmed Progressive Disease
U.S.	United States
U/S	Ultrasound
UV	Ultraviolet
V, v, Vol	Volume
V_d	Volume of Distribution
VS	Vital Signs
W, w	Week
w/v	Weight to Volume
WBC	White Blood Cell
WES	Whole-exome Sequencing
WHO	World Health Organization
WOCBP	Woman of Childbearing Potential

1 SYNOPSIS

CLINICAL TRIAL PROTOCOL	
Trial Title	A Phase 1, Open-Label, Multicenter Trial Investigating the Safety, Tolerability, and Preliminary Antineoplastic Activity of Sym023 (Anti-TIM-3) in Patients with Advanced Solid Tumor Malignancies or Lymphomas
Trial ID	Sym023-01
Trial Phase	Phase 1
INVESTIGATIONAL MEDICINAL PRODUCT	
Investigational Medicinal Product	The Investigational Medicinal Product (IMP) is Sym023 (also referred to as study drug). Sym023 is a recombinant T-cell immunoglobulin and mucin-domain containing-3 (anti-TIM-3) human monoclonal antibody (mAb) **Supplies** Labeled supplies of study drug will be provided by the Sponsor. Each single-use glass vial contains Sym023: • As a liquid formulation for intravenous (IV) infusion • With a nominal fill volume of 8.0 milliliter (mL) • At a concentration of 20 mg/mL for a total vial content of 160 milligrams (mg) **Formulation Excipients** Provided herein **Storage** Refrigerate (2ºC to 8ºC); store in an access-controlled, secure location; protect from direct sunlight
Combination Agent	None
TRIAL OBJECTIVES	
Sym023 Dose-Escalation	**Primary** Evaluation of the safety, tolerability, and dose-limiting toxicities (DLTs) to establish the maximum tolerated dose (MTD) and/or recommended Phase 2 dose (RP2D) of sequential escalating doses of Sym023 when administered once every 2 weeks (Q2W) by 30-minute IV infusion to patient cohorts with locally advanced/unresectable or metastatic solid tumor malignancies or lymphomas that are refractory to available therapy or for which no standard therapy is available Note: Q2W dosing; 4 weeks equals 1 dosing cycle. Goal is identification of the MTD or determination of a RP2D based on clinical data, including safety, pharmacokinetic (PK), and pharmacodynamic outcomes. The MTD, if identified, and the RP2D may not be the same as the RP2D may be lower. If an MTD is not identified, a maximum administered dose (MAD) will be determined and will not exceed 20 mg/kg. **Secondary** • Evaluation of the immunogenicity of Sym023 • Characterization of the PK profile of Sym023 • Evaluation of the preliminary antineoplastic effects of Sym023, including: o Evidence of objective response (OR) or stable disease (SD)* o Duration of OR or SD* o Time to progression (TTP) of disease* **As assessed by Response Evaluation Criteria in Solid Tumors (Version 1.1) (RECIST v1.1), Immunotherapeutics Response Evaluation Criteria in Solid Tumors (iRECIST), and Response Evaluation Criteria in Lymphoma (2017) (RECIL 2017)* **Exploratory** • Evaluation of potential pharmacodynamic markers, e.g., receptor occupancy in peripheral blood mononuclear cells (PBMCs) (peripheral blood to be collected) • Evaluation of potential biomarkers including but not limited to assessment of: o In peripheral blood: circulating tumor deoxyribonucleic acid (ctDNA), ribonucleic acid (RNA), relevant proteins/cytokines, and cellular biomarkers o In tumor tissue: DNA, RNA, protein, and cellular biomarkers *(biopsies optional)* Note: Assay methodology and biomarker assessments to be determined (TBD). Potential analyses may include but are not limited to: ctDNA sequencing; RNA sequencing (RNA-seq)/whole-exome sequencing (WES); measurement of relevant proteins/cytokines in the blood; cytometric analysis of cells in blood; and immunohistochemistry (IHC) of tumor material when collected *(tumor sampling is optional)*

TRIAL DESIGN	
Design Summary	This is a Phase 1, multicenter, open-label, dose-escalation study designed to evaluate safety, tolerability, and DLTs to establish the MTD or MAD, and the RP2D of sequential escalating doses of Sym023 (study drug) when administered Q2W (4 weeks equals 1 cycle) by 30-minute IV infusion, to patients with advanced, refractory solid tumor malignancies or lymphomas. Approximately 20-48 male and female patients will be entered. Initially a modified, accelerated-titration, dose-escalation design will be used, with entry of single patient cohorts for up to 2 dose levels, based on tolerability. Thereafter, dose-escalation will follow a standard 3+3 design, with a target toxicity level of 33.3% or less as determined by DLTs. It is planned that 7 dose levels up to a maximum dose of 20 mg/kg will be evaluated. The number of patients treated, the number of cohorts evaluated, and the MTD/MAD will depend upon the observed tolerability of Sym023 during Cycle 1. In the absence of documented progressive disease (PD) or unacceptable toxicity, patients may continue to receive additional 4-week cycles of study drug at the same dose, infusion duration, and schedule established for the patient.
PATIENT SELECTION	
Recruitment Period	**Enrollment Dates** • Anticipated date of enrollment of first patient: Q2 2018 • Anticipated date of enrollment of last patient: Q3 2019 **End of Trial** (i.e., data cut-off for primary analysis) Will be reached 1 month (30 +7 days) after all patient have discontinued trial treatment or 6 months after the last patient has started trial treatment, whichever occurs earlier.
Investigational Sites	This is a multicenter trial. It is anticipated that approximately 2-4 centers in North America may participate based on accrual.
Number of Patients	Considerations for estimating the number of patients are as follows: **Sym023 Dose-Escalation** Approximately 20-48 patients in escalating dose cohorts: • Minimum of 1 patient per cohort for up to 2 dose cohorts • Minimum of 3 patients per dose cohort thereafter • Assume approximately 7 cohorts to establish the MTD, and/or RP2D • Expansion of any cohort to 6 patients in the event of a Cycle 1 DLT in any of the initial 1 to 3 patients • Minimum of 6 patients to be treated at the MTD and/or RP2D; expansion of this cohort (or any other) up to 12 patients may be considered to further evaluate tolerability In addition, there is potential for entry of additional patients to: • Ensure sufficient evaluable patients by adding an additional patient to a cohort • Expand a lower dose cohort(s) if an initially identified MTD and/or RP2D is subsequently determined to be not tolerated either with single or repeated cycles of therapy • Add and evaluate a previously unplanned intermediate dose level if indicated *(inclusion of a dose higher than those listed would require a protocol amendment)* Note: This action would be taken in the event of an unacceptably high frequency of toxicities observed in patients treated at one dose level considered to be in marked contrast to the tolerability noted at the preceding dose level, or if after review of study data, a more gradual dose-escalation appears warranted.
Eligibility	**Patients to be Included** *(patients must meet all the following criteria)* 1. Male or female patients, ≥ 18 years 2. Patients with a documented (histologically- or cytologically-proven) solid tumor malignancy that is locally advanced or metastatic; patients with documented lymphomas 3. Patients with a malignancy (solid tumor or lymphoma) that is currently not amenable to surgical intervention due to either medical contraindications or non-resectability of the tumor 4. Patients refractory to or intolerant of existing therapy(ies) known to provide clinical benefit. Note: Patients may have received and failed prior therapy with a programmed cell death protein 1/ programmed death-ligand 1 (PD-1/PD-L1) inhibitor and be considered eligible for this trial. 5. Patients with measurable or non-measurable disease according to RECIST v1.1 or standard criteria for lymphoma (RECIL 2017).

6. Patients with an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0 or 1, and anticipated life expectancy of ≥ 3 months
7. Patients, both male and female, who are either not of childbearing potential or who agree to use a highly effective method of contraception during the study beginning within 2 weeks prior to the first dose and continuing until 6 months after the last dose of study drug.
8. Patients with the ability to understand and give written informed consent for participation in this trial, including all evaluations and procedures as specified by this protocol.

Patients to be Excluded *(patients must not meet any of the following criteria)*

1. Women who are pregnant or lactating, or intending to become pregnant before, during, or within 6 months after the last dose of study drug. Women of childbearing potential (WOCBP) and fertile men with WOCBP partner(s), not using and not willing to use a highly effective method of contraception.
2. Patients with central nervous system (CNS) malignancies; patients with known, untreated CNS or leptomeningeal metastases, or spinal cord compression, patients with any of the above not controlled by prior surgery or radiotherapy, or patients with symptoms suggesting CNS involvement for which treatment is required.
   Note: Patients with treated CNS metastases will be eligible if they are asymptomatic, do not require corticosteroids, and have confirmation of at least stable brain disease status as assessed by 2 imaging studies performed ≥ 4 weeks apart with the most recent performed within 4 weeks prior to first trial drug administration. Prophylactic anticonvulsant medications are allowed.
3. Patients with hematologic malignancies other than lymphomas
4. Patients with any of the following hematologic abnormalities at baseline*:
   - Hemoglobin < 9 g/dL
   - Absolute neutrophil count (ANC) < 1,000 per mm^3
   - Platelet count < 75,000 per mm^3

   **Throughout this protocol "baseline" is defined as the last available observation prior to the first administration of study drug on Cycle 1/Day 1 (C1/D1).*
5. Patients with any of the following serum chemistry abnormalities at baseline:
   - Total bilirubin > 1.5 × the upper limit of normal (ULN) for the institution
   - Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) > 3 × the ULN for the institution (> 5× ULN if due to hepatic involvement by tumor)
   - Serum creatinine > 1.5 × ULN for the institution
6. Patients with any of the following coagulation parameter abnormalities at baseline (unless on a stable dose of anticoagulant therapy for a prior thrombotic event, as determined by the Investigator):
   - Prothrombin time (PT) (or international normalized ratio [INR]) > 1.5 × ULN for the institution (> 3× ULN for the institution if anticoagulated)
   - Partial thromboplastin time (PTT) (or activated partial thromboplastin time [aPTT]) > 1.5 × ULN for the institution (> 3× ULN for the institution if anticoagulated)
7. Patients with:
   - Active thrombosis, or a history of deep vein thrombosis (DVT) or pulmonary embolism (PE) within 4 weeks prior to first administration of study drug unless adequately treated and considered by the Investigator to be stable
   - Active uncontrolled bleeding or a known bleeding diathesis
8. Patients with a clinically significant (CS) cardiovascular disease or condition, including:
   - Need for antiarrhythmic medical therapy for a ventricular arrhythmia or other uncontrolled arrhythmia (patients with controlled atrial fibrillation (heart rate [HR] < 90) for > 30 days prior to study entry are eligible)
   - Severe conduction disturbance (e.g., 3rd degree heart block)
   - HR-corrected QT interval (QTc interval) ≥ 480 milliseconds (msec)
   - Uncontrolled hypertension (per the Investigator's discretion)
   - History of myocarditis
   - Left ventricular ejection fraction (LVEF)* known to be below the lower limit of normal (LLN) for the center, or < 50% by multi-gated acquisition (MUGA) scan or echocardiogram (ECHO) if no LLN is defined by the site
   - Congestive heart failure (CHF) currently requiring therapy
   - Class III or IV cardiovascular disease according to the New York Heart Association (NYHA) Functional Classification
   - History of acute coronary syndromes (including myocardial infarction [MI] and unstable angina), coronary angioplasty, stenting, or bypass within 6 months prior to first study

drug administration

9. Patients with a significant ocular disease or condition, including history of an autoimmune or inflammatory disorder, e.g., episcleritis, uveitis, iritis
   Note: Patients with a history of dry eye for reasons other than an autoimmune disease or condition may be included if adequately treated. Patients with non-significant, non-inflammatory disorders (e.g., cataracts, glaucoma) will be allowed.
10. Patients with a significant pulmonary disease or condition, including:
    - History of interstitial lung disease (ILD), pulmonary fibrosis
    - History of pulmonary inflammatory disease, interstitial or other pneumonitis*, acute respiratory distress syndrome (ARDS)

    **Patients with prior evidence of Grade 1 pneumonitis will be eligible provided they were asymptomatic and did not require treatment and provided pneumonitis has resolved prior to entry to this trial.*
11. Patients with a current or recent (within 6 months) significant gastrointestinal (GI) disease or condition, including:
    - History of inflammatory bowel disease
    - Diarrhea ≥ Grade 2 within 2 weeks prior to first administration of study drug
12. Patients with an active, known or suspected autoimmune disease, or a documented history of autoimmune disease or syndrome, requiring systemic steroids or other immunosuppressive medications
    Note: Exceptions permitted include: type I diabetes mellitus, hypothyroidism only requiring hormone replacement, skin disorders such as vitiligo, psoriasis or alopecia not requiring systemic treatment, conditions not expected to recur in the absence of an external trigger.
13. Patients with a history of organ transplantation (e.g., stem cell or solid organ transplant)
14. Patients with a known or suspected hypersensitivity to any of the excipients of formulated study drug
15. Patients with a history of significant toxicities associated with previous administration of immune checkpoint inhibitors that necessitated permanent discontinuation of that therapy
16. Patients with unresolved > Grade 1 toxicity associated with any prior antineoplastic therapy except for persistent Grade 2 alopecia, peripheral neuropathy, decreased hemoglobin, lymphopenia, hypomagnesemia, and/or end-organ failure being adequately managed by hormone replacement therapy
17. Patients with inadequate recovery from any prior surgical procedure, or patients having undergone any major surgical procedure within 4 weeks prior to first administration of study drug
18. Patients who are known or suspected drug or alcohol abusers where compliance with protocol requirements may be a concern
19. Patients with a known history of human immunodeficiency virus (HIV) or known active infection with hepatitis B virus (HBV) or hepatitis C virus (HCV)
20. Patients with any other serious/active/uncontrolled infection, any infection requiring parenteral antibiotics, or unexplained fever > 38ºC within 2 weeks prior to first administration of study drug
21. Patients with any other serious, life-threatening, or unstable pre-existing medical condition (aside from the underlying malignancy) including significant organ system dysfunction or failure, or CS laboratory abnormality(ies), which, in the opinion of the Investigator, would either compromise the patient's safety or interfere with obtaining informed consent, compliance with study procedures, or evaluation of the safety of study drug
22. Patients with a psychiatric disorder or altered mental status that would preclude understanding of the informed consent process and/or completion of the necessary study-related evaluations
23. Patients with known or foreseeable inability, in the opinion of the investigator, to comply with the protocol requirements

Drugs and Other Treatments to be Excluded *(patients must not have received any of the following)*

1. Other inhibitors of TIM-3 (e.g., mAbs)
2. Any antineoplastic agent for the primary malignancy (standard or investigational) without delayed toxicity within 4 weeks or 5 plasma half-lives, whichever is shortest, prior to first administration of study drug and during study, except for:
   - Nitrosoureas and mitomycin C within 6 weeks prior to first administration of study drug and during study

   Note: Patients may have received and failed prior therapy with a PD-1/PD-L1 and be considered eligible for this trial.

	3. Any other investigational treatments within 4 weeks prior to and during study. This includes participation in any medical device or other therapeutic intervention clinical trials. 4. Radiotherapy: • For target lesions within 4 weeks prior to first administration of study drug unless PD has been documented in the lesion following treatment, and during study. • For non-target lesions within 1 week prior to first administration of study drug, Note: Palliative (limited-field) radiotherapy for management of pain associated with bone metastases present at baseline is permitted during study. Patients with suspected new bone lesions requiring pain management should be treated and evaluated for potential PD 5. Use of live vaccines against infectious diseases (e.g., varicella) 4 weeks prior to first administration of study drug and during study 6. Immunosuppressive or systemic hormonal therapy (> 10 mg daily prednisone equivalent) within 2 weeks prior to first administration of study drug and during study. *The following therapies are allowed:* • Hormonal therapy for appetite stimulation • Nasal, ophthalmic, inhaled, and topical glucocorticoid preparations • Hormone replacement therapy at standard doses for end-organ failure • Stable hormonal therapy for prostate carcinoma • Stable hormonal therapy for ovarian suppression, hormonal contraceptive therapy, or post-menopausal hormone replacement therapy (HRT) • Neuroendocrine tumor patients: stable hormonal therapy with a somatostatin analog (SSA) • Steroid therapy for contrast reaction prophylaxis • Intra-articular steroid injections • Low-dose maintenance steroid therapy for other conditions (e.g., asthma exacerbation, stable steroid therapy [excluding tapering dose of steroids] for brain edema/metastases/radiation) • Higher dose steroid therapy for treatment of an acute intercurrent illness (e.g., immune-related AEs or other adverse conditions) in patients with SD or an ongoing response. In such situations, study drug treatment should be interrupted for the duration of immunosuppressive therapy. 7. Prophylactic use of hematopoietic growth factors within 1 week prior to first administration of study drug and during Cycle 1 of study; thereafter-prophylactic use of growth factors is allowed as clinically indicated. Use of growth factors as treatment is permitted at any time after initiation of study drug as clinically indicated. Transfusions are permitted as needed. *Questions regarding patient eligibility must be addressed and resolved by the Investigator in consultation with the Sponsor prior to enrollment.*
EXPERIMENTAL PLAN	
Design Elements	• Open-label, uncontrolled, non-randomized • Escalating doses of study drug in sequential patient cohorts • Enrollment staggered between first and second patient in each new higher 3-patient dose cohort to allow for initial safety observations
Study Schedule	**Screening Period** • Written informed consent • Safety screening, disease assessment, and eligibility confirmation **Treatment Period** • C1/D1 initial dose of study drug • Continued dosing Q2W • 28-day cycles until confirmed PD, unacceptable toxicity, or another discontinuation criterion is met • End of Treatment (EOT) visit within approximately 10 days following treatment discontinuation, or before initiation of a new treatment, whichever occurs first. • 1-Month Follow-up (1M FUP) visit 30 days (+7 days) following last dose **Follow-Up Period** • Response follow-up (FUP) every 2 months (Q2M) following discontinuation for reasons other than confirmed PD until the end of trial
Observation Requirements	Patients will be treated and followed on an outpatient basis. • Patients will be observed for a minimum of 2 hours following completion of the first

	administration of study drug on C1/D1 and a minimum of 1 hour following completion of subsequent infusions of study drug (C1/D15, onward). • At the end of each infusion the IV line must remain in place during the observation period to allow for administration of IV drugs, if necessary. Infusions will take place under the close supervision of a physician or other study personnel experienced in administration of IV agents, and in an environment where full resuscitation facilities are immediately available.
INVESTIGATIONAL MEDICINAL PRODUCT ADMINISTRATION	
Doses to be Administered	**Doses to be Evaluated** Dose cohorts will be numbered and entered sequentially. The number of cohorts evaluated will be based upon toxicities experienced by patients during Cycle 1. Sym023 will be administered at up to 7 planned dose levels; anticipated dose levels include: • Dose Cohort 1: 0.03 mg/kg • Dose Cohort 2: 0.1 mg/kg • Dose Cohort 3: 0.3 mg/kg • Dose Cohort 4: 1.0 mg/kg • Dose Cohort 5: 3.0 mg/kg • Dose Cohort 6: 10.0 mg/kg • Dose Cohort 7: 20.0 mg/kg **Changes in Dose to be Administered** Once assigned to a dose cohort, patients will continue to be treated with study drug at that same dose level throughout the duration of their time on study. There will be no intra-patient dose-escalation. *Dose adjustments should be made in the event of noted weight change (± 10%; less at the site's discretion or if required by institution procedures) at visits that require weight measurement. Adjustments may be made more frequently at the site's discretion.*
Route of Administration	IV infusions via indwelling venous access catheter, utilizing a controlled infusion device
Infusion Materials	Infusion set containing a 0.22 micron in-line filter.
Diluent and Delivery	Commercially available sterile 0.9% sodium chloride (NaCl) for IV infusion Once diluted for IV administration, study drug should be administered within 8 hours.
Infusion Volume	• 50 mL for doses < 1 mg/kg • 100 mL for doses ≥ 1 mg/kg to ≤ 3 mg/kg • 100 mL for doses of > 3 mg/kg to ≤ 10 mg/kg for patients with body weight ≤ 80 kg • 250 mL for doses of > 3 mg/kg to ≤ 10 mg/kg for patients with body weight > 80 kg • 250 mL for doses > 10 mg/kg for patients with body weight ≤ 100 kg • 500 mL for doses > 10 mg/kg for patients with body weight > 100 kg
Infusion Duration	• Approximately 30 minutes (+10 minutes) for infusion volumes ≤ 250 mL • Approximately 60 minutes (+10 minutes) for infusion volumes of 500 mL Start and stop times of each infusion, and any interruptions in infusion will be recorded.
Schedule	Q2W (± 2 days) on Day 1 and Day 15 of each cycle (4 weeks [28 days] equals 1 dosing cycle) End of Cycle 1 (EOC1) assessments are to be performed on C1/D28 (±2 days). Subsequent cycles may be administered Q2W (± 2 days), unless further delay is required to allow for amelioration of toxicities (or in the event of scheduling difficulties associated with weekends, holidays, etc.).
Premedication	**Premedication for Infusion-Related Reactions** Since the mechanism of action of the study drug is to stimulate the immune system premedication with agents such as glucocorticoids which are immunosuppressive is to be avoided. As a result, no premedication is required to be administered prior to patients receiving the first dose of study drug. In patients with a history of infusion-related reactions (IRRs) to mAbs or similar products, it is recommended that premedication be administered. In such cases, patients should be premedicated with a regimen that includes acetaminophen as well as an H1 (e.g., diphenhydramine/hydroxyzine) and possibly an H2-antagonist (e.g., ranitidine/famotidine). In the event of an IRR during study: • For Grade 1 or Grade 2 reactions, premedication prior to subsequent infusions should be considered. Thereafter, if a patient is without recurrence of an IRR, the Investigator may

	choose to withdraw premedication to determine whether such continued therapy is necessary for that patient. • For Grade 3 reactions, not applicable as this is considered a DLT; therefore, no further treatment with study drug is allowed. **Premedication for Other Toxicities** In the event of other study-drug related toxicities (e.g., nausea, vomiting, diarrhea, etc.), patients may be premedicated with standard therapies to reduce the potential for such reactions in the future. Based on ongoing review of patient safety data, the Sponsor may implement mandatory premedication for all patients should a pattern begin to emerge of mild-to-moderate study drug-related reactions that are amenable to prophylaxis with standard agents.
DOSE-ESCALATION DECISION POINTS	
Dose-Escalation	**Cycle 1** A minimum of 1 cycle of study drug will be administered, if tolerated. Determinations regarding dose-escalation and MTD will be based on tolerability during these initial 4 weeks (Cycle 1) of treatment, and the occurrence of DLTs thought to be related (i.e., possibly-related, probably-related, or related) to study drug. • Patients completing Cycle 1, and receiving their full planned doses of study drug in the absence of a DLT, will be considered to have tolerated the dose level they were assigned to receive. • Patients will be replaced if they have received < 2 full doses of study drug plus follow-up through EOC1 (C1/D28 ± 2 days) for any reason other than a DLT to ensure MTD determination rules can be followed with an adequate number of evaluable patients in any dose cohort. **Dose Escalation and Cohort Expansion Decision Rules** Initially a modified, accelerated-titration, dose-escalation design will be used with entry of single patient cohorts for up to 2 dose levels, based on tolerability. Thereafter, a standard 3+3 dose-escalation design will be used, with a target toxicity level of 33.3% or less as determined by DLTs. The decision rules for dose-escalation are as follows: 1. A minimum of 1 patient will be entered into dose Cohort 1 and 2 ONLY • If during the initial 2 weeks of Cycle 1 no ≥ Grade 2 toxicity considered possibly-, probably-, or related to study drug is encountered in the patient, dose-escalation may continue to the next level when the patient has been followed for safety until C1/D15 • If at any time during Cycle 1, a patient experiences a ≥ Grade 2 toxicity considered possibly-, probably-, or related to study drug, the cohort will be expanded to 3 patients • If during Cycle 1 a patient experiences a DLT considered possibly-, probably-, or related to study drug, the cohort will be expanded to 6 patients 2. Beginning with Cohort 3, or earlier if required by observed toxicity, a minimum of 3 patients will be entered to each cohort. • If during Cycle 1 no DLTs are encountered in any of the first 3 patients, dose-escalation may continue to the next level when all patients have completed Cycle 1 • If during Cycle 1, any 1 patient experiences a DLT considered possibly-, probably-, or related to study drug, the cohort will be expanded to 6 patients. If no DLTs are encountered in the additional 3 patients, dose-escalation may continue to the next level when all patients have completed and tolerated Cycle 1. • If during Cycle 1, > 1 patient experiences a DLT, dose-escalation will STOP. *This will indicate that the MTD has been exceeded.* 3. If it is determined that a dose level is not tolerated: • The previous lower dose cohort will be expanded to 6 patients (if this has not already been accomplished) as a total of 6 patients must be treated before establishing a dose as the MTD. • There is also the potential to evaluate and expand a previously unplanned intermediate dose level between 2 established dose levels to 6 patients to more fully characterize tolerability. 4. The MTD will be the highest dose level of study drug at which no more than 1 of 6 evaluable patients has had a DLT. 5. Once the MTD (or maximum dose to be studied) is achieved and/or the RP2D is identified, that cohort may be expanded up to 12 patients to more fully evaluate safety and tolerability at that dose level, at the Sponsor's discretion. Should the DLT rate equal or exceed 33.3% in an expanded cohort, it will be determined that the dose is not tolerated. If this occurs, the

	previous lower dose cohort or an intermediate dose level may be expanded as above. Therefore: • There is potential for expansion of lower dose cohort(s) if an initially identified MTD and/or RP2D is subsequently determined to be not tolerated (either with single or repeat cycles of therapy), and • There is potential to evaluate and expand a previously unplanned intermediate dose level(s) between 2 established dose levels to more fully characterize tolerability The RP2D may be equal to or lower than the MTD or the MAD. The RP2D will be selected based on safety data, as well as available PK, pharmacodynamic/biomarker results, and other data, as applicable. **Duration of Exposure Prior to Start of Next Patient and Start of Next Cohort** Single patient cohorts: Dose-escalation and accrual to the next cohort will occur only after the patient has completed and tolerated the first dose of Cycle 1, including follow-up until C1/D15 to allow for review of clinical and laboratory assessments, and consultation with the Study Safety Team. **The DLT evaluation period for single patient cohorts will continue through to the EOC1.** The following rules apply to single patient cohorts: • Should a patient experience an AE of concern in the latter half of Cycle 1 that would, per protocol, result in cohort expansion, protocol rules as outlined herein will be followed. • Additional patients entered to an expanded single patient cohort will follow rules as outlined below for 3+3 patient cohorts. • If a patient has been entered to receive the next higher dose level, that patient will be allowed to continue provided adequate tolerability is being demonstrated; however, further enrollment to the higher dose level cohort will be halted. 3+3 patient cohorts: Enrollment will be staggered by 2 weeks between the first and second patient in each new higher 3+3 dose level cohort tested. The first patient within a cohort must complete and tolerate the first dose of Cycle 1, including follow-up until C1/D15 to allow for review of clinical and laboratory assessments. Thereafter patients within a cohort may be added concurrently. All cohorts: Dose-escalation and accrual to the next cohort will occur only after the minimum number of patients required for tolerability assessment in the current cohort have completed until C1/D15 in a single patient cohort, or completed Cycle 1 in a 3+3 patient cohort,, and only after acceptable tolerance has been demonstrated in at least 1 of 1, 3 of 3 or 5 of 6 patients treated in the current cohort (depending on cohort size), and after consultation with the Study Safety Team. For all patients, EOC1 assessments are to be performed on C1/D28 (± 2 days). **Establishment of the MTD and/or RP2D** The MTD will be the highest dose level of study drug at which no more than 1 of 6 evaluable patients has had a DLT. The MAD, MTD, or a dose lower than the MAD or MTD, will be identified as the RP2D, provided a minimum of 6 evaluable patients have been treated at that dose, and provided acceptable tolerance has been demonstrated in at least 5 of 6 patients treated. The RP2D will be based on the MTD evaluation as well as other toxicities observed in the study, including observations in later cycles of administration of study drug, as well as on PK, pharmacodynamic/biomarkers, and/or other data. **Rules for Stopping the Study** The study will be stopped if the MTD is exceeded at the lowest dose level.
CONTINUED TREATMENT	
Continued Treatment after Cycle 1	Upon completion of Cycle 1, in the absence of unacceptable toxicity or documented disease progression, patients may continue to receive additional cycles of study drug unless further delay is required to allow for amelioration of ongoing AEs. Administration will be at the same dose level and infusion duration established for the patient, and on the same Q2W schedule provided retreatment guidelines are met. If a delay is required, additional cycles should be initiated within approximately 2 weeks of the completion of the previous cycle, if feasible. **Retreatment Guidelines:** To start any new cycle, a patient must meet the following criteria: • ANC ≥ 1,000 per mm^3

	• Platelets ≥ 75,000 per mm^3 • Ongoing study drug-related AEs should NOT meet the criteria for DLT • Ongoing study drug-related AEs should have either ameliorated to ≤ Grade 1 severity, returned to baseline status, or resolved, with the exceptions of: o Grade 2 alopecia, o Grade 2 clinical events that are being adequately controlled with best supportive care (e.g., fatigue, nausea, vomiting, diarrhea), and o Grade 2 asymptomatic laboratory abnormalities that are considered clinically insignificant and clinically uncomplicated, and/or that are resolving spontaneously or with conventional medical interventions • Dosing must be delayed in patients with evidence of Grade 2 immune-mediated toxicities, including: o Pneumonitis, myocarditis, adrenal insufficiency, encephalitis, nephritis/renal dysfunction (serum creatinine elevation), episcleritis/uveitis/iritis o Colitis, hypophysitis, hyperglycemia, inflammatory arthritis, myositis, rash o Hepatitis (transaminitis, total bilirubin elevation) Retreatment cycles may continue up to 12 months at which time plans for continued therapy will be discussed by the Medical Monitor(s) and Investigator. Patients who stop therapy with an ongoing OR or prolonged SD may be retreated in the event of relapse, if the trial is still open.
Continued Treatment after Radiologic Disease Progression	Immunotherapeutic agents may produce antitumor effects that can manifest as response after initial evidence of PD, a phenomenon referred to as "pseudoprogression" (PSPD). Patients will be permitted to continue treatment beyond initial RECIST v1.1 (or RECIL 2017) defined PD while waiting for confirmation of PD, provided they are clinically stable as defined by the following criteria (per iRECIST): • Investigator-assessed clinical benefit and absence of rapid disease progression • Tolerating study drug • Stable PS • Absence of progressive tumor at critical anatomical sites (e.g., cord compression) requiring urgent alternative medical intervention.
Retreatment Following an Objective Response	Treatment with study drug may be restarted in a patient who previously achieved a documented OR or prolonged SD (> 16 weeks) in this study, stopped treatment, and subsequently progresses. Such action may be taken at the Investigator's discretion, following discussion with the Medical Monitor(s), provided retreatment criteria are met, no anti-cancer treatment was administered since the last dose of study drug, and the trial is still open. This option for retreatment does not apply to patients who previously experienced a DLT that required permanent discontinuation from study drug *(see DLT and Treatment Discontinuation Criteria*).
ADVERSE EVENTS AND DOSE-LIMITING TOXICITIES	
Adverse Event Grading	For reported adverse events (AEs), the Common Terminology Criteria for Adverse Events (Version 5.0) (CTCAE v5.0), will be used to grade the severity of the AE.
Management of Dose-Limiting Toxicities and Other Toxicities	**Management of Dose-Limiting Toxicities** AEs that meet the protocol definition of DLT will require discontinuation from study treatment, without exception. **Management of Other Toxicities** AEs that do not meet the protocol definition of DLT, but nevertheless warrant dose modification may be managed by delay of study drug to allow for amelioration of the toxicity.

Dose-Limiting Toxicities Definition	Any of the following toxicities occurring during Cycle 1, if judged to be related to study drug (i.e., possibly-related, probably-related, or related), will be considered a DLT for the purposes of tolerability assessment during this trial. 1. ≥ Grade 3 evidence of any of the following immune-mediated toxicities: • Pneumonitis • Myocarditis • Adrenal insufficiency • Encephalitis • Nephritis, renal dysfunction (serum creatinine elevation) • Episcleritis, uveitis, or iritis 2. ≥ Grade 3 evidence of any of the following immune-mediated toxicities: • Colitis • Hypophysitis, hyperglycemia • Inflammatory arthritis • Myositis • Rash 3. ≥ Grade 2: • Uveitis, eye pain or blurred vision that does not resolve with topical therapy within 2 weeks • AEs that are prolonged excessively based upon the medical judgment of the investigator, and/or lead to permanent discontinuation of the investigational agent due to poor tolerance • Immune-mediated toxicity that requires use of glucocorticoids at a dose of ≥ 1 mg/kg/day of prednisone equivalents for treatment of the toxicity 4. Any confirmed reduction in visual acuity, regardless of grade or duration 5. Hepatic-related findings consistent with Hy's Law criteria: • AST and/or ALT elevation > 3 × ULN (or > 3 × baseline if elevated at study entry due to hepatic involvement by tumor), with • total bilirubin ≥ 2 × ULN without initial findings of cholestasis (i.e., serum alkaline phosphatase [ALP] < 2 × ULN), and • No explanation for the above findings such as viral hepatic injury, preexisting or acute liver disease, or another drug or condition capable of causing the observed liver injury 6. Any other ≥ Grade 3 or 4 non-hematologic toxicity regardless of duration with the exceptions of: • Grade 3 fatigue • Grade 3 nausea, vomiting, or diarrhea lasting ≤ 2 days with best supportive care • Grade 3 asymptomatic electrolyte abnormalities lasting ≤ 3 days that are not clinically complicated, and resolve spontaneously or respond to conventional medical interventions • Other Grade 3 asymptomatic laboratory abnormalities that are clinically non-significant in the investigator's opinion, and that resolve spontaneously or with conventional medical interventions 7. Any Grade 4 non-hematologic laboratory toxicity regardless of duration 8. Neutropenia that is: • Grade 3 meeting the CTCAE v5.0 criteria for febrile neutropenia (ANC < 1000 per mm^3 and a single temperature > 38.3º C [101º F] or sustained temperature ≥ 38º C [100.4º F] for > 1h) • Grade 4 9. Thrombocytopenia that is: • Grade 3 with CS hemorrhage or requirement for transfusion • Grade 4 (platelets < 25,000 per mm^3) 10. Anemia that is Grade 4 and not explained by underlying disease 11. Any other Grade 4 hematologic toxicity (other than those specifically excluded) lasting > 5 days 12. Any death where a relationship to study drug cannot be ruled out 13. Inability to complete Cycle 1 at the assigned dose (i.e., receipt of < 2 full planned doses of study drug plus 2 weeks of follow-up) due to any toxicity 14. Treatment delays > 2 weeks from the scheduled next dose during Cycle 1 due to any toxicity *Other toxicities may be considered a DLT as determined by the Investigator in conjunction with*

	the Study Safety Team. The above criteria will be used to make individual patient determinations regarding dose delays or discontinuation throughout the course of the trial, however, ***only those DLTs occurring during Cycle 1 will be used to make decisions regarding cohort dose-escalation and tolerability.*** Events occurring after Cycle 1 will also be evaluated by the Study Safety Team and taken into consideration when deciding upon further dose levels to be assessed as well as establishment of the RP2D.
TOXICITY SAFETY MANAGEMENT AND SAFETY MONITORING	
Infusion-Related Reaction Management	In addition to premedication as management for IRRs, the following infusion prolongation instructions are provided: • For Grade 1 reactions, the infusion may be slowed to 50% of the prior rate such that the remaining dose to be delivered is administered in 2× the amount of time as was initially scheduled. • For Grade 2 reactions, the infusion should be interrupted for a minimum of 30 minutes, and at least until there is either amelioration to ≤ Grade 1 severity or return to baseline status. Supportive care should be provided. The infusion should then be restarted and slowed to 50% of the prior rate, as described. Subsequent infusions should be administered at the prolonged rate. • For Grade 3 reactions, the infusion will be STOPPED and supportive care will be provided. The occurrence will be considered a DLT and the patient will be discontinued from treatment. • For Grade 4 reactions, the infusion will be STOPPED and supportive care will be provided. The occurrence will be considered a DLT and the patient will be discontinued from treatment. In all cases the Investigator should use best clinical judgment in managing such reactions. For Grade 1 and Grade 2 IRRs, rechallenge with a shorter duration of infusion (no less than the duration designated by the patient's dose assignment and weight) may be attempted at the Investigator's discretion, after a minimum of 2 doses with no evidence of infusion-related toxicity at the prolonged rate.
Dose Delays	Toxicities may be managed by delay in dosing, provided they do not meet the criteria for study discontinuation. For toxicities that are to be managed by dose delay, dosing may be restarted at the same dose, once study retreatment criteria have been met.
Safety Monitoring	Clinical and laboratory safety data will be reviewed on an ongoing basis throughout the study by the Investigators and Sponsor's Medical Representative(s) so that decisions regarding the advisability of continuing accrual to a dose cohort, and/or escalating the dose and allowing accrual to a higher dose cohort may be made. In addition, patients will be carefully evaluated for evidence of potential cumulative and/or delayed toxicities throughout the duration of their time on study. To do so, Serious Adverse Events (SAEs), immune-related AEs of significance, AEs resulting in permanent discontinuation from study (regardless of seriousness or relationship to study drug), DLTs, IRRs, and dose delays will be promptly reported to the Sponsor (or designee). A Study Safety Team will be established and will be comprised of the Investigators(s) and the Sponsor's Medical Representative(s). Biweekly Study Safety Team teleconferences will be held to discuss ongoing patient status and any emerging safety concerns; the frequency of teleconferences may fluctuate based on accrual and study activity, as indicated.
STUDY ASSESSMENTS	
Screening *(within 14 days prior to 1st dose unless otherwise stipulated)*	• Informed consent • Eligibility assessment • Demography • Past medical history • History of the primary malignancy (including data on the extent, duration, and best response to prior therapy, if available)

Safety Assessments	Patients to be monitored throughout the treatment and follow-up period for occurrence of AEs (acute, delayed, and/or cumulative), as well as for changes in clinical status, vital signs (VS), and laboratory data. **Safety Assessments (1)** *(within 14 days prior to 1st dose unless otherwise stipulated)* • Concomitant Medication/Procedure surveys • AE reporting *(collection of data from signing of informed consent to 30 days after final dose, with long-term follow-up to surveil for [up to 6 months]and follow [up to 2 years] immune-mediated toxicities)* • DLT assessment (Cycle 1) • PS evaluation (ECOG) • VS assessment (including temperature, pulse, respiratory rate, blood pressure [BP], and oxygen saturation by pulse oximetry at rest and exertion) • Physical examination (with weight, and pulmonary/cardiac assessment at each visit) • Hematology panel • Biochemistry panel (to include creatine kinase [CK] for cardiac assessment) • Coagulation panel • Thyroid function studies (to include measurement of thyroid stimulating hormone [TSH], free triiodothyronine [fT3] and free thyroxine [fT4]) • Urinalysis (by multi-panel chemical test strip analysis; include microscopic examination of sediment if clinically indicated) • Pregnancy testing (if applicable) *(serum test within 14 days, urine test repeated within 2 working days prior to 1st dose)* • Electrocardiogram (ECG), 12-lead **Safety Assessments (2)** *(results from assessments previously performed as standard of care within 28 days [+2 days] prior to 1st dose may be utilized, provided no antineoplastic therapy has been delivered between assessment and 1st dose; otherwise within 14 days prior to 1st dose)* • Ophthalmology examination • MUGA scan or ECHO *(To be performed ONLY in patients with a history of CHF)* • Pulmonary function tests (PFTs) (to include spirometry and assessment of diffusing capacity of carbon monoxide [DL_{CO}])
Disease Assessments	**Disease Status** *(within 28 days [+2 days] prior to 1st dose)* • Tumor marker measurement *(as indicated by tumor type)* • Diagnostic imaging for assessment of disease (computed tomography [CT]/magnetic resonance imaging [MRI]) *(The same method and technique should be used throughout the study.)* For safety, imaging of the chest required at each evaluation to assess pulmonary status • Response assessment (per RECIST v1.1, RECIL 2017, and iRECIST). Data on evidence of and duration of any OR (CR or PR) or SD, as well as disease progression to be collected.
Other Assessments (Specialty Lab)	**Immunogenicity** Serum sampling to assess the potential for anti-drug antibody (ADA) formation **Pharmacokinetics** Serum sampling to assess the PK profile of the study drug **Pharmacodynamic and other Biomarker Studies** Peripheral blood sampling (pre- and post-dosing) • Pharmacodynamic evaluation (e.g., receptor occupancy) • Evaluation of DNA, RNA, proteins/cytokines, and cellular biomarkers Tumor tissue sampling (pre- and post-dosing) *(biopsies optional)* • Evaluation of DNA, RNA, protein, and cellular biomarkers
DISCONTINUATION AND FOLLOW-UP	
Key Treatment Discontinuation Criteria	Patients are to be discontinued from treatment in the event of any of the following: 1. Adverse Events, including: • Any AE or SAE that meets the study DLT criteria at any time during the study • Another AE or SAE considered by the Investigator to require treatment discontinuation 2. Progressive Disease: Confirmed radiologically 3. Clinical Progression: Treatment failure not meeting the criteria for PD, but considered by the Investigator to require treatment discontinuation 4. Physician Decision, including: • Use of or requirement for a non-permitted concomitant medication

	• Requirement for a significant surgical procedure • Intercurrent illness that would prevent completion of study-related evaluations • Any other reason in the opinion of the Investigator that would justify treatment discontinuation 5. Withdrawal by Patient: Withdrawal of consent and election to discontinue treatment
Replacements	Should a patient discontinue treatment with study drug for reasons other than the occurrence of a DLT prior to completing Cycle 1, a replacement patient will be obtained using the original eligibility criteria.
Follow-up	All follow-up visits and assessments, as described, should be conducted to the extent possible. • End of Treatment (EOT) evaluations to be conducted within approximately 10 days following treatment discontinuation, or before initiation of a new treatment, whichever occurs first • 1-Month Follow-up (1M FUP) evaluations to be conducted approximately 30 days (+7 days) following the last dose of study drug. • Long-Term FUP for Safety: If an observed toxicity (non-immune-mediated) thought to be related to study drug has not resolved by the 1M FUP evaluation, an additional FUP AE assessment will be conducted approximately 2 months (may be repeated at 4 months if needed) following the last dose of study drug, if feasible, to confirm that the event has either resolved, returned to baseline status, or been adequately explained and assessed by the Investigator as chronic and/or stable, and that no long-term deleterious effects have become evident Since late-occurring immune-mediated toxicities have been reported to occur several weeks to months after treatment with other immune checkpoint inhibitors, long-term surveillance for such toxicities will be conducted in this study. Patients will be followed at approximately 2-month intervals following the last dose of study drug for up to 6 months to assess for the onset of any post-therapy immune-mediated event thought to be related to study drug. Any patient who develops an immune-mediated toxicity during study, or during the 6-month post-therapy FUP period, will be followed at approximately 2-month intervals following the last dose of study drug for up to 2 years to assess the course of the condition and evaluate potential reversibility of the finding. • Long-Term FUP for Response: In the event of an ongoing OR or SD at the EOT, response assessments based on imaging studies will continue to be performed every 2 months following the last dose of study drug, until confirmed PD or another therapeutic intervention is initiated, until the end of trial, so that data may be collected on the duration of SD or OR, as well as disease progression
ANALYSIS PLAN	
Endpoints	**Primary Endpoint** DLTs to establish MTD and/or recommended RP2D **Secondary Endpoints** • Safety profile • Incidence and characterization of immunogenicity (ADA) • PK profile • Preliminary antineoplastic activity, to include occurrence/duration of OR or SD, and TTP
Pharmacokinetic Parameters	Evaluations to delineate dose-response and PK parameter-response relationships will be undertaken. Based on the concentrations determined, the following PK parameters for the study drug will be calculated for each subject: area under the concentration-time curve (AUC) from start of first infusion (SOI) to 336 hours (AUC_{τ}), from SOI to infinity (AUC_{inf}), terminal elimination half-life ($T_{1/2}$), clearance (CL), volume of distribution (V_d), maximum concentration (C_{max}), concentration at end of infusion (C_{EOI}), trough concentration (C_{trough}), and time to reach C_{max} (T_{max})
Exploratory Pharmacodynamic and Biomarker Parameters	A summary of the changes in potential pharmacodynamic and other biomarker(s) will be presented.
Statistical Methods and Sample Size Calculation	The primary endpoint of Sym023 dose-escalation is the occurrence of DLTs during Cycle 1 for each dosing regimen. The number of enrolled patients will depend on the extent of observed DLTs independently in each cohort. Based on the dose-escalation design, it is planned to enroll approximately (20-48) patients during this part of the trial.

	All DLT events will be listed by dose cohort and patient. A summary table of DLTs across dose cohorts by System Organ Class (SOC) and preferred term will be presented, if applicable. The summaries will include number of DLTs and number and percentages of patients experiencing a DLT. Safety evaluation will be based on reported AEs and safety laboratory test results, immunogenicity, and other safety data. Unless otherwise specified, all summaries will be descriptive.
Interim Analysis	Safety evaluation will be performed prior to each dose-escalation. No other interim analyses are planned.
TRIAL REPORTING	
Final Clinical Trial Report	Final integrated clinical/statistical trial report to be prepared at the end of trial

2 SCIENTIFIC BACKGROUND AND RATIONALE

2.1 Background

2.1.1 Tumor Malignancies

Cancers are malignant tumors formed by an abnormal growth of cells and tissue leading to organ failure. They fall into two categories: solid and hematological cancers. Solid tumors are formed by an abnormal growth of body tissue cells other than blood, bone marrow (BM), or lymphatic cells. A solid tumor consists of an abnormal mass of cells, which may stem from different tissue types such as lung, breast, colon, prostate, stomach, and liver, and which initially grows in the organ of its cellular origin. In advanced stages of the disease, solid tumors may spread to other organs through metastatic tumor growth.

Cancer is the second-leading cause of death and disability in the world, only surpassed by heart disease. In 2012, 14.1 million people were diagnosed with cancer worldwide. An estimated 8.2 million people died from the disease. The World Health Organization (WHO) projected that by 2035, these figures could increase to 24 million new cases and 14.6 million cancer deaths worldwide. Lung, breast, colorectal, prostate, and stomach cancer are the most common malignancies (1).

2.1.2 Overview of the Target: TIM-3

TIM-3 (T-cell immunoglobulin and mucin-domain containing-3), also known as HAVCR2 (hepatitis A virus cellular receptor 2) or CD366, is an immune checkpoint receptor expressed by a range of different immune cells, including T-cells, dendritic cells, macrophages, and natural killer (NK) cells. On naïve T-cells, TIM-3 expression is low, but becomes upregulated upon T-cell activation. In contrast to T-cells, dendritic cells, NK cells and monocytes have high basal TIM-3 expression.TIM-3 has been associated with several, mostly promiscuous, ligands, including galectin-9, phosphatidylserine (PtdS), carcinoembryonic antigen related cell adhesion molecule 1 (CEACAM1) and high mobility group box 1 (HMGB1) protein. The exact roles of these ligands are currently not well understood and most likely are context dependent (2-4).

The role of TIM-3 in regulating immune cell function is complex and appears context-dependent; both activating and inhibiting functions have been described (3, 4). TIM-3 engagement on myeloid cells, such as dendritic cells and macrophages, has been reported to increase their state of activation. TIM-3 on T-cells, on the other hand, has been described to correlate with an “exhausted” phenotype. Most of the functional data related to TIM-3 and its role in tumor immunology come from studies in mice using various antibodies (5, 6).

Antibody-mediated engagement of TIM-3 has been shown to induce increased proliferation and cytokine production by T-cells activated *in vitro*, as well as tumor growth inhibition in tumor xenograft models, especially in combination with Programmed Cell Death Protein 1 (PD-1) blockade (5, 6). In most of these studies, due to poor antibody validation, it is not clear whether the effects of the TIM-3 antibodies are mediated by inhibition of ligand binding, by antibody mediated target engagement, or both. Furthermore, due to the expression of TIM-3 in both myeloid cells and lymphocytes, the exact cellular mechanisms underlying the *in vivo* antitumor activity of anti-TIM-3 antibodies are still not understood.

Three anti-TIM-3 antibodies, MGB453 (Novartis), TSR-022 (Tesaro) and LY3321367 (Lilly) are in early clinical development for use as cancer immunotherapy in solid and hematologic malignancies. All three antibodies are to be tested alone (i.e., as monotherapy) and in combination with anti-PD-1 antibodies. Additional TIM-3 antibodies and small-molecule inhibitors are in pre-clinical development. TSR-022, a humanized IgG4 monoclonal anti-TIM-3 antibody that enhances T-cell activation, is the only antibody drug candidate for which any clinical results have been published to date (7). The results indicate that TSR-022 monotherapy is well tolerated across multiple dose levels and that adverse events (AEs) are manageable and consistent with the safety profiles of other checkpoint inhibitors. Clinical activity in the form of disease stabilization and one case of partial response has been observed in patients with various cancer types, including rectal, thyroid, neuroendocrine, head and neck cancer, and soft-tissue sarcoma (7, 8). TSR-022 is currently being evaluated in the clinic in combination with an anti-PD-1 antibody.

2.1.3 Overview of the Product: Sym023

The investigational medicinal product (IMP) tested in this trial is Sym023. Sym023 is a recombinant, fully human, IgG2 antibody that binds human TIM-3 with nanomolar affinity and cynomolgus TIM-3 with 100-fold reduced affinity. Sym023 does not cross-react with mouse or rat TIM-3. Sym023 blocks PtdS binding to TIM-3 and induces cytokine secretion and activation of immune cells *in vitro*.

2.2 Summary of Nonclinical Studies

2.2.1 Nonclinical Pharmacology Studies

The pharmacologic characterization of Sym023 includes *in vitro* functional evaluation in various relevant cell-based assays and *in vivo* testing in mouse models of human cancer. Sym023 stimulates T-cell and dendritic cell activation and cytokine production *in vitro*.

Sym023 enhances cytokine production and T-cell proliferation in one-way and two-way mixed lymphocyte reaction (MLR) assays and shows comparable activity in the 2-way MLR assay with human and cynomolgus cells. Sym023 has a direct effect on dendritic cells leading to increased expression of activation markers and secretion of cytokines. The functional activity of Sym023 is dependent on interaction with Fcγ receptors; however, Sym023 does not induce secondary effector functions, such as antibody-dependent cellular cytotoxicity (ADCC) and complement-dependent cytotoxicity (CDC) *in vitro*.

The ability of Sym023 to stimulate immune cells *in vitro* translates into tumor growth suppression *in vivo*. Sym023 induced activation of immune cells and reduced tumor growth in humanized mouse models engrafted with human cell-line derived or patient-derived tumor xenografts. In a human xenograft tumor model in mice reconstituted with human peripheral blood mononuclear cells (PBMCs), the combination of Sym023 and an anti-PD-1 antibody enhanced the tumor growth inhibition compared to the limited effect of single antibody treatment. These *in vivo* studies demonstrate that administration of Sym023 induces a tumor-specific immune response.

2.2.2 Nonclinical Toxicology Studies

The relevance of the cynomolgus monkey as the only species for prediction of potential human toxicity of Sym023 was demonstrated by amino acid sequence homology, target binding affinity and avidity, and functional activity.

The non-clinical development program in the cynomolgus monkey consisted of two non-Good Laboratory Practice (GLP) studies as well as a GLP-compliant 4-week study. No adverse findings were observed in the 4-week dose-range-finding (DRF) study in cynomolgus monkeys, where Sym023 was administered at 10 and 40 mg/kg/week by four weekly intravenous (IV) injections. In the non-GLP pharmacokinetic (PK) study, single IV infusions of Sym023 at 1 or 10 mg/kg were well tolerated by cynomolgus monkeys. No test article related effects on in-life parameters were noted.

In a subsequent pivotal 4-week GLP-compliant toxicology study, Sym023 was administered once weekly IV at 0 (control), 10, or 100 mg/kg to the cynomolgus monkey for 4 weeks (a total of five doses). An assessment of delayed onset toxicity and/or reversibility of toxicity was made during a 12-week recovery period for the animals administered 10 mg/kg. The purpose of this study was to support a safe starting dose in first-in-human studies. Standard toxicology evaluations as well as specific immunotoxicology endpoints were included in this pivotal study.

There were no decedents during the study. Weekly IV infusion of 10 or 100 mg/kg/week Sym023 was generally well tolerated, with no adverse findings noted.

All animals were anti-drug antibody (ADA)-negative on Day 1 and Day 29, and the animals were adequately exposed to Sym023 throughout the study.

No immunotoxicity was observed in this study. The results indicated that repeated IV administration of Sym023 did not result in any adverse test article-related changes to immune function as determined by cytokine levels in blood, *ex vivo* stimulation with staphylococcal enterotoxin B (SEB), immunophenotyping of blood and spleen, T-cell dependent antibody response (TDAR) to keyhole limpet hemocyanin (KLH), or *ex vivo* recall stimulation with KLH.

No test article-related effects on body weight, food consumption, clinical observations, dosing observations, dose site observations, ophthalmic observations, blood pressures, functional observation battery, electrocardiogram (ECG), respiration, or rectal temperatures were recorded during the dosing phase. Likewise, there were no changes considered related to administration of Sym023 for hematology, coagulation, clinical chemistry, thyroid stimulating hormone (TSH), urinalysis, organ weights, and macroscopic or microscopic pathology. Based on the data from this study, the no-observed-adverse-effect level (NOAEL) for Sym023 is ≥100 mg/kg/week.

In vitro safety pharmacology was addressed by assessing cytokine release, complement activation, as well as platelet counts, and white blood cell counts in human whole blood from 6 healthy donors, and by assessing mast cell degranulation in human mast cells cultured from peripheral blood CD133+ stem cells. Sym023 responses in the human whole blood assay were overall comparable to vehicle for cytokine levels (IFN-γ, IL-2, IL-6, and TNF-α), complement activation, platelet count, and white blood cell count. Sym023 did not affect the immediate degranulatory response of mast cells in the human mast cell assay. Therefore, the likelihood of acute cytokine release syndrome or mast cell degranulation associated with administration of Sym023 to humans is considered to be low.

The half-life in cynomolgus monkeys was approximately 7 days and the half-life of Sym023 in humans is anticipated to be approximately 12 days. The planned dosing, every 2 weeks, is predicted to ensure sustained exposure to Sym023 during repeated dosing with little or no accumulation. No PK or pharmacodynamic properties have been identified which precludes administering Sym023 to humans.

2.3 Clinical Experience

2.3.1 Clinical Experience with Agents Related to Sym023

2.3.1.1 Clinical Evidence of Activity in Malignant Diseases

As noted, anti-PD-1 and anti-programmed death-ligand 1 (PD-L1) monoclonal antibodies (mAbs) have been approved (accelerated and full approvals) for the treatment of various human cancers. These include: (a) solid tumors (non-small cell lung carcinoma, renal cell carcinoma, malignant melanoma, squamous cell carcinoma of the head and neck, urothelial carcinoma, Merkel cell carcinoma; (b) hematological malignancies (classical Hodgkin Lymphoma); as well as (c) a number of tumors in adults or children characterized by high microsatellite instability without other available therapies (9-13). Additional agents targeting PD-1 are in development.

These agents continue to be studied alone and in combination with other modalities including other agents with immune system targets. For example, the combination of anti-PD-1 mAbs and an antibody targeting Cytotoxic T-Lymphocyte-Associated Protein 4 (CTLA-4) (ipilimumab) has been approved in patients with melanoma. These agents are also being studied with standard therapeutics such as chemotherapy, radiotherapy, and various targeted agents, all in efforts to both improve the initial efficacy of immune checkpoint blockers and/or to circumvent the refractoriness that emerges during or after treatment with these agents.

Anti-PD-L1 mAbs have also been approved and are being developed alone and in combination with other agents.

2.3.1.2 Safety and Tolerability of anti-TIM-3 mAbs

Data are available from a single Phase 1 study of TSR-022, a human monoclonal IgG4 antibody to TIM-3. As of October 2017, 38 pts had been treated with TSR-022 monotherapy: 3 pts at 0.03 mg/kg, 3 pts at 0.1 mg/kg, 3 pts at 0.3 mg/kg, 9 pts at 1 mg/kg, 8 pts at 3 mg/kg, and 12 pts at 10 mg/kg (7). TSR-022 monotherapy was well tolerated across multiple dose levels. AEs that occurred in >15% of patients were fatigue (8 pts, 26%); abdominal pain (7 pts, 23%); nausea (6 pts, 19%); elevated alanine aminotransferase (ALT); elevated aspartate aminotransferase (AST); back pain, constipation, and vomiting was each reported in 5 pts (16%). One dose-limiting toxicity (DLT) event occurred with TSR-022 monotherapy (immune-related Grade 3 lipase elevation), which did not require treatment modification. No treatment-related serious adverse events (SAEs) were observed. These data were updated in a presentation at the SITC meeting in November 2017. There were no Grade 4 or 5 AEs reported and additional AEs included: decreased neutrophil and lymphocyte counts; chills; dyspnea; decreased appetite; pain and peripheral sensory neuropathy. TSR-022 exposure and peripheral receptor occupancy increased in a dose proportional manner from 0.3 to 10 mg/kg (7, 8).

The authors concluded that the AEs seen in patients receiving TSR-022 monotherapy were manageable and consistent with the safety profiles of other checkpoint inhibitors (7).

Although the mechanism of action is distinct, inhibitors of TIM-3 have many similarities to blockers of other immune checkpoint pathways. Preclinical data have documented that inhibition of the PD-1/PD-L1 pathway results in immune stimulation that may lead to antitumor effects, autoimmunity, effects on immune responses to viral infections, and alloimmunity following hematopoietic stem cell transplantation (HSCT). Because of these similarities, data on the potential AEs seen after treatment with antibodies to PD-1 and PD-L1 are being included in this clinical trial protocol (CTP) since there are limited available data on toxicities associated with administration of antibodies to TIM-3 alone (7).

AEs associated with immune checkpoint blockers targeting PD-1 or PD-L1 have been well described in publications of clinical trials of these agents, in prescribing information from approved products (8-12), as well as in literature reviews (14-17). Unlike AEs observed after standard cancer therapy, many of the toxicities of these agents are only observed after several weeks to months and may not be clearly dose-related. The wide variety of potential AEs as well as their variable times of onset have complicated development, although the safety profiles of these agents have become clearer over time as additional agents targeting these pathways have been evaluated.

The warnings and precautions variably associated with checkpoint inhibitors, specifically those directed to PD-1/PD-L1, have included risk of developing: immune-mediated pneumonitis, immune-mediated colitis, immune-mediated hepatitis, immune-mediated endocrinopathies, immune-mediated nephritis and renal dysfunction, immune-mediated skin adverse reactions, and immune-mediated encephalitis/meningoencephalitis, immune-mediated myasthenic syndrome, myasthenia gravis, or Guillain-Barre, immune-mediated ocular inflammatory toxicity, and immune-mediated pancreatitis. Increased infection risk, embryo-fetal toxicity, as well as increased complications associated with allogeneic HSCT have also been noted. Other immune-mediated and non-immune-mediated AEs have been reported in the archival literature and/or prescribing information for PD-1/PD-L1 pathway inhibitors and are listed in **Appendix 8** (8-12).

2.3.1.3 Patient Selection for Treatment with Sym023

Preliminary studies have been undertaken to evaluate biomarkers that allow for selection of patients who may have an increased likelihood of responding to anti-TIM-3 mAbs, but there are no definitive data available at this time.

2.3.1.4 Potential Pharmacodynamic Biomarkers

Limited information is available on potential pharmacodynamic biomarkers measuring responses to therapy with anti-TIM-3 mAbs. Assessment of antitumor effect in this study will be performed using standard response criteria as well as a modification of the Response Evaluation Criteria in Solid Tumors (Version 1.1) (RECIST v1.1) referred to as Immunotherapeutics Response Evaluation Criteria in Solid Tumors (iRECIST) (18, 19).

2.3.2 Clinical Experience with Sym023

The study described in this clinical trial protocol is ongoing. Sym023 is also being studied in a Phase 1 study in combination with Sym021 (anti-PD-1 monoclonal antibody; ClinicalTrials.gov number NCT03311412).

2.4 Trial Rationale

Data from the literature as well as nonclinical pharmacology, toxicology, PK and the *in vitro* safety study in human whole blood indicate that Sym023 can be safely evaluated in human cancer patients at an appropriate starting dose. Data on both Sym023 as well as other anti-TIM-3 mAbs have been considered in developing this clinical trial. Sym023 is being evaluated as a single agent in preparation for subsequent studies in combination with other mAbs designed to improve antitumor responses by further interactions with other immune system targets. Combinations of immune checkpoint inhibitors and other agents that either increase immune function directly or interrupt immune suppressive pathways are under active development with an aim of improving the efficacy of currently available therapies.

2.5 Dose Rationale

The starting dose and dose-escalation steps are based on a combination of the toxicity studies in cynomolgus monkeys (using the NOAEL as one criterion), *in vitro* safety pharmacology, observations in *in vitro* cell studies, and the Minimal Anticipated Biological Effect Level (MABEL) for Sym023 based on pre-clinical *in vitro* and *in vivo* pharmacology data.

Based on a combined evaluation of the data, a cautious approach was used and a starting dose of 0.03 mg/kg every 2 weeks (Q2W) equal to the MABEL was selected. The evaluation takes into account the uncertainties for predicting the effects of Sym023 in humans while recognizing the lack of toxicity in cynomolgus monkeys at exposure levels well above the predicted serum concentration for the first dose in humans. All relevant *in vitro* and *in vivo* PK and pharmacodynamic data were considered for Sym023. In the pivotal toxicity study in cynomolgus monkeys, Sym023 was dosed at 10 and 100 mg/kg/week for 4 weeks. The 100 mg/kg weekly dose for 4 weeks (5 dosing occasions) in this study was determined to be the NOAEL. The Maximum Recommended Starting Dose (MRSD) was determined to be 0.1 mg/kg Q2W after applying a standard safety factor (10) and adjusting for differences in affinity of Sym023 to human and cynomolgus TIM-3 (100).

A starting dose of 0.03 mg/kg Q2W using the MABEL approach was selected based on evaluation of all available data for predicting the Sym023 effects in humans:

- The potentially unique mechanism of action of Sym023 compared to other anti-TIM-3 antibodies in early clinical development, yet the absence of safety signals and lack of cytokine release detected in the in vitro safety pharmacology studies using human whole blood.
- The lack of toxicity in cynomolgus monkeys at exposure levels well above the predicted serum concentration for the first dose in humans, even when corrected for differences in affinity for Sym023 against human TIM-3 (KD 3.3 µg/mL) and cynomolgus TIM-3 (dissociation constant [KD] 330 µg/mL).
- The NOAEL of 100 mg/kg in the toxicity studies and a resulting affinity-corrected MRSD of 0.1 mg/kg Q2W, which is 3-fold higher than the proposed starting dose using the MABEL.
- The MABEL of 0.03 mg/kg Q2W represents an average Sym023 serum concentration, which could elicit 20% of the maximal response in the in vitro 1-way MLR

pharmacology assay using dendritic cells and T-cells derived from two donors. Thus, as the MABEL is based on a low level of effect in an in vitro assay with isolated blood cells, it represents a cautiously selected benchmark for potential initial pharmacological activity and aims to mitigate the risk of potential acute effects.

The starting dose (0.03 mg/kg, Q2W) and the subsequent dose level (0.1 mg/kg, Q2W) is intended to be administered to a limited number of patients to investigate the potential acute AEs while exposing as few patients as possible to potentially sub-therapeutic dose levels. The therapeutic effect is predicted to occur at higher dose levels; thus 10-20 mg/kg Q2W may be needed to ensure full saturation *in vivo*. The subsequent dose levels (from 0.1 mg/kg, Q2W) are to be administered to more patients per cohort as described in the study protocol. Dose levels are planned with 3-fold increase at all dose-escalations, except for the last one from 10 to 20 mg/kg. The 3-fold increase was based on a combined evaluation of the steepness of concentration-response and non-clinical studies. The concentration-response curve based on the 1-way MLR assay did not indicate a steep concentration-response, which would have called for smaller escalation increases. The maximum proposed dose of **20 mg/kg** is predicted to ensure full saturation of the target and full effect as assessed by the 1-way MLR assay (>95%) in humans. The maximum dose also takes in to account that the local concentration in tissue is typically less than 10% of the serum concentration for antibodies (20).

In conclusion, the proposed starting dose is **0.03 mg/kg** administered Q2W. The maximum dose to be administrated in this trial is not to exceed **20 mg/kg** administered Q2W.

2.6 Overall Benefits/Risk

No clinical information is available for patients treated with Sym023; therefore, the benefits and the safety profile of Sym023 have not been fully established. However, responses have been reported in a single Phase 1 trial of the anti-TIM-3 mAb TSR-022 in patients with rectal, thyroid, neuroendocrine, head and neck cancer, and soft-tissue sarcoma (7, 8). Results from preclinical studies indicate that Sym023 has antitumor activity in different cancer models. Sym023 has also been shown to be efficacious in preclinical models at dose levels that are well tolerated in cynomolgus monkeys.

During this trial, there will be an ongoing assessment of the risks with periodic evaluation of safety data. The trial will be discontinued in the event of any new finding indicating a risk that would render continuation of the trial unjustifiable. A Study Safety Team will review clinical and laboratory safety data on an ongoing basis and make decisions regarding the advisability of continuing accrual and/or dose-escalation.

To mitigate potential risks, the trial is designed to detect DLTs, if any, and to define a maximum tolerate dose (MTD) in accordance with the dose-escalation scheme planned for the trial. Enrollment will be staggered by 2 weeks between the first and second patient in each new dose level tested to evaluate safety before allowing concurrent enrollment of further patients at the given dose level. If the dose administered in a cohort is well tolerated, dose-escalation may proceed, and enrollment of subsequent cohorts may occur to establish a recommended Phase 2 dose (RP2D). The options to slow infusions, interrupt dosing, and discontinue administration of study drug in the event of specific AEs are outlined in this CTP (**Section 8.5**).

Information on AEs observed with an agent targeting the TIM-3 pathway is included (**Section 2.3.1.2, Section 11.2**). Information on AEs observed with agents targeting the PD-1/PD-L1 pathways is also included (**Section 11.2, Appendix 8**), along with recommendations for the management of infusion-related reactions (IRRs) (**Appendix 9**) and immune-mediated toxicities (**Appendix 10**).

Patients participating in Sym023 studies will be closely monitored for anticipated adverse reactions as well any unanticipated safety findings. Because the risks associated with immune checkpoint inhibitors can occur several weeks to months after treatment, patients will be monitored for up to 6 months following the last dose to assess for the onset of any post-therapy immune-mediated event thought to be related to study drug. Any patient who develops an immune-mediated toxicity during study, or during the 6-month post-therapy follow-up period, will be followed for up to 2 years after the end of treatment to assess the course of the condition and evaluate potential reversibility of the finding.

FOR ADDITIONAL INFORMATION, PLEASE REFER TO THE INVESTIGATOR'S BROCHURE (IB)

3 TRIAL OBJECTIVES AND DESIGN SUMMARY

3.1 Objectives: Sym023 (anti-TIM-3) Dose-Escalation

3.1.1 Primary Objective

Evaluation of the safety, tolerability, and DLTs to establish the MTD and/or RP2D of sequential escalating doses of Sym023 (anti-TIM-3) when administered Q2W by 30-minute IV infusion to patient cohorts with locally advanced/unresectable or metastatic solid tumor malignancies or lymphomas that are refractory to available therapy or for which no standard therapy is available

Note: Q2W dosing; 4 weeks equals 1 dosing cycle. Goal is the identification of the MTD or determination of a RP2D dose based on clinical data, including safety, PK, and pharmacodynamic (e.g., receptor occupancy in peripheral blood) outcomes. The MTD, if identified, and the RP2D dose may not be the same as the RP2D may be lower. If an MTD is not identified a maximum administered dose (MAD) will be determined and will not exceed 20 mg/kg.

3.1.2 Secondary Objectives

- Evaluation of the immunogenicity of Sym023
- Characterization of the PK profile of Sym023
- Evaluation of the preliminary antineoplastic effects of Sym023, including:
    - Evidence of objective response (OR) or stable disease (SD)*
    - Duration of OR or SD*
    - Time to progression (TTP) of disease*

* As assessed by RECIST v1.1 (**Appendix 5**), iRECIST (**Appendix 6**), and Response Evaluation Criteria in Lymphoma (RECIL 2017; **Appendix 7**)

3.1.3 Exploratory Objectives

- Evaluation of potential pharmacodynamic markers, e.g., receptor occupancy in peripheral blood mononuclear cells (PBMCs) (peripheral blood to be collected)
- Evaluation of potential biomarkers, including but not limited to assessment of:
    - In peripheral blood: circulating tumor deoxyribonucleic acid (ctDNA), ribonucleic acid (RNA), relevant proteins/cytokines, and cellular biomarkers
    - In tumor tissue: DNA, RNA, protein, and cellular biomarkers *(biopsies optional)*

Note: Assay methodology and biomarker assessments to be determined (TBD). Potential analyses may include but are not limited to: ctDNA sequencing; RNA sequencing (RNA-seq)/whole-exome sequencing (WES); measurement of relevant proteins/cytokines in the blood; cytometric analysis of cells in blood; and immunohistochemistry (IHC) of tumor material when collected *(tumor sampling is optional)*.

3.2 Trial Design Summary

Patient Population and Objectives

Approximately 20-48 male and female patients with documented either solid tumor malignancies that are locally advanced/unresectable or metastatic, or lymphomas, and with disease that is either refractory to standard therapy or for whom no standard therapy is available, will be entered into this Phase 1, multicenter, open-label, dose-escalation, cohort study. The trial is designed to evaluate the safety, tolerability, and DLTs to establish the MAD or MTD and the RP2D of sequential escalating doses of Sym023 (study drug), an anti-TIM-3 mAb.

Secondary objectives include evaluation of immunogenicity, characterization of the PK profile, and preliminary assessment of the antineoplastic effects of Sym023 in this patient population. Exploratory evaluation of the utility of potential pharmacodynamic and other biomarkers of Sym023 will also be undertaken in pre- and post-dosing peripheral blood samples and tumor tissue (tumor biopsies optional). Patients will be treated and followed on an outpatient basis throughout the trial, unless hospitalization is required for other reasons, or to ensure patient safety.

Dosing Schedule and Treatment Duration

- No premedication is required prior to receiving the first dose of study drug, except in patients with a history of IRRs to mAbs or similar products; in these patients, it is recommended that premedication be administered. Thereafter, premedication of individuals is at the Investigator's discretion. Mandatory premedication will be implemented for all patients should a pattern begin to emerge of mild-to-moderate study drug-related reactions that are amenable to prophylaxis with standard agents.
- On Day 1 of study, patients will receive study drug administered by 30-minute (+10 min) or by 60-minute (+ 10 min) IV infusion (depending on dose and body weight) in a fixed 50 mL, 100 mL, 250 mL, or 500 mL volume depending on dose and body weight. Sym023 will be administered Q2W with administration on Day 1 and Day 15, with each dose followed by a 2-week recovery period. This 4-week (28 day) period will be considered Cycle 1. Determinations regarding cohort escalation, DLTs, and MTD will be based on the toxicities observed during this initial cycle. Patients must receive their full planned doses of study drug, plus complete the designated 2-week follow-up period, to be considered evaluable for tolerability, unless dose delay or discontinuation was the result of a DLT. End of Cycle 1 (EOC1) assessments are to be performed no sooner than Cycle 1/Day 28 (C1/D28) (± 2 days).
- In all patients entered, a minimum of at least Cycle 1 of study drug will be completed, if tolerated, after which in the absence of confirmed progressive disease (PD) or unacceptable toxicity a patient may continue to receive additional 4-week cycles of study drug at the same dose and infusion duration established for the patient, and on the same Q2W schedule, at the Investigator's discretion and provided specified retreatment criteria have been met. Retreatment cycles may continue for up to 12 months at which time plans for continued therapy will be discussed by the Medical Monitor(s) and Investigator. Patients who stop therapy with an ongoing OR or prolonged SD may be retreated in the event of relapse, if the trial is still open. Confirmed PD as defined by response criteria (RECIST v1.1, iRECIST, RECIL 2017) at any point in the study will necessitate withdrawal of the patient from further participation so that alternative management of their malignancy may be considered.

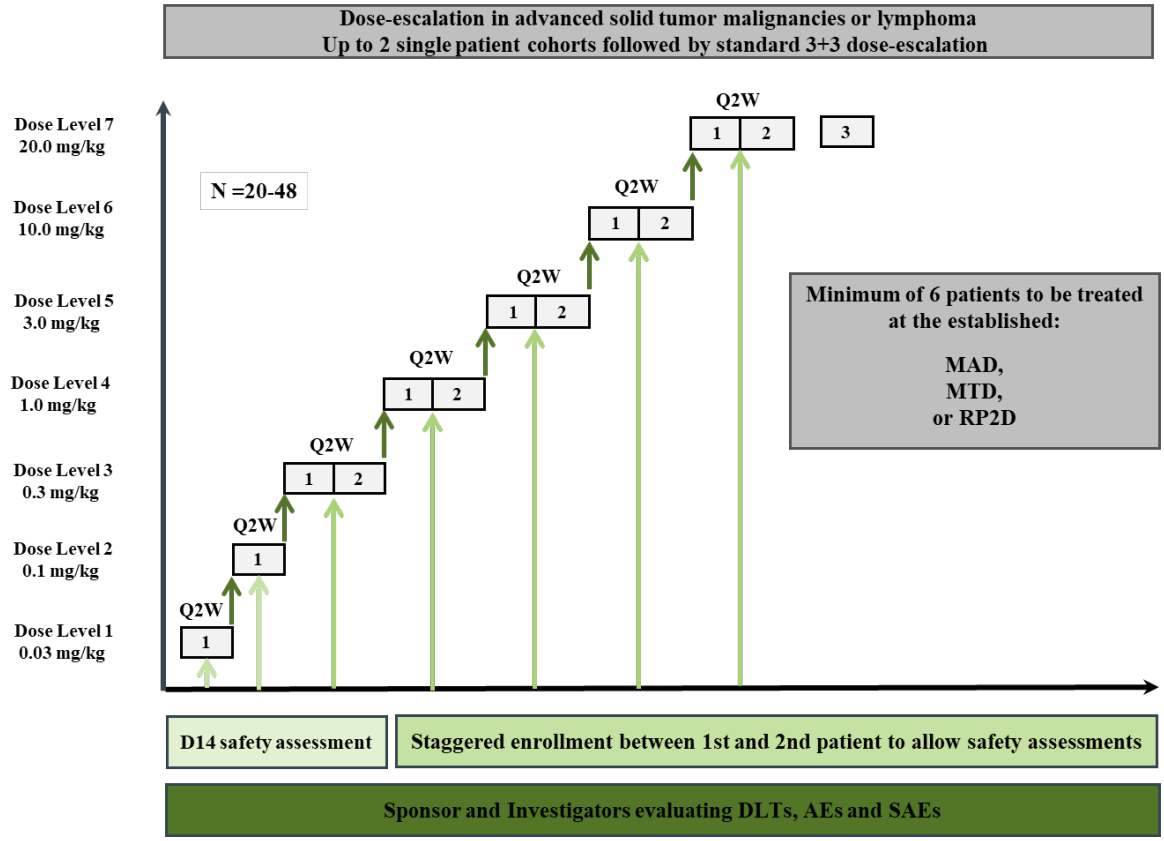
Doses to be Evaluated

At study entry, patients will be sequentially assigned to fill escalating dose cohorts of Sym023 beginning at the dose of **0.03 mg/kg**, with potential doses 0.1 mg/kg, 0.3 mg/kg, 1.0 mg/kg, 3.0 mg/kg, 10 mg/kg, and 20.0 mg/kg to follow. These doses will be evaluated until the MTD is identified, a MAD is reached, or until a RP2D is determined based on clinical data, including safety, PK, and pharmacodynamic (e.g., receptor occupancy in peripheral blood) outcomes. The MAD, MTD if identified, and the RP2D may not be the same, as the RP2D may be lower.

Initially, a modified, accelerated-titration, dose-escalation design will be used with entry of single patient cohorts for up to 2 dose levels, based on tolerability. Thereafter, a standard 3+3 dose-escalation design will be used with a target toxicity level of 33.3% or less as determined by DLTs. The number of cohorts evaluated and the MAD will depend upon the observed tolerability of Sym023 during Cycle 1 of patient treatment; however, the maximum dose to be administered in this trial is not to exceed **20 mg/kg.** Dose-escalation is shown in **Figure 1**.

The Investigator(s) and Sponsor's Medical Representative(s) as members of a Study Safety Team will review clinical and laboratory safety data on an ongoing basis throughout the study and make decisions regarding the advisability of continuing accrual to a dose cohort, and/or escalating the dose and allowing accrual to a higher dose cohort. Patients will also be monitored for evidence of cumulative or delayed toxicities, including the occurrence of delayed immune-mediated toxicities.

Figure 1: Dose-Escalation Schema



Abbreviations (in alphabetical order): AE, adverse event; DLT, dose-limiting toxicity; kg, kilogram; MAD, maximum administered dose; MTD, maximum tolerated dose; mg, milligram; N, number; Q2W, dosing every 2 weeks; RP2D, recommended phase 2 dose; SAE, serious adverse event.
Note: 20-48 patients anticipated for dose-escalation. Minimum of 6 patients to be treated at the MAD, MTD and/or RP2D dose; expansion of this cohort (or any other) up to 12 patients may be considered to further evaluate tolerability; therefore approximately 20-48 patients to be entered.

Filling of Cohorts

In single patient cohorts, dose-escalation and accrual to the next cohort will occur only after the patient has completed and tolerated the first dose of Cycle 1, including follow-up until C1/D15 to allow for review of clinical and laboratory assessments, and consultation with the Study Safety Team. **The DLT evaluation period for single patient cohorts will continue through to the EOC1.** Should a patient experience an AE of concern in the latter half of Cycle 1 that would, per protocol, result in cohort expansion, protocol rules as outlined herein will be followed. Additional patients entered to an expanded single patient cohort will follow rules as outlined below for 3+3 patient cohorts. If in the meantime a patient has been entered to receive the next higher dose level, that patient will be allowed to continue provided adequate tolerability is being demonstrated; however, further enrollment to the higher dose level cohort will be halted.

In 3+3 patient cohorts, the first patient within a cohort must complete and tolerate the first dose of Cycle 1, including follow-up until C1/D15 before entry of the next patient to a cohort (i.e., 2-week stagger); thereafter patients within a cohort may be added concurrently. Dose-escalation and accrual to the next cohort will occur after the minimum number of patients required for tolerability assessment in the current cohort have completed until C1/D15 in a single patient

cohort, or completed Cycle 1 in a 3+3 patient cohort, and only after acceptable tolerance has been demonstrated in at least 1 of 1, 3 of 3, or 5 of 6 patients treated in the current cohort (depending on cohort size), and review of the data with the Study Safety Team.

Should the DLT rate equal or exceed 33.3% in any cohort, the previous lower dose cohort will be expanded to 6 patients (if not already accomplished). Thus, there is potential for expansion of a lower dose if an initially identified MTD and/or RP2D is found to exceed tolerability, as well as potential to evaluate and expand a previously unplanned intermediate dose between 2 established dose levels, if indicated, to more fully characterize safety and tolerability. Once the MTD (or maximum dose to be studied) is achieved and/or the RP2D is identified, that cohort may be expanded up to 12 patients to more fully evaluate safety and tolerability at that dose level, at the Sponsor's discretion. Should the DLT rate equal or exceed 33.3% in an expanded cohort, it will be determined that the dose is not tolerated and exceeds the MTD. If this occurs, the previous lower dose cohort or an intermediate dose level may be expanded as above. There will be no intrapatient dose-escalation in this trial.

Study Assessments

For safety, patients will be monitored throughout the treatment and 1-month follow-up (1M FUP) period for evidence of AEs, including changes in clinical status, laboratory data, electrocardiogram (ECG) findings, and either multi-gated acquisition (MUGA) scans or echocardiograms (ECHO) in patients with a history of congestive heart failure (CHF). Patients will be evaluated for evidence of immune-mediated toxicities. Patients will also be evaluated for evidence of antibody formation to study drug. Patients experiencing a DLT regarded as possibly-, probably-, or related to study drug at any point during treatment will be discontinued from study treatment, without exception. Patients may not be retreated following the occurrence of a DLT. Only DLTs occurring during Cycle 1 will be used to make determinations regarding dose-escalation and tolerability.

The overall trial plan is introduced in **Table 1**.

Table 1: Overall Trial Plan	
Screening Period	
Screening	• Written informed consent • Disease assessment and eligibility confirmation *(within 28 days [+2 days] prior to 1st dose)* • Safety screening and eligibility confirmation (*within 14 days prior to 1st dose unless otherwise stipulated*) • Allocated dose of study drug dependent upon cohort assignment; to be confirmed on Screening and Allocation Form
Treatment Period	
Treatment	• C1/D1 initial dose of study drug • Continued dosing once Q2W • 28-day cycles until confirmed PD, unacceptable toxicity, or other discontinuation criterion is met for up to 12 months at which time plans for continued therapy to be discussed by the Medical Monitor(s) and Investigator. Patients who stop therapy with an ongoing OR or prolonged SD may be retreated in the event of relapse, if the trial is still open. • EOT visit within approximately 7-10 days following treatment discontinuation, or before initiation of a new treatment, whichever occurs first • 1M FUP visit 30 days (+7 days) following last dose* **Completion of the 1M FUP visit will be considered the end of the treatment period*
Follow-up Period	
Post-Treatment Follow-up	• Safety FUP if an observed non-immune-mediated toxicity thought to be related to study drug has not resolved by the 1M FUP evaluation (2 and 4 months following last study drug dose) • Safety FUP surveillance to assess for delayed onset immune-mediated toxicity (Q2M for up to 6 months following last study drug dose) • Safety FUP for ongoing at the 1M FUP, and for delayed onset, immune-mediated toxicity (Q2M for up to 2 years following last study drug dose) • Response FUP following discontinuation for reasons other than confirmed PD until the end of trial (Q2M until PD or initiation of another therapy) **Completion of all indicated follow-up will be considered the EOS*

Abbreviations (in alphabetical order): 1M FUP, 1-month follow-up; C1/D1, Cycle1/Day1; EOS, end of study; EOT, end of treatment; FUP, follow-up; PD, progressive disease; Q2M, every 2 months; Q2W, every 2 weeks

4 PATIENT NUMBER AND SELECTION CRITERIA

4.1 Number of Patients

4.1.1 Investigational Sites

This is a multicenter trial. It is anticipated that approximately 2-4 investigational sites in North America may participate based on accrual.

4.1.2 Number of Patients

Considerations for estimating the number of patients to be entered are as follows:

- Approximately 20-48 patients in escalating dose cohorts
    - Minimum of 1 patient per cohort for up to 2 dose cohorts
    - Minimum of 3 patients per dose cohort thereafter
    - Assume approximately 7 dose cohorts to be evaluated to establish the MTD and/or RP2D dose
    - Expansion of any cohort to 6 patients in the event of a Cycle 1 DLT in any of the initial 1 to 3 patients
    - Minimum of 6 patients to be treated at the MTD and/or RP2D dose; expansion of this cohort (or any other) up to 12 patients may be considered to further evaluate tolerability

In addition, there is potential for entry of additional patients to:

- Ensure sufficient evaluable patients by adding an additional patient to a cohort (e.g., increase a 1-patient cohort to 2 patients, a 3-patient cohort to 4 patients, or a 6-patient cohort to 7 patients)

    Note: Should this action be taken, cohort tolerability assessment and subsequent dose-escalation will occur when the minimum number of patients required to evaluate tolerability have completed Cycle 1. However, if any additional patient experiences an event that would, per protocol, result in either cohort expansion or the halting of dose-escalation, protocol rules as outlined herein will be followed (**Section 6.6.1**).

- Expand a lower dose cohort(s) if an initially identified MTD and/or RP2D is subsequently determined to be not tolerated either with single or repeated cycles of therapy
- Add and evaluate a previously unplanned intermediate dose level(s) to further characterize safety and tolerability, if indicated *(inclusion of a dose higher than those listed would require a protocol amendment)*

    Note: This action would be taken in the event of an unacceptably high frequency of toxicities observed in patients treated at one dose considered to be in marked contrast to the tolerability noted at the preceding dose level, or if after review of study data, a more gradual dose-escalation appears warranted.

Expanded accrual in any cohort will take place at the Sponsor's discretion, after discussion with the Investigator(s).

4.2 Criteria for Inclusion

Patients must meet all the following criteria to be eligible for participation in the trial:

1. Male or female patients, ≥ 18 years of age at the time of obtaining informed consent
2. Patients with a documented (histologically- or cytologically-proven) solid tumor malignancy that is locally advanced or metastatic; patients with documented lymphomas
3. Patients with a malignancy (solid tumor or lymphoma) that is currently not amenable to surgical intervention due to either medical contraindications or non-resectability of the tumor
4. Patients refractory to or intolerant of existing therapy(ies) known to provide clinical benefit.

   Note: Patients may have received and failed prior therapy with a PD-1/PD-L1 inhibitor and be considered eligible for this trial.

5. Patients with measurable or non-measurable disease according to RECIST v1.1 or RECIL 2017 (**Appendix 5** and **Appendix 7**, respectively)
6. Patients with an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0 or 1 (or equivalent Karnofsky PS; **Appendix 1**), and anticipated life expectancy of ≥ 3 months
7. Patients, both male and female, who are either not of childbearing potential or who agree to use a highly effective method of contraception during the study beginning within 2 weeks prior to the first dose and continuing until 6 months after the last dose of study drug.

   Note: Women are considered of childbearing potential unless they have undergone hysterectomy and/or bilateral tubal ligation or oophorectomy, or have been postmenopausal for at least one year. Postmenopausal status in non-surgerized females under 55 years of age should be confirmed with a serum follicle-stimulating hormone (FSH) level within laboratory reference range for postmenopausal women.

   A highly effective method of contraception is defined as non-hormonal contraception equivalent to a double-barrier method (includes a single-barrier method in combination with a spermicide) or intrauterine device (**Section 11.1**).

   Women of childbearing potential (WOCBP) must have a negative pregnancy test, serum at screening, serum or urine thereafter; negative test must be confirmed within **≤ 2 working days** prior to administration of the first dose of study drug.

8. Patients with the ability to understand and give written informed consent for participation in this trial, including all evaluations and procedures as specified by this protocol

   Note: Informed consent must be obtained prior to patient screening, and before any evaluations or procedures specifically related to this study are performed.

4.3 Criteria for Exclusion

Patients meeting any of the following criteria are ineligible for participation in the trial.

4.3.1 Patients to be Excluded

1. Women who are pregnant or lactating or intending to become pregnant before, during, or within 6 months after the last dose of study drug. WOCBP, and fertile men with WOCBP-partner(s) not using and not willing to use a highly effective method of contraception.

   Note: WOCBP includes any female who has experienced menarche and who has not undergone surgical sterilization (hysterectomy, bilateral tubal ligation, or bilateral oophorectomy), or is not postmenopausal. Post-menopause is defined as: 1) amenorrhea for > 12 months with no other cause, or 2) irregular menstrual periods, on hormone replacement therapy (HRT), with a documented FSH level > 35 mIU/mL.

   WOCBP and fertile men will be informed as to the potential risk of procreation while participating in this trial. A pregnancy test will be performed, and the results reviewed, on each premenopausal WOCBP prior to first study drug administration. A negative pregnancy test performed within **≤ 2 working days** prior to first study drug administration must be documented in the patient's case report form (CRF) (**Section 11.1**).

2. Patients with central nervous system (CNS) malignancies; patients with known, untreated CNS or leptomeningeal metastases, or spinal cord compression, patients with any of the above not controlled by prior surgery or radiotherapy, or patients with symptoms suggesting CNS involvement for which treatment is required

   Note: Patients with treated CNS metastases will be eligible if they are asymptomatic, do not require corticosteroids, and have confirmation of at least stable brain disease status as assessed by 2 imaging studies performed ≥ 4 weeks apart with the most recent performed within 4 weeks prior to first trial drug administration. Prophylactic anticonvulsant medications are allowed.

   Patients with newly identified CNS disease during study treatment will be considered to have disease progression and will be discontinued from study to allow for appropriate management.

3. Patients with hematologic malignancies other than lymphomas
4. Patients with any of the following hematologic abnormalities at baseline*:
   - Hemoglobin < 9.0 g/dL
   - Absolute neutrophil count (ANC) < 1,000 per mm^3
   - Platelet count < 75,000 per mm^3

   Note: Patients may have received a blood/blood product transfusion prior to study, if clinically warranted.

   **Throughout this protocol "baseline" is defined as the last available observation prior to the first administration of study drug on C1/D1.*

5. Patients with any of the following serum chemistry abnormalities at baseline:
   - Total bilirubin > 1.5 × the upper limit of normal (ULN) for the institution*
   - Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) > 3 × the ULN for the institution (> 5 × ULN if due to hepatic involvement by tumor)
   - Serum creatinine > 1.5 × ULN for the institution

**Patients with evidence of Gilbert's Syndrome as the etiology of elevated total bilirubin will be eligible, provided all other eligibility criteria are met.*

6. Patients with any of the following coagulation parameter abnormalities at baseline (unless on a stable dose of anticoagulant therapy for a prior thrombotic event, as determined by the Investigator):
    - Prothrombin time (PT) (or international normalized ratio [INR]) > 1.5 × ULN for the institution (> 3× ULN for the institution if anticoagulated)
    - Partial thromboplastin time (PTT) (or activated partial thromboplastin time [aPTT]) > 1.5 × ULN for the institution (> 3× ULN for the institution if anticoagulated)
7. Patients with:
    - Active thrombosis, or a history of deep vein thrombosis (DVT) or pulmonary embolism (PE), within 4 weeks prior to first study drug administration, unless adequately treated and considered by the Investigator to be stable
    - Active uncontrolled bleeding or a known bleeding diathesis
8. Patients with a clinically significant (CS) cardiovascular disease or condition, including:
    - Need for antiarrhythmic medical therapy for a ventricular arrhythmia or other uncontrolled arrhythmia (patients with controlled atrial fibrillation (heart rate [HR] < 90) for > 30 days prior to study entry are eligible)
    - Severe conduction disturbance (e.g., 3rd degree heart block)
    - HR-corrected QT interval (QTc interval) ≥ 480 milliseconds (msec)
    - Uncontrolled hypertension (per the Investigator's discretion)
    - History of myocarditis
    - Left ventricular ejection fraction (LVEF)* known to be below the lower limit of normal (LLN) for the center, or < 50% by MUGA scan or ECHO if no LLN is defined by the site
    - CHF currently requiring therapy
    - Class III or IV cardiovascular disease according to the New York Heart Association (NYHA) Functional Classification (**Appendix 2**)
    - History of acute coronary syndromes (including myocardial infarction [MI] and unstable angina), coronary angioplasty, stenting, or bypass within 6 months prior to first study drug administration

**Assessment of LVEF will not be performed routinely in all patients. Patients with a history of CHF will have either a MUGA scan or ECHO at Screening. If LLN is not defined for a given institution, then LVEF must be ≥ 50%.*

9. Patients with a significant ocular disease or condition, including history of an autoimmune or inflammatory disorder, e.g., episcleritis, uveitis, iritis

   Note: Patients with a history of dry eye for reasons other than an autoimmune disease or condition may be included if adequately treated. Patients with non-significant, non-inflammatory disorders (e.g., cataracts, glaucoma) will be allowed.

10. Patients with a significant pulmonary disease or condition, including:

    - History of interstitial lung disease (ILD), pulmonary fibrosis
    - History of pulmonary inflammatory disease, interstitial or other pneumonitis*, acute respiratory distress syndrome (ARDS)

      **Patients with prior evidence of Grade 1 pneumonitis will be eligible provided they were asymptomatic and did not require treatment and provided pneumonitis has resolved prior to entry to this trial.*

11. Patients with a current or recent (within 6 months) significant gastrointestinal (GI) disease or condition, including:

    - History of inflammatory bowel disease
    - Diarrhea ≥ Grade 2 within 2 weeks prior to first study drug administration

    Note: Patients with recent Grade 2 diarrhea secondary to administration of oral contrast are allowed, provided symptoms have resolved prior to first study drug administration

12. Patients with an active, known or suspected autoimmune disease, or a documented history of autoimmune disease or syndrome, requiring systemic steroids or other immunosuppressive medications

    Note: Exceptions permitted include: type I diabetes mellitus, hypothyroidism only requiring hormone replacement, skin disorders such as vitiligo, psoriasis or alopecia not requiring systemic treatment, conditions not expected to recur in the absence of an external trigger.

13. Patients with a history of organ transplantation (e.g., stem cell or solid organ transplant)
14. Patients with a known or suspected hypersensitivity to any of the excipients of formulated study drug
15. Patients with a history of significant toxicities associated with previous administration of immune checkpoint inhibitors that necessitated permanent discontinuation of that therapy
16. Patients with unresolved > Grade 1 toxicity* associated with any prior antineoplastic therapy except for persistent Grade 2 alopecia, peripheral neuropathy, decreased hemoglobin, lymphopenia, hypomagnesemia, and/or end-organ failure being adequately managed by hormone replacement therapy

    **Toxicity assessments based on Common Terminology Criteria for Adverse Events (Version 5.0) (CTCAE v5.0)*

17. Patients with inadequate recovery from any prior surgical procedure, or patients having undergone any major surgical procedure within 4 weeks prior to first study drug administration

    Note: Patients having undergone recent placement of a central venous access device will be considered eligible for enrollment.

18. Patients who are known or suspected drug or alcohol abusers where compliance with protocol requirements may be a concern
19. Patients with a known history of human immunodeficiency virus (HIV) or known active infection with hepatitis B virus (HBV) or hepatitis C virus (HCV)
20. Patients with any other serious/active/uncontrolled infection, any infection requiring parenteral antibiotics, or unexplained fever > 38ºC within 2 weeks prior to first study drug administration
21. Patients with any other serious, life-threatening, or unstable pre-existing medical condition (aside from the underlying malignancy), including significant organ system dysfunction, or CS laboratory abnormality(ies), which, in the opinion of the Investigator, would either compromise the patient's safety or interfere with obtaining informed consent, compliance with study procedures, or evaluation of the safety of the study drug
22. Patients with a psychiatric disorder or altered mental status that would preclude understanding of the informed consent process and/or completion of the necessary study-related evaluations
23. Patients with the inability or with foreseeable incapacity, in the opinion of the Investigator, to comply with the protocol requirements

4.3.2 Drugs and Other Treatments to be Excluded

1. Other inhibitors of TIM-3 (e.g., mAbs)
2. Any antineoplastic agent for the primary malignancy (standard or investigational) without delayed toxicity within 4 weeks or 5 plasma half-lives, whichever is shortest, prior to first administration of study drug and during study, except for:

    - Nitrosoureas and mitomycin C within 6 weeks prior to first study drug administration and during study

    Note: Patients may have received and failed prior therapy with a PD-1/PD-L1 inhibitor and may still be considered eligible for this trial.

3. Any other investigational treatments within 4 weeks prior to and during study. This includes participation in any medical device or other therapeutic intervention clinical trials.
4. Radiotherapy:

    - For target lesions within 4 weeks prior to first administration of study drug unless disease progression has been documented in the lesion following treatment, and during study

- For non-target lesions within 1 week prior to first administration of study drug

  Note: Palliative (limited-field) radiotherapy for management of pain associated with bone metastases present at baseline is permitted during study. Patients with suspected new bone lesions requiring pain management should be treated and evaluated for potential disease progression.

5. Use of live vaccines against infectious diseases (e.g., varicella) 4 weeks prior to first study drug administration and during study
6. Immunosuppressive or systemic hormonal therapy (> 10 mg daily prednisone equivalent) within 2 weeks prior to first study drug administration and during study. *The following therapies are allowed:*

   - Hormonal therapy for appetite stimulation (e.g., Megace)
   - Nasal, ophthalmic, inhaled, and topical glucocorticoid preparations
   - Hormone replacement therapy at standard doses for end-organ failure
   - Stable hormonal therapy for prostate carcinoma*
   - Stable hormonal therapy for ovarian suppression, hormonal contraceptive therapy, or post-menopausal HRT*
   - Neuroendocrine tumor patients: stable hormonal therapy with a somatostatin analog (SSA)**
   - Steroid therapy for contrast reaction prophylaxis
   - Intra-articular steroid injections
   - Low-dose maintenance steroid therapy for other conditions (e.g., asthma exacerbation, stable steroid therapy [excluding tapering dose of steroids] for brain edema/metastases/radiation)
   - Higher dose steroid therapy for treatment of an acute intercurrent illness (e.g., immune-related AEs or other adverse conditions) in patients with stable disease or an ongoing response. In such situations, study drug treatment should be interrupted for the duration of immunosuppressive therapy.

   **Prior or concomitant therapies are permitted; however, patients must have been on a stable dose for at least 6 months prior to study start, and if continuing must remain on the stable dose while receiving study treatment (i.e., such treatment will not be considered as systemic hormonal therapy for the purpose of study eligibility).*

   *** Patients with metastatic low-grade neuroendocrine tumors (carcinoid tumors) are permitted to remain on concomitant SSA therapy; however, patients must have been on a stable dose for at least 2 months (8 weeks) prior to study start and progressed on that dose, and if continuing, must remain on the stable dose while receiving study treatment (i.e., such treatment will not be considered as systemic hormonal therapy for the purpose of study eligibility).*

7. Prophylactic use of hematopoietic growth factors within 1 week prior to first study drug administration and during Cycle 1 of study; thereafter prophylactic use of growth factors is allowed as clinically indicated

   Note: Interventional/therapeutic use of growth factors is allowed at any time during study, including during Cycle 1, if deemed necessary by the Investigator. Growth factor use must be consistent with product package insert instructions. Transfusions are permitted as needed.

Questions regarding patient eligibility must be addressed and resolved by the Investigator in consultation with the Sponsor's Medical Monitor(s) prior to enrollment.

5 INVESTIGATIONAL MEDICINAL PRODUCT

In advance of study start, the Sponsor (or designee) will provide labeled supplies of investigational medicinal product (IMP) (also referred to as study drug) to the site pharmacy. Instructions for handling, administration, and disposal will be provided in the IMP Manual and are summarized below.

5.1 Sym023

The study drug Sym023 will be provided by Symphogen.

Sym023 is a clear to opalescent, colorless to slightly yellow liquid formulation for IV infusion after dilution. Each single-use, glass vial contains a nominal fill volume of 8.0 mL. Each vial contains Sym023 at a concentration of 20 mg/mL for a total vial content of 160 mg.

5.1.1 Formulation Excipients

Formulation excipients include:

5.2 Storage and Handling of IMP

Unused vials of IMP must be stored refrigerated between 2°C to 8°C (36 to 46°F) and protected from direct sunlight. IMP may not be frozen.

There is no evidence that ultraviolet (UV) light exposure affects study drug, but as a precaution, vials should be stored protected from direct sunlight in the carton until use.

All handling, storage and preparation of IMP should take place at the site pharmacy.

The site will be required to maintain a temperature log documenting study drug storage conditions. The temperature must be logged and evaluated at minimum on all working days.

Any deviations from the recommended storage conditions should be immediately reported to the Sponsor (or designee) and the use of study drug interrupted until authorization for its continued use has been given.

Study drug may be accessed only by the Investigator, a member of the Investigator's staff specifically authorized by the Investigator, or a pharmacist, as appropriate. The site must ensure that study drug is accessible to authorized personnel only.

5.3 Stability of IMP

Long-term stability of study drug is being assessed on an ongoing basis and expiry will be updated as data accrue. The stability of the IMP will be monitored for at least the duration of the proposed clinical trial.

When diluted for use, the study drug has been found to be stable at room temperature and should be administered within an 8-hour time window (**Section 5.8**).

5.4 Labeling of IMP

Vials of study drug will be open-label; label text will be in accordance with applicable local regulatory requirements. Each vial will be uniquely numbered for allocation, dispensing, and traceability purposes.

5.5 Packaging of IMP

Study drug will be packed in cartons containing multiple vials. The vial number range in each carton will be detailed on the carton label.

5.6 Administration of IMP

Study drug will be administered by IV infusion via an indwelling catheter. An appropriate dose, based on the patient's cohort assignment, diluted to the total volume specified with 0.9% sodium chloride (NaCl) for IV infusion will be administered initially over:

- Approximately 30 minutes (+10 minutes) for infusion volumes ≤ 250 mL
- Approximately 60 minutes (+10 minutes) for infusion volumes of 500 mL

Dosing will be once every 2 weeks (Q2W; 4 weeks [28 days] equals 1 dosing cycle).

5.7 Dose Calculation

The Investigator (or designee) will be responsible for calculating the amount of study drug and the appropriate dose to dispense to the patient as determined by the patient's dose cohort assignment.

The dose level will be multiplied by the patient's weight in kilograms to arrive at the total dose to be delivered. In situations where this calculation results in a value with an unwieldy number of decimal places, it is permissible to round the value to the nearest "tenth". As a convention, values > 5 should be "rounded" to the next higher number.

Dose adjustments should be made in the event of noted weight change (± 10%; less at the site's discretion or if required by institution procedures) at visits that require weight measurement. Adjustments may be made more frequently at the site's discretion.

5.8 Dose Preparation

The designated dose of study drug must be prepared by the study pharmacist (or designee) and should be administered by the study staff as soon as possible following preparation, within 8 hours, and considering:

- The total volume of study drug to be delivered will be withdrawn from the study drug vial(s) and added to a prefilled IV bag containing 0.9% NaCl for IV infusion (prior to adding the study drug and an appropriate volume of NaCl solution is removed, such that the final volume to be infused equals:
    - 50 mL for doses < 1 mg/kg
    - 100 mL for doses ≥ 1 mg/kg to ≤ 3 mg/kg
    - 100 mL for doses of > 3 mg/kg to ≤ 10 mg/kg for patients with body weight ≤ 80 kg

- 250 mL for doses of > 3 mg/kg to ≤ 10 mg/kg for patients with body weight > 80 kg
- 250 mL for doses > 10 mg/kg for patients with body weight ≤ 100 kg
- 500 mL for doses > 10 mg/kg for patients with body weight > 100 kg

Note: In a case where the amount of IMP is ≥ 40% of the total infusion volume, a larger IV solution bag should be used.

- The IV bag containing the diluted study drug solution to be administered should be gently inverted to ensure that the material is well mixed.
- Infusion sets must contain a 0.22 micron in-line filter.

5.9 Accountability

The Investigator acknowledges that study drug supplies are investigational and, as such, must be used strictly in accordance with the protocol and only under the supervision of the Principal Investigator. No study drug will be sent to the site until all required regulatory documents, including Institutional Review Board (IRB) or Ethics Committee (EC) approval, are received by the Sponsor or its designee.

The Investigator and site staff are responsible for maintaining an accurate inventory and accounting of study drug. Receipt, use, and destruction of study drug will be recorded on the dispensing log in use.

5.10 Disposition of Used IMP

Once study drug is prepared for delivery and administered, the health care professional will maintain an inventory of all open/used vials of study drug. Such residual supplies may be destroyed in an appropriate manner according to institutional policy.

Note: **No other use of study drug intended for use in this trial is authorized by the Sponsor.** The Investigator (or designee) will be responsible for the appropriate handling and disposition of residual study drug in partially used vials.

5.11 Unused IMP

Unused study materials MUST be returned to the Sponsor (or designee) upon expiry or at the conclusion of the site's participation in the trial, unless otherwise authorized in writing.

5.12 Destruction of IMP

No unused IMP may be destroyed or discarded at the site without the written authorization of the Sponsor (or designee). The destruction of study drug materials must be carefully documented per instructions outlined in the IMP Manual. Disposition records must be available for review by a representative of the Sponsor.

6 EXPERIMENTAL PLAN

6.1 Design Elements

- Open-label, uncontrolled, non-randomized
- Escalating doses of study drug in sequential patient cohorts
- Enrollment staggered between first and second patient in each new higher 3-patient dose cohort to allow for initial safety observations

6.2 Projected Recruitment Period and Duration of this Trial

It is anticipated that enrollment to this study will be completed in approximately 12 months.

- Anticipated date of enrollment of first patient: Q2 2018
- Anticipated date of enrollment of last patient: Q3 2019
- End of Trial (i.e., data cut-off for primary analysis): Will be reached 1 month (30 + 7 days) after all patients have discontinued trial treatment, or 6 months after the last patient has started trial treatment, whichever occurs earlier, at which point the trial objectives will be considered to have been met.
- Patients still in treatment will be given the opportunity to continue receiving study drug. In such an event, while the Sponsor still needs to collect certain safety-related data to meet its regulatory obligations (AEs, SAEs, study drug dosing, reason for discontinuation, etc.), the Sponsor may elect to reduce non-safety-related protocol-stipulated assessments, and/or transition patients to an extension/rollover protocol

6.3 Cohort Management

For the purposes of this study, "enrollment" is defined as patient registration to participate in this trial; at that time, the patient's study identification code and dose cohort will be assigned.

6.3.1 Patient Screening and Dose Cohort Assignment

Once a patient has given written informed consent, screening assessments will be conducted, and if the patient is identified as meeting the study eligibility criteria, the Investigator (or designee) will contact the Sponsor's representative to authorize enrollment of the patient into the trial.

Patients will be enrolled into the study in the order of confirmation of their eligibility, and assigned to a cohort on a "first-come-first-served" basis.

6.3.1.1 Screening of Potential Patients

All screening activities must be performed within 14 days prior to the first day of dosing (C1/D1), unless otherwise specified.

The Sponsor (or designee) will be made aware of potential patients for enrollment to track such study-related activities.

Patients who sign informed consent and are ultimately deemed to be screen failures will be followed for the occurrence of SAEs/AEs during the screening process until such time that it is determined that they will not be participating in this trial.

6.3.1.2 Submission of Patient Enrollment Documentation

Once eligibility has been confirmed in accordance with the protocol-stipulated inclusion and exclusion criteria, patient enrollment information must be submitted to the Sponsor (or designee) via a Patient Screening and Allocation Form signed by the Principal Investigator (or designee). This information will serve to confirm patient eligibility and initiate the enrollment process. The following information must be provided by the site:

- Patient gender
- Date of birth (or age), as allowed by local regulatory requirements
- Date written informed consent was obtained
- Underlying diagnosis
- Confirmation of compliance with all inclusion/exclusion criteria.

The following information may be requested of the site:

- Patient weight (for dose calculation)
- Date of screening
- Stage of disease and current PS
- Sites of metastases (if applicable)
- Brief description of the prior therapy for the primary diagnosis, including dates of initiation and discontinuation as well as best response
- Planned date of first dosing

The Sponsor (or designee) will review the information provided and by signing the form will authorize eligible patients for start of treatment. A copy of the fully executed Patient Screening and Allocation Form will be returned to the trial site for archiving. This form will document the allocated dose of study drug, and will serve to assign patients to a dose cohort at the time of enrollment.

6.3.1.3 Patient Identification Code Assignment

Each patient who completes the study screening assessments and is enrolled for study participation will be assigned a unique identification code by the Sponsor (or designee). Identification codes will be assigned in chronological order, and will be concatenated to indicate relevant study information, including at minimum: the participating trial site and the patient's order of enrollment to the trial.

6.3.1.4 Screen Failures

A patient found not eligible for the trial after giving informed consent will be considered a screen failure. A list of patients failing screening and the reason for ineligibility will be maintained by the site on a Patient Screening Log or other similar document.

Re-screening of a patient is allowed using the specified criteria and timing, if felt to be justified by the Investigator.

6.3.2 Cohort Closure

The Sponsor (or designee) will be in communication with the sites when the target total enrollment for a cohort has been attained. Once recruitment to a cohort is completed, accrual to the cohort will be closed, and sites will be so notified in writing. Cohorts will remain closed to further accrual, unless a decision is later made by the Sponsor (or designee) to further expand that cohort, based on protocol-defined criteria.

6.4 Requirements for Patient Observation

Patients will be treated on an outpatient basis, and will be evaluated and discharged from the clinic on days of scheduled study visits*, unless hospitalization is required for other reasons or to ensure patient safety.

Study drug must be administered under close supervision of a physician, or other study personnel experienced in administration of IV agents, and in an environment where full resuscitation facilities are immediately available. IV infusions will be carefully monitored to assess safety and tolerability by qualified site medical personnel. Such personnel must be available to evaluate and treat any AEs, as well as to evaluate whether continued participation of the patient in the study is warranted or advisable.

- Patients will be carefully observed for a minimum of 2 hours following completion of the first administration of study drug (C1/D1) for evidence of any treatment-related AE(s), and a minimum of 1 hour following completion of subsequent infusions (C1/D15 and onward).
- At the end of each infusion, the IV line must remain in place during the observation period to allow for administration of IV drugs, if necessary.

Patients will be followed on an outpatient basis during the interval between each scheduled study visit.

Clinical and laboratory assessments will occur at the frequencies indicated (Section 7**). In the event of an AE, assessment frequencies may be increased, as clinically indicated.*

6.5 Drug Treatment Regimen

6.5.1 Study Start Day

All patients will receive the initial dose of study drug on Day 1 of Cycle 1 (C1/D1).

On the day of the first scheduled study drug infusion, and prior to the start of infusion (SOI), the Investigator must assess whether any changes have occurred in the clinical state of the patient since Screening which would exclude the patient from the trial.

6.5.2 Patient Availability

The site should calculate study assessment days as well as sample collection dates and times in advance of scheduling a patient's first day of study drug administration in order to plan

accordingly to avoid assessment or collection requirements during non-routine clinic times such as weekends, holidays, etc.

Given the schedule of study drug administration outlined herein, and the PK sampling schedule (**Section 7.6**), patients must be available:

- Cycle 1: Days 1, 2, 3 (± 1 day); Days 8, 15, and 22 (each ± 2 days); therefore, consideration should be given to scheduling Day 1 on a Monday, Tuesday, or Wednesday*
- Cycles thereafter: Day 1 and Day 15 (± 2 days)
- Patients must also be available at the end of cycles to determine whether continuation to the next cycle is feasible based on tolerability, and at the end of even-numbered cycles to evaluate disease status.

**unless the study site has weekend hours of operation*

6.5.3 Therapy with Study Drug

Based on their cohort assignment, patients will receive the assigned dose of study drug by the route and schedule as described below:

6.5.3.1 Doses to be Administered

6.5.3.1.1 Doses to be Evaluated

Dose cohorts will be numbered sequentially (i.e., Cohort 1, Cohort 2, etc.). The number of cohorts evaluated will depend upon toxicities experienced during Cycle 1.

Anticipated dose levels include:

- Dose Level 1: 0.03 mg/kg
- Dose Level 2: 0.1 mg/kg
- Dose Level 3: 0.3 mg/kg
- Dose Level 4: 1.0 mg/kg
- Dose Level 5: 3.0 mg/kg
- Dose Level 6: 10 mg/kg
- Dose Level 7: 20 mg/kg

6.5.3.1.2 Changes in Dose to be Administered

Once assigned to a dose cohort, patients will continue to be treated with study drug at that same dose level throughout the duration of their time on study. There will be no intrapatient dose-escalation.

Dose adjustments should be made in the event of noted weight change (± 10%; less at the site's discretion or if required by institution procedures) at visits that require weight measurement. Adjustments may be made more frequently at the site's discretion.

6.5.3.2 Route of Administration

Study drug will be administered by the IV route, via indwelling venous access catheter, utilizing a controlled infusion device. Infusion sets must contain a 0.22 micron in-line filter.

The catheter may be placed into a peripheral vein (if accessible); administration via central venous catheter or port (if in place) is allowed.

In those instances when study drug administration is associated with PK sampling, and administration is via peripheral IV catheter, infusions will be delivered into the arm contralateral to that from which blood samples for PK analysis are being obtained.

6.5.3.3 Diluent and Delivery

Commercially available sterile 0.9% NaCl for IV infusion is to be used as the diluent. Once diluted for IV administration, study drug should be administered within 8 hours.

6.5.3.4 Volume of Infusion

Infusions will be delivered in a final volume of:

- 50 mL for doses < 1 mg/kg
- 100 mL for doses ≥ 1 mg/kg to ≤ 3 mg/kg
- 100 mL for doses of > 3 mg/kg to ≤ 10 mg/kg for patients with body weight ≤ 80 kg
- 250 mL for doses of > 3 mg/kg to ≤ 10 mg/kg for patients with body weight > 80 kg
- 250 mL for doses > 10 mg/kg for patients with body weight ≤ 100 kg
- 500 mL for doses > 10 mg/kg for patients with body weight > 100 kg

Note: In a case where the amount of IMP is ≥ 40% of the total infusion volume, a larger IV solution bag should be used.

6.5.3.5 Duration of Infusion

Study drug will be administered over:

- Approximately 30 minutes (+10 minutes) for infusion volumes ≤ 250 mL
- Approximately 60 minutes (+10 minutes) for infusion volumes of 500 mL

Administration should be at a constant rate using a programmable volumetric infusion pump to ensure accuracy of delivery (as well as integrity of PK sampling). Start and stop times of each infusion, and any interruptions in infusion will be recorded on the appropriate page of the patient's CRF.

Note: In the event of a Grade 2 IRR, see **Section 8.5.1, Appendix 9** for further instructions.

Study drug will be administered over a longer period for all patients entered to the trial in the following situations:

- In the event of a Grade 2 IRR in ≥ two thirds of the patients entered to a cohort, the duration of infusion for subsequent patients entered to the trial will be extended by 30 minutes (or longer, if indicated).

- In the event of a Grade 3 or greater IRR in any patient within a cohort, the duration of infusion for subsequent patients entered to the trial will be extended by 30 minutes (or longer, if indicated). Such a case will also be considered to have met the protocol criteria for a DLT, thus requiring expansion of the cohort.

These same criteria will be applied in the event IRRs occur on the extended infusion schedule. In such a case, the duration of infusion for subsequent patients entered to the trial will be further extended by 30 minutes (or longer, if indicated).

6.5.3.6 Schedule

Study drug is to be administered once Q2W on Day 1 and Day 15 of each cycle (4 weeks [28 days] equals 1 dosing cycle).

EOC1 assessments are to be performed on C1/D28 (± 2 days). Subsequent cycles may be administered Q2W (± 2 days), unless further delay is required to allow for amelioration of toxicities (or in the event of scheduling difficulties associated with weekends, holidays, etc.).

6.5.4 Premedication

Since the mechanism of action of the study drug is to stimulate the immune system, premedication with agents such as glucocorticoids which are immunosuppressive is to be avoided. As a result, no premedication is required to be administered prior to patients receiving the first dose of study drug.

In patients with a history of IRRs to mAbs or similar products, it is recommended that premedication be administered. In such cases, patients should be premedicated with a regimen that includes acetaminophen as well as an H1 (e.g., diphenhydramine/hydroxyzine) and possibly an H2-antagonist (e.g., ranitidine/famotidine).

Should a patient experience an IRR while on study, guidelines for instituting premedication prior to subsequent infusions are provided (**Section 8.4.3**). Guidelines for the grading and management of IRRs of all severities are also provided (**Appendix 9**).

6.6 Cycle 1

A minimum of 1 cycle of study drug will be administered, if tolerated. Any delays in dosing and the reasons for such delays must be documented. If an AE is the cause for dosing delay, it must be detailed on the Adverse Events page of the CRF.

Determinations regarding cohort escalation and MTD will be based on the toxicities observed during this 4-week period (Cycle 1) of treatment, and the occurrence of DLTs* thought to be related (i.e., possibly-related, probably-related, or related) to study drug.

- Patients completing Cycle 1, and receiving their full planned doses of study drug in the absence of a DLT, will be considered to have tolerated the dose level they were assigned to receive.
- Patients will be replaced if they have received < 2 full doses of study drug plus follow-up through EOC1 (C1/D28 ± 2 days) for any reason other than a DLT, to ensure MTD determination rules can be followed with an adequate number of evaluable patients in any dose cohort.
- All treated patients will be considered in the assessment of safety and tolerability.

See **Section 6.8.3 and **Section 6.9***

6.6.1 Rules for Dose-Escalation and Cohort Expansion

Initially, a modified, accelerated-titration, dose-escalation design will be used with entry of single patient cohorts for up to 2 dose levels, based on tolerability.

Thereafter, a standard 3+3 dose-escalation design will be used, with a target toxicity level of 33.3% or less as determined by DLTs.

Dose cohorts will be filled sequentially. Up to 6 patients may be treated at each dose level until the MTD and/or RP2D is determined. The decision rules for dose-escalation and cohort expansion are as follows:

1. A minimum of 1 patient will be entered into dose Cohorts 1 and 2 ONLY.
    - If during the initial 2 weeks of Cycle 1 no ≥ Grade 2 toxicity considered possibly-, probably-, or related to study drug is encountered in the patient, dose-escalation may continue to the next level when the patient has been followed for safety until C1/D15
    - If at any time during Cycle 1, a patient experiences a ≥ Grade 2 toxicity considered possibly-, probably-, or related to study drug, the cohort will be expanded to 3 patients
    - If during Cycle 1, a patient experiences a DLT considered possibly-, probably-, or related to study drug, the cohort will be expanded to 6 patients
2. Beginning with Cohort 3, or earlier if required by observed toxicity, a minimum of 3 patients will be entered to each cohort.
    - If during Cycle 1 no DLTs are encountered in any of the first 3 patients, dose-escalation may continue to the next level when all patients have completed Cycle 1.
    - If during Cycle 1, any 1 patient experiences a DLT considered possibly-, probably-, or related to study drug, the cohort will be expanded to 6 patients. If no DLTs are encountered in the additional 3 patients, dose-escalation may continue to the next level when all patients have completed and tolerated Cycle 1.

- If during Cycle 1, >1 patient experiences a DLT, dose-escalation will STOP. *This will indicate that the MTD has been exceeded.*

3. If it is determined that a dose level is not tolerated:
    - The previous lower dose cohort will be expanded to 6 patients (if this has not already been accomplished) as a total of 6 patients must be treated before establishing a dose as the MTD.
    - There is also the potential to evaluate and expand a previously unplanned intermediate dose level between 2 established dose levels to 6 patients to more fully characterize tolerability.
4. The MTD will be the highest dose level of study drug at which no more than 1 of 6 evaluable patients has had a DLT.
5. Once the MTD (or maximum dose to be studied) is achieved and/or the RP2D is identified, that cohort may be expanded up to 12 patients to more fully evaluate safety and tolerability at that dose level at the Sponsor's discretion. Should the DLT rate equal or exceed 33.3% in an expanded cohort, it will be determined that the dose is not tolerated. If this occurs, the previous lower dose cohort or an intermediate dose level may be expanded as above. Therefore:
    - There is potential for expansion of a lower dose cohort(s) if an initially identified MTD and/or RP2D is subsequently determined not to be tolerated (either with single or repeat cycles of therapy), and
    - There is potential to evaluate and expand a previously unplanned intermediate dose level(s) between 2 established dose levels to more fully characterize tolerability.

        Note: Such action would be taken by the Sponsor (or designee) in the event of an unacceptably high frequency of toxicities observed in patients treated at one dose level considered to be in marked contrast to the tolerability noted in the immediately preceding dose cohort, or if after review of study data, a more gradual dose-escalation appears warranted.

The RP2D may be equal to or lower than the MTD or the MAD. The RP2D will be selected based on safety data, as well as available PK, pharmacodynamic/biomarker, and other data, as applicable.

6.6.2 Rules for Duration of Exposure Prior to Start of Next Patient and Next Cohort

Single patient cohorts: Dose-escalation and accrual to the next cohort will occur only after the patient has completed and tolerated the first dose of Cycle 1 including follow-up until C1/D15 to allow for review of clinical and laboratory assessments, and consultation with the Study Safety Team. **The DLT evaluation period for single patient cohorts will continue through to the EOC1.**

The following rules apply to single patient cohorts throughout the Cycle 1 DLT evaluation period (Cohort 1 and 2 only, receiving treatment at the lowest doses of 0.03 and 0.1 mg/kg, respectively):

- Should a patient experience an AE of concern in the latter half of Cycle 1 that would, per protocol, result in cohort expansion, protocol rules as outlined herein will be followed (**Section 6.6.1**). For example, in the event of a ≥ Grade 2 toxicity, the cohort (and all cohorts thereafter) will be expanded to 3 patients; in the event of a DLT the cohort will be expanded to 6 patients.
- Additional patients entered to an expanded single patient cohort will follow rules as outlined below for 3+3 patient cohorts. Enrollment will be staggered by at minimum 2 weeks between the first and second patient, Thereafter, patients within a cohort may be added concurrently.
- If in the meantime, if a patient has been entered to receive the next higher dose level, that patient will be allowed to continue provided adequate tolerability is being demonstrated; however, further enrollment to the higher dose level cohort will be halted until the lower dose level cohort has been fully expanded and evaluated.

3+3 patient cohorts: Enrollment will be staggered by 2 weeks between the first and second patient in each new higher 3+3 dose level cohort. The first patient within a cohort must complete and tolerate the first dose of Cycle 1 including follow-up until C1/D15 to allow for review of clinical and laboratory assessments. Thereafter, patients within a cohort may be added concurrently.

All cohorts: Dose-escalation and accrual to the next cohort will occur only after the minimum number of patients required for tolerability assessment in the current cohort have completed until C1/D15 in a single patient cohort, or completed Cycle 1 in a 3+3 patient cohort, and only after acceptable tolerance has been demonstrated in at least 1 of 1, 3 of 3, or 5 of 6 patients treated in the current cohort (depending on cohort size), and after consultation with the Study Safety Team.

For all patients, EOC1 assessments are to be performed no sooner than C1/D28 (± 2 days).

6.6.3 Rules for Establishing the MTD and/or RP2D

The MTD will be the highest dose level of study drug at which no more than 1 of 6 evaluable patients has had a DLT.

The MAD, MTD, or a dose lower than the MAD or MTD, will be identified as the RP2D, provided a minimum of 6 patients have been treated at that dose, and provided acceptable tolerance has been demonstrated in at least 5 of 6 patients treated. The RP2D choice will be based on the MTD evaluation as well as other toxicities observed in the study, including observations in later cycles of administration of study drug, as well as on PK, pharmacodynamics/biomarkers, and/or other data.

6.6.4 Rules for Stopping the Study

The study will be stopped if the MTD is exceeded at the lowest dose level.

6.7 Continued Treatment After Cycle 1

Upon completion of Cycle 1, in the absence of unacceptable toxicity or documented PD, patients may continue to receive additional cycles of study drug, unless further delay is required to allow for amelioration of ongoing AEs.

Administration of subsequent dosing cycles is allowable at the discretion of the Investigator, provided the patient meets the retreatment criteria listed below. Additional cycles should be initiated as soon as possible, but not longer than 2 weeks after the completion of the previous cycle, if feasible.

6.7.1 Retreatment Guidelines

Clinical judgment will be used when determining whether it is advisable to continue a patient on to the next cycle(s) of dosing. To start any new cycle, a patient must meet the following criteria:

- ANC ≥ 1,000 per mm^3
- Platelets ≥ 75,000 per mm^3
- Any ongoing study drug-related AE should NOT meet the criteria for DLT
- Any ongoing study drug-related AE should have either ameliorated to ≤ Grade 1 severity, returned to baseline status, or resolved, with the exceptions of:
    - Grade 2 alopecia,
    - Grade 2 clinical events that are being adequately controlled with best supportive care (e.g., fatigue, nausea, vomiting, diarrhea), and
    - Grade 2 asymptomatic laboratory abnormalities that are considered clinically insignificant, clinically uncomplicated, and/or that are resolving spontaneously or with conventional medical interventions.
- Dosing must be delayed in patients with evidence of Grade 2 immune-mediated toxicities, including (**Appendix 10**):
    - Pneumonitis, myocarditis, adrenal insufficiency, encephalitis, nephritis/renal dysfunction (serum creatinine elevation), episcleritis/uveitis/iritis
    - Colitis, hypophysitis, hyperglycemia, inflammatory arthritis, myositis, rash
    - Hepatitis (transaminitis, total bilirubin elevation)

Note: Patients may receive standard doses of replacement hormonal therapy for adrenal insufficiency, hypothyroidism, or other endocrine end-organ failure, and may resume study drug once considered by the Investigator to be stable on such therapy provided a DLT criterion has not been met.

Should above criteria not be met, dosing must be delayed until further evaluation is completed and it is determined that the patient is eligible for continued treatment.

6.7.2 Doses and Regimens

For a given patient, subsequent cycles of therapy with study drug will be administered at the same dose level* and infusion duration established for the patient, and on the same Q2W schedule.

** Unless a dose adjustment is necessary due to ± 10% fluctuation in patient weight (less at the site's discretion or if required by institution procedures)*

6.7.3 Evaluation Schedules

The same evaluations required during Cycle 1 of the study will be conducted during subsequent cycles, at the frequencies indicated (**Section 7**).

6.7.4 Duration of Treatment

Additional cycles of study drug may continue to be administered if tolerated and in the absence of documented PD, at the Investigator's discretion, provided retreatment criteria have been met (**Section 6.7.1**).

Such extended therapy will continue for a period of up to 12 months after achieving the "best response," at which time the Medical Monitor(s) and Investigator will discuss the advisability of continued therapy based upon the patient's ongoing response status and the degree of demonstrated tolerability. Patients who stop therapy with an ongoing OR or prolonged SD may be retreated in the event of relapse, if the trial is still open (**Section 6.7.6**).

6.7.5 Continued Treatment after Radiologic Disease Progression

Immunotherapeutic agents may produce antitumor effects that can manifest as response after initial evidence of PD, a phenomenon referred to as "pseudoprogression" (PSPD).

Patients will be permitted to continue treatment beyond initial RECIST v1.1 (or RECIL 2017) defined PD while waiting for confirmation of PD, provided they are clinically stable as defined by the following criteria (per iRECIST):

- Investigator-assessed clinical benefit and absence of rapid disease progression
- Tolerating study drug
- Stable PS
- Absence of progressive tumor at critical anatomical sites (e.g., cord compression) requiring urgent alternative medical intervention.

6.7.6 Retreatment Following an Objective Response

Treatment with study drug may be restarted in a patient who previously achieved a documented OR or prolonged SD (> 16 weeks) on this study, stopped treatment, and subsequently progresses. Such action may be taken at the Investigator's discretion, following discussion with the Medical Monitor(s), provided retreatment criteria are met, no anti-cancer treatment was administered since the last dose of study drug, and the trial is still open.

This option for retreatment does not apply to patients who previously experienced a DLT that required permanent discontinuation from study drug (**Section 6.8.3**, **Section 9.1**).

Retreatment with study drug may be initiated at the same dose and infusion duration established for that patient during their previous course of treatment, and on the same schedule.

The same evaluations required during previous treatment will be conducted during subsequent cycles, at the frequencies indicated.

Retreatment cycles of study drug may continue to be administered if tolerated and in the absence of further PD, at the Investigator's discretion, as long as retreatment criteria continue to be met.

6.8 Adverse Events and Dose-Limiting Toxicities

6.8.1 Adverse Event Grading

For reported AEs, the CTCAE v5.0* will be used to grade the severity or the AE.

**See < https://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm >*

6.8.2 Management of Dose-Limiting Toxicities and Other Toxicities

If a significant toxicity thought to be related to study drug is experienced at any point during the patient's participation in the study, the Investigator will determine:

- Whether that toxicity is dose-limiting (**Section 6.8.3**), thus requiring discontinuation from study treatment, without exception.
- Whether the toxicity does not meet the protocol definition of DLT, but nevertheless warrants dose modification, in which case the Investigator may elect to temporarily delay dosing with study drug to allow for amelioration of the toxicity.

For additional information on toxicity management and dose modification, see **Section 8**.

6.8.3 Definition of Dose-Limiting Toxicity

Any of the following toxicities occurring during Cycle 1, if judged to be related to study drug (i.e., possibly-related, probably-related, or related), will be considered a DLT for the purposes of tolerability assessment during this trial.

1. ≥ Grade 3 evidence of any of the following immune-mediated toxicities:
    - Pneumonitis
    - Myocarditis
    - Adrenal insufficiency
    - Encephalitis
    - Nephritis, renal dysfunction (serum creatinine elevation)
    - Episcleritis, uveitis, or iritis
2. ≥ Grade 3 evidence of any of the following immune-mediated toxicities:
    - Colitis
    - Hypophysitis, hyperglycemia
    - Inflammatory arthritis
    - Myositis
    - Rash
3. ≥ Grade 2:
    - Uveitis, eye pain or blurred vision that does not resolve with topical therapy within 2 weeks
    - AEs that are prolonged excessively based upon the medical judgment of the investigator, and/or lead to permanent discontinuation of the study drug due to poor tolerance

- Immune-mediated toxicity that requires use of glucocorticoids at a dose of ≥ 1 mg/kg/day of prednisone equivalents for treatment of the toxicity

4. Any confirmed reduction in visual acuity, regardless of grade or duration

   Note: Noted changes in visual acuity must be reevaluated by an ophthalmologist and confirmed within 48 hours *(if feasible, based on weekends or holidays)* of the initial observation; study drug will be held pending evaluation by the ophthalmologist.

   Changes in visual acuity assessment, if associated with either an immune-related AE, including but not limited to iritis, episcleritis, uveitis, or any other condition that may be considered to be related to therapy with study drug will be considered to be a DLT.

   Patients in whom a minor fluctuation in visual acuity is due to another known or recently diagnosed underlying condition may continue to be treated once visual acuity fluctuation returns to baseline status, but must be reevaluated by an ophthalmologist prior to each cycle and upon the occurrence of any subsequent ophthalmologic sign or symptom, including but not limited to recurrent changes in visual acuity measurement, in order to reassess for DLT status.

5. Hepatic-related findings consistent with Hy's Law criteria:
   - AST and/or ALT elevation > 3 × ULN (or > 3 × baseline if elevated at study entry due to hepatic involvement by tumor), with
   - Total bilirubin ≥ 2 × ULN without initial findings of cholestasis (i.e., serum alkaline phosphatase [ALP] < 2 × ULN), and
   - No explanation for the above findings such as viral hepatic injury, preexisting or acute liver disease, or another drug or condition capable of causing the observed liver injury

6. Any other ≥ Grade 3 non-hematologic toxicity regardless of duration, with the exceptions of:
   - Grade 3 fatigue
   - Grade 3 nausea, vomiting, or diarrhea lasting ≤ 2 days with best supportive care
   - Grade 3 asymptomatic electrolyte abnormalities lasting ≤ 3 days that are not clinically complicated, and resolve spontaneously or respond to conventional medical interventions
   - Other Grade 3 asymptomatic laboratory abnormalities that are clinically non-significant in the investigator's opinion, and that resolve spontaneously or with conventional medical interventions

7. Any Grade 4 non-hematologic laboratory toxicity regardless of duration
8. Neutropenia that is:

- Grade 3 meeting the CTCAE v5.0 criteria for febrile neutropenia (ANC < 1000 per mm^3 and a single temperature > 38.3ºC [101ºF] or sustained temperature ≥ 38ºC [100.4ºF] for > 1 hour)
- Grade 4

9. Thrombocytopenia that is:
    - Grade 3 with CS hemorrhage or requirement for transfusion
    - Grade 4 (platelets < 25,000 per mm^3)
10. Anemia that is Grade 4 and not explained by underlying disease
11. Any other Grade 4 hematologic toxicity (other than those specifically excluded) lasting > 5 days
12. Any death where a relationship to study drug cannot be ruled out
13. Inability to complete Cycle 1 at the assigned dose (i.e., receipt of < 2 full planned doses of study drug plus 2 weeks of follow-up) due to any toxicity
14. Treatment delays > 2 weeks from the scheduled next dose during Cycle 1 due to any toxicity

Other toxicities may be considered a DLT as determined by the Investigator in conjunction with the Study Safety Team.

The above criteria will be used to make individual patient determinations regarding dose delays or discontinuation throughout the course of the trial; however, **only those DLTs occurring during Cycle 1 will be used to make decisions regarding cohort dose-escalation and tolerability.**

Events occurring after Cycle 1 will also be evaluated by the Study Safety Team and taken into consideration when deciding upon further doses to be assessed as well as to establish the RP2D.

6.9 Definition of Maximum Tolerated Dose

MTD will be defined as the dose below that which produces, during Cycle 1 of treatment, any of the indicated DLTs either in > 1 patient in a 3 to 6 patient cohort, or in ≥ 33.3% of patients in the event of an expanded 7 to 12 patient cohort.

The MTD will not be established until all patients in the cohort under evaluation have either completed Cycle 1 or discontinued further participation in the trial due to the occurrence of a DLT.

Previously established tolerability of a dose level will be reevaluated if DLTs thought to be possibly-, probably-, or related to study drug are observed in later cycles or in the event of expansion of a cohort to > 6 patients.

6.10 Review of Safety Data During Study

Clinical and laboratory safety data will be reviewed on an ongoing basis throughout the study by the Investigators and Sponsor's Representative(s) so that decisions regarding the advisability of

continuing accrual to a dose cohort, and/or escalating the dose and allowing accrual to a higher dose cohort may be made. In addition, patients will be carefully evaluated for evidence of potential cumulative and/or delayed toxicities throughout the duration of their time on study.

To do so, SAEs, immune-related AEs of significance, AEs resulting in permanent discontinuation from study (regardless of seriousness or relationship to study drug), DLTs, IRRs, and dosing delays will be promptly reported to the Sponsor (or designee).

A Study Safety Team will be established and will be comprised of the Investigator(s) and the Sponsor's Medical Representative(s). Biweekly Study Safety Team Teleconferences will be held to discuss ongoing patient status and any emerging safety concerns; frequency of teleconferences may fluctuate based on accrual and study activity, as indicated (**Section 12.1**).

6.11 Duration of Study Follow-Up

Upon discontinuation of a patient from further treatment with study drug, every effort will be made to conduct follow-up assessments as detailed below.

For patients continuing to another therapy, the expectation is that Investigators will show due diligence in obtaining adequate follow-up for this study, as indicated. In the event of ongoing toxicities, Investigators will do their best to continue patient follow-up, based on both patient availability and Investigator ability to determine the etiology of noted toxicities within the context of initiation of any new therapy (i.e., whether the finding is due to study drug or due to the other therapy).

- End of Treatment (EOT) evaluations will be conducted within approximately 10 days following treatment discontinuation, or before initiation of a new treatment, whichever occurs first.
- 1-Month Follow-up (1M FUP) evaluations will be conducted approximately 30 days (+7 days) following the last dose of study drug.

  Note: The 1M FUP evaluation should be conducted ≥ 30 days following the last dose of study drug as all patients are to be followed for a minimum of 30 days after study drug discontinuation to monitor for the occurrence of suspected AEs that are both serious and unexpected.

- Long-Term Follow-up (FUP) for Safety: If an observed toxicity (non-immune-mediated) thought to be related to study drug has not resolved by the 1M FUP evaluation, an additional FUP AE assessment will be conducted approximately 2 months (may be repeated at 4 months if needed) following the last dose of study drug, if feasible, to confirm that the event has either resolved, returned to baseline status, or been adequately explained and assessed by the Investigator as chronic and/or stable, and that no long-term deleterious effects have become evident*

  Since late-occurring immune-mediated toxicities have been reported to occur several weeks to months after treatment with other immune checkpoint inhibitors, long-term surveillance for such toxicities will be conducted in this study. Patients will be followed at approximately 2-month intervals following the last dose of study drug for up to 6 months to assess for the onset of any post-therapy immune-mediated event thought to be related to study drug.*

Any patient who develops an immune-mediated toxicity during study, or during the 6-month post-therapy FUP period, will be followed at approximately 2-month intervals following the last dose of study drug for up to 2 years to assess the course of the condition and evaluate potential reversibility of the finding.*

**Investigator discretion may be used with respect to the method of contact for this AE assessment; clinical events may be followed in writing or by telephone; an in-person visit will not be required.*

- Long-Term FUP for Response: In the event of an ongoing OR or SD at the EOT, response assessment-based imaging studies (as indicated by disease type) will continue to be performed every 2 months following the last dose of study drug, until confirmed PD or another therapeutic intervention is initiated, so that data may be collected on the duration of SD or OR, as well as disease progression*

  **To continue at the intervals specified until disease progression or another therapeutic intervention is initiated, or until the end of trial; documentation may be submitted in writing or by e-mail, an in-person visit will not be required.*

6.12 Concurrent Treatments and Supportive Care

Therapy for other ongoing medical conditions, as well as palliative and supportive care for the underlying malignancy will be provided prior to and during this trial, as clinically indicated, and in accordance with the standard practices of the institution, except as stipulated by study eligibility criteria (**Section 4.3.2**).

Other therapies allowed during the conduct of this trial include:

1. Prophylaxis for IRRs and Study Drug-Related Toxicities: Patients with a history of IRRs to mAbs or similar products, and patients who experience IRRs while on study, should receive premedication with standard therapies as defined herein prior to each dose of study drug to reduce the risk of such events. Patients experiencing other study drug-related reactions may be premedicated with standard therapies to reduce the potential for such reactions in the future (**Section 8.4**).

2. Treatment of Study Drug-Related AEs or Concurrent Diseases: Clinical judgment should be used in the treatment of any treatment-related AEs or concurrent diseases that occurs during the study and follow-up period.

3. Blood Products and Growth Factors: Prophylactic hematopoietic growth factors should not be administered during Cycle 1 of study; thereafter prophylactic use of growth factors is allowed as clinically indicated. Interventional/therapeutic use of growth factors is allowed during study, including Cycle 1, if deemed necessary by the Investigator. Growth factor use must be consistent with product package insert instructions.

4. Radiotherapy: Radiotherapy for pain control against non-target lesions, provided it does not influence BM function. Such treatment should be discussed with the Sponsor's Medical Monitor(s).

5. Bisphosphonates and denosumab: Bisphosphonates and denosumab for bone metastases and other skeletal conditions are allowed, provided the patient is on a stable dose for at least 2 months prior to study start and remains on the stable dose while receiving study treatment.

6. Immunosuppressive or systemic hormonal therapy not exceeding 10 mg daily prednisone equivalent, as well as:

    - Hormonal therapy for appetite stimulation (e.g., Megace)
    - Nasal, ophthalmic, inhaled, and topical glucocorticoid preparations
    - Hormone replacement therapy at standard doses for end-organ failure
    - Stable hormonal therapy for prostate carcinoma*
    - Stable hormonal therapy for ovarian suppression, hormonal contraceptive therapy, or post-menopausal HRT*
    - Steroid therapy for contrast reaction prophylaxis
    - Intra-articular steroid injections
    - Low-dose maintenance steroid therapy for other conditions (e.g., asthma exacerbation, stable steroid therapy [excluding tapering dose of steroids] for brain edema/metastases/radiation)
    - Higher dose steroid therapy for treatment of an acute intercurrent illness (e.g., immune-related AEs or other adverse conditions) in patients with SD or an ongoing response. In such situations study drug treatment should be interrupted for the duration of immunosuppressive therapy.

    **Concomitant therapies are permitted; however, patients must have been on a stable dose for at least 6 months prior to study start, and if continuing must remain on the stable dose while receiving study treatment (i.e., such treatment will not be considered as systemic hormonal therapy for the purpose of study eligibility).*

Information on all concomitant therapies administered, as well as other interventions or procedures occurring during the trial period, must be recorded on the appropriate page of the patient's CRF.

7 STUDY ASSESSMENTS

All patients will be assessed by scheduled clinical, laboratory, and other diagnostic assessments throughout the study. All efforts should be made to perform assessments as close as possible to the scheduled timepoints. The projection of visit days within each cycle should be made from Day 1 of the respective cycle. Visit windows are provided below. Study assessments are to be performed as follows:

- Screening evaluations are to be performed within 14 days prior to first study drug dose, unless otherwise specified (for exceptions see **Section 7.2.7.6**, **Section 7.3**, **Section 7.4**).
- The day of first administration of study drug will be considered Day 1 of study.
- C1/D3 evaluations may be conducted +1 day.
- On-study evaluations (including laboratory assessments) are to be performed on or about the indicated study day (i.e., ± 2 working days) (*a slightly longer allowance for routine assessments is permissible in the event of scheduling difficulties associated with weekends, holidays, etc.*).
- End of Cycle assessments may be conducted at any time during the week prior to Day 1 of the next cycle, including on Day 1 of the next cycle, prior to dosing.
- EOT* evaluations are to be performed within approximately 10 days following treatment discontinuation, or before initiation of a new treatment, whichever occurs first.
- 1M FUP* evaluations are to be performed approximately 30 days (+7 days) following the last dose of study drug (i.e., as all patients are to be followed for a minimum of 30 days after study drug discontinuation to monitor for the occurrence of AEs).

  Note: When a patient discontinues treatment with study drug, for any reason, every effort will be made to collect routine EOT evaluations as well as subsequent 1M FUP evaluations, per protocol, until all protocol-specified assessments have been conducted.

If during the study, significant changes from baseline are noted, additional monitoring or on-study assessments may be undertaken by the Investigator, or requested by the Sponsor (or designee), to determine both the relevance of the finding(s) and the duration of the event(s).

Refer to **Appendix 11** and **Appendix 12** for the maximum total blood collection volumes and the schedule of assessments, respectively.

7.1 Consent and Medical History

7.1.1 Signing of Informed Consent/Assessment of Eligibility

- Screening

Note: All patients must sign an IRB/EC-approved informed consent form (ICF) prior to enrollment and prior to submitting to any protocol-related procedure, unless such testing was performed previously as part of the routine clinical management of the patient. Disease evaluations (e.g., computed tomography [CT] scan, magnetic resonance imaging [MRI]) performed as part of standard of care and obtained prior to patient consent for this trial may be allowed as screening evaluations if conducted within 28

days (+2) prior to the first study drug dose. A copy of the fully executed ICF will be given to the patient.

7.1.2 Demography

(To include date of birth, sex, race, and ethnicity)

- Screening

7.1.3 Past Medical History

(To include prior and ongoing medical illnesses and conditions, prior surgical procedures [not related to the primary diagnosis])

- Screening
- C1/D1 (prior to dosing)*

** Need not be assessed prior to Cycle 1 if ≤ 7 days since screening*

7.1.4 History of the Primary Malignancy

(To include details of the primary malignancy, including: diagnosis and histological/ cytological classification; date of initial diagnosis; date metastatic disease is identified; stage of disease at entry; current sites of metastases; prior surgical procedures for the malignancy and dates; prior antineoplastic therapy; prior radiation therapy; dates of treatments, numbers of cycles, and best response to each therapy; and date of most recent disease progression)

- Screening

7.2 Safety Assessments (1)

(To be performed within 14 days prior to first dose of study drug unless otherwise specified)

7.2.1 Medication and Procedure Surveys

(To include all medications taken other than study drug and all procedures performed during trial. For medications: Include name, indication for use, route of administration, start and stop dates or if ongoing at 1M FUP Visit. For procedures: Include date and reason for procedure. Corresponding illness or condition must appear on the Medical History or Adverse Event pages of the CRF, as appropriate)

- Prior Medication/Procedure Surveys
  - Screening (to assess eligibility)
  - For 14 days prior to first study drug dose
- Concomitant Medication/Procedure Surveys
  - Throughout the study
  - For 30 days following last study drug dose

7.2.2 Adverse Event Reporting

- Starting from signing of informed consent*

- Throughout the study
- For 30 days following last study drug dose
- Long-Term FUP for Safety
  - For AEs (non-immune-mediated) ongoing at the 1M FUP
    - For 2 to 4 months following last study drug dose, if events related to study drug persist**#
  - For immune-mediated toxicity surveillance following 1M FUP
    - For up to 6 months (at 2-month intervals) following the last study drug dose, to assess for delayed onset of immune-related toxicity***#
  - For immune-mediated toxicity ongoing at the 1M FUP, and for delayed onset immune-mediated toxicity noted in the initial 6-month FUP period
    - For up to 2 years (at 2-month intervals) following the last study drug dose***#
- As clinically indicated

**To detail any symptoms that may be present prior to first study drug dose. Patients who sign informed consent and are subsequently deemed to be screen failures will be followed for the occurrence of SAEs/AEs until it is determined that they will not be participating in the trial.*

***To confirm that events have resolved, returned to baseline status, or been adequately explained.*

**** Patients will be followed to assess for the onset of any post-therapy immune-mediated event thought to be related to study drug. Any patient who develops an immune-mediated toxicity during study, or during the 6-month post-therapy FUP period, will be followed to assess the course of the disease and evaluate potential reversibility of the finding.*

#Investigator discretion may be used with respect to the method of contact for this AE assessment; clinical events may be followed in writing or by telephone; an in-person visit will not be required.

7.2.3 Dose-Limiting Toxicity Assessment

*(To include details about AEs meeting DLT criteria; **Section 6.8.3**)*

- Starting from first dose of study drug (C1/D1)
- Through EOC1 (C1/D28 ± 2 days)

7.2.4 Performance Status Evaluation

*(To be assessed by ECOG score; **Appendix 1**)*

- Screening
- Cycle 1
  - Day 1 (within ≤ 7 working days prior to dosing)*
- Each cycle thereafter
  - Day 1 (prior to dosing)
- EOT
- 1M FUP
- As clinically indicated

**Need not be assessed prior to the first dose of Cycle 1 if ≤ 7 days since screening*

7.2.5 Vital Signs

(Vital signs [VS] to include temperature, pulse, respiratory rate, blood pressure [BP], and oxygen saturation by pulse oximetry)

- Screening
- Cycle 1
  - Day 1
    - Prior to SOI
    - End of infusion (EOI) (± 10 min)
    - 2, 4 hours after EOI (± 30 min)
    - 8 hours* after EOI (± 90 min)
  - Day 2 (24 hours after EOI) (± 6 hours)
  - Day 3 (48 hours after EOI) (- 12 to + 24 hours)
  - Day 15
    - Prior to SOI
    - EOI (± 10 min)
- Each cycle thereafter
  - Day 1 (prior to dosing)
- EOT
- 1M FUP
- As clinically indicated

**Comprehensive assessment of VS is critical to the conduct of this study. In situations where an assessment at 8 hours after EOI is logistically difficult due to clinic staff availability, the observation period may be shortened, and an "end of day" assessment may be obtained at the latest practical time. Such an option (if to be routinely employed) is available only after discussion with and approval by the Sponsor.*

Note: C1/D1 through C1/D3 window allowances align with PK timepoints windows

7.2.6 Physical Examination

*(Complete at screening including height, weight, general appearance, skin, head, eyes, ears, nose, throat, neck/thyroid, chest [includes pulmonary assessment, breasts], cardiovascular [includes heart, peripheral pulses] abdomen, musculoskeletal system, lymph nodes, neurologic and mental status; directed thereafter, must include weight** and pulmonary and cardiac assessments*** at each physical exam)*

- Screening
- Cycle 1
  - Day 1 (within ≤ 7 working days prior to dosing)*
- Each cycle thereafter
  - Day 1 (prior to dosing)
- EOT
- 1M FUP
- As clinically indicated

** Need not be assessed prior to the first dose of Cycle 1 if ≤ 7 days since screening*

*** Dose adjustments may be made in the event of noted weight change (± 10% [less at the site's discretion or if required by institution procedures]).*

**** Pulmonary and cardiac findings will be evaluated in detail at each visit by the Principal Investigator (or physician designee); evaluation to include review of pulmonary symptoms including but not limited to: cough, sputum production, hemoptysis, wheezing, dyspnea, dyspnea on exertion, chest pain, and/or chest pain associated with respirations, as well as review of cardiac symptoms including but not limited to chest pain, orthopnea, nocturia, edema, and palpitations*

7.2.7 Laboratory Assessments and Pregnancy Test

All routine laboratory analyses will be performed at a laboratory facility local to the trial site.

Sponsor (or designee) must be provided with trial site laboratory normal ranges for all required parameters prior to screening of the first patient at the site. Likewise, any change in laboratory normal ranges during the trial should be forwarded to the Sponsor (or designee) promptly during the trial.

Blood samples will be taken at the scheduled visits and analyzed for the following parameters as clinically indicated (**Table 2**, **Appendix 12**). Results must be available and assessed prior to dosing of study drug, when sampling is scheduled on days of dosing.

Table 2: Schedule of Safety Blood and Urine Sampling

Sample Analysis	Screening	Cycle 1				Cycles Thereafter		EOT	1M FUP
		D1	D3 D8	D15	D22	D1	D15		
Hematology Panel	X	X[1]	X	X	X	X	X	X	X
Biochemistry Panel	X	X[1]	X	X	X	X	X	X	X
Coagulation Panel	X	X[1]		X		X		X	X
Thyroid Function Tests	X	X[1]				X		X	X
Urinalysis	X	X[1]		X		X		X	X
Pregnancy Test	X	X						X	

Abbreviations (in alphabetical order): D, day; EOT, end of treatment; 1M FUP, 1-month follow-up
1) Does not need to be performed prior to C1/D1, if performed during screening ≤7 days from C1/D1

7.2.7.1 Hematology Panel

(To include complete blood count [CBC] with hemoglobin, hematocrit, differential, ANC, and platelet count)

- Screening
- Cycle 1
  - Day 1 (within ≤ 7 working days prior to dosing)*
  - Day 3 (+1 day)
  - Day 8
  - Day 15 (prior to dosing)
  - Day 22
- Each cycle thereafter

  - Day 1 (prior to dosing)
  - Day 15 (prior to dosing)
- EOT
- 1M FUP
- As clinically indicated**

**Need not be performed prior to the first dose of Cycle 1 if ≤ 7 days since screening*

***In the event of hematologic toxicity, the evaluation frequency should be increased to include additional evaluations between the scheduled assessments, as clinically indicated.*

7.2.7.2 Biochemistry Panel

*(Fasting not required; to include sodium [Na], potassium [K], chloride [Cl], bicarbonate or carbon dioxide, blood urea nitrogen [BUN], creatinine, glucose, bilirubin [total and direct], AST, ALT, ALP, calcium [Ca], magnesium [Mg], phosphorus, albumin, total protein, uric acid, amylase, lipase, and creatine kinase [CK]***)*

- Screening
- Cycle 1
  - Day 1 (within ≤ 7 working days prior to dosing)*
  - Day 3 (+ 1 day)
  - Day 8
  - Day 15 (prior to dosing)
  - Day 22
- Each cycle thereafter
  - Day 1 (prior to dosing)
  - Day 15 (prior to dosing)
- EOT
- 1M FUP
- As clinically indicated**

**Need not be performed prior to the first dose of Cycle 1 if ≤ 7 days since screening*

***In the event of significant serum chemistry abnormalities, the evaluation frequency should be increased to include additional evaluations between the scheduled assessments, as clinically indicated. CS electrolyte abnormalities should be corrected prior to dosing.*

****In the event of CK abnormalities while on study, please perform isoenzyme analysis (to include at minimum CK-MB); in the event of ECG abnormalities while on study, please perform isoenzyme analysis (to include at minimum CK-MB), serial troponins, and measurement of brain natriuretic peptide (BNP)*

7.2.7.3 Coagulation Panel

(To include PTT [or aPTT], PT and/or INR)

- Screening
- Cycle 1
  - Day 1 (within ≤ 7 working days prior to dosing)*

- Day 15 (prior to dosing)

- Each cycle thereafter
  - Day 1 (prior to dosing)
- EOT
- 1M FUP
- As clinically indicated

**Need not be performed prior to the first dose of Cycle 1 if ≤ 7 days since screening*

7.2.7.4 Thyroid Function Tests

(To include measurement of thyroid stimulating hormone [TSH], free triiodothyronine [fT3], and free thyroxine [fT4])

- Screening
- Cycle 1
  - Day 1 (within ≤ 7 working days prior to dosing)*
- Each cycle thereafter
  - Day 1 (prior to dosing)
- EOT
- 1M FUP
- As clinically indicated

**Need not be performed prior to the first dose of Cycle 1 if ≤ 7 days since screening*

7.2.7.5 Urinalysis

(Multi-panel chemical test strips are acceptable and should include assessment of specific gravity, pH, protein, glucose, ketones, leukocytes, nitrite, bilirubin, urobilinogen, and blood. Microscopic examination of sediment, if clinically indicated, to include assessment of cells [white blood cells {WBC} per high power field {HPF} and red blood cells {RBC} per HPF] and casts)

- Screening
- Cycle 1
  - Day 1 (within ≤ 7 working days prior to dosing)*
  - Day 15 (prior to dosing)
- Each cycle thereafter
  - Day 1 (prior to dosing)
- EOT
- 1M FUP
- As clinically indicated

**Need not be performed prior to the first dose of Cycle 1 if ≤ 7 days since screening*

7.2.7.6 Pregnancy Testing

(Beta-human chorionic gonadotropin [β-hCG] in WOCBP; serum at screening, serum or urine thereafter; negative test must be confirmed within 2 working days prior to first dose of study drug)

- Screening
- Cycle 1
  - Day 1 (within ≤ 2 working days prior to dosing)
- EOT
- As clinically indicated

7.2.8 Electrocardiogram

(To include standard 12-lead ECG with measurement of PR interval, QRS duration, QT interval, and QTc interval [msec], as well as HR [beats per minute {BPM}])

(To be evaluated locally; to be performed after patient has been supine or semi-recumbent for ≥ 10 minutes) (Repeat subsequent timepoints in triplicate separated by 5 minutes for 4 cycles in patients with a Cycle 1 QTc interval that is either: a) >500 msec; b) increased by 60 msec over baseline; or c) decreased by 20 msec below baseline*) (If abnormalities suggest new evidence of myocardial ischemia, perform isoenzyme analysis [to include at minimum CK-MB], serial troponins, and measurement of BNP)*

- Screening
- Cycle 1
  - Day 1
    - Prior to SOI
    - EOI (+ 15 min)
- Cycle 2
  - Day 1
    - Prior to SOI
    - EOI (+ 15 min)
- Subsequent 4 cycles, if QTc interval abnormalities are observed during Cycle 1 or 2
  - Day 1
    - Prior to SOI (in triplicate)
    - EOI (+ 15 min) (in triplicate)
- EOT
- As clinically indicated**

**When evaluating QTc interval, baseline should be considered the ECG immediate preceding the start of study drug infusion on the day of assessment.*

***In the event of significant electrolyte abnormalities, the evaluation frequency should be increased to include additional evaluations between the scheduled assessments, as clinically indicated.*

7.3 Safety Assessments (2)

(Results from assessments previously performed as standard of care within 28 days [+2 days] prior to first dose of study drug may be utilized, provided no antineoplastic therapy has been delivered between assessment and first dose of study drug; otherwise within 14 days of first dose)

7.3.1 Multi-Gated Acquisition Scan or Echocardiogram

(For measurement of LVEF; to be performed ONLY in patients with a history of CHF; individual patients should be followed with the same testing procedure throughout the study)

- Screening
- EOT
- As clinically indicated

7.3.2 Ophthalmology Examination

(To include funduscopic and slit lamp evaluations for assessment of retinal and corneal integrity, visual acuity as assessed by standardized chart or other appropriate measurement tool, and any other noted ocular abnormality)

- Screening
- EOC1 (visual acuity only; by Snellen chart or similar measurement tool)*
- EOC2 and every even-numbered cycle thereafter*, **
- EOT**
- As clinically indicated

**End of Cycle assessments may be conducted at any time during the week prior to Day 1 of the next cycle, including on Day 1 of the next cycle, prior to dosing. Due to inherent variability of Snellen chart assessments (21), if changes in visual acuity are noted, a thorough ophthalmologic evaluation should be performed within 48 hours (if feasible, based on weekends or holidays) of the initial observation in order to confirm the finding and determine if there is evidence of an immune-mediated AE, or other event that would preclude further treatment with study drug. No patient with any documented decrease in visual acuity will receive further therapy with Sym023 unless the event is considered unrelated to study drug and unless cleared for retreatment by an ophthalmologist.*

***May be combined if patient discontinues treatment at the end of an even-numbered cycle*

7.3.3 Pulmonary Function Tests

(To include spirometry and diffusing capacity of carbon monoxide [DL_{CO}] to assess for evidence of pulmonary fibrosis. Spirometry assessments to include at minimum: forced vital capacity [FVC], forced expiratory volume in 1 second [FEV1], functional residual capacity [FRC], residual volume [RV], and total lung capacity [TLC])

- Screening
- EOT
- As clinically indicated*

*To be repeated if evidence of interstitial pneumonitis, pulmonary fibrosis or other potential evidence of drug-related pulmonary toxicity is documented on imaging studies or if pulmonary symptomatology indicates

7.4 Disease Assessments

(Screening disease assessments to be performed within 28 days [+2 days] prior to first dose of study drug)

Standard response criteria will be applied for disease assessments and response evaluations (RECIST v1.1, **Appendix 5**; iRECIST, **Appendix 6**; and RECIL 2017, **Appendix 7**). Assessments should be performed at the intervals specified and in the event of suspected PD.

If PD and/or initiation of another therapeutic intervention is documented at any time, no further disease assessments will be required. Patients with confirmed PD will be discontinued from further treatment with study drug so that alternative management of their malignancy may be considered.

Duration of OR to be measured from date initial response is observed to date PD is confirmed. To be assigned a status of partial response (PR) or complete response (CR), changes in disease status must be confirmed by repeat studies performed 4 weeks (+7 days) after the criteria for response are first met. In the case of SD, follow-up measurements must have met the SD criteria at least twice after study entry for a minimum duration in general not less than 16 weeks.

In the event of an ongoing OR or SD at the EOT, data will continue to be collected on the duration of OR or SD, as well as on disease progression.

7.4.1 Tumor Marker Measurement

(As indicated by tumor type)

- Screening
- EOC2 and every even-numbered cycle thereafter*
- At least 4 weeks following documentation of an OR
- EOT (if > 6 weeks since previous assessment)
- 1M FUP (if PD was not confirmed before or at EOT)
- Long-Term FUP for Response** *(in the event of an ongoing OR or SD at EOT)*
  - Every 2 months

7.4.2 Diagnostic Imaging for Assessment of Disease (and Pulmonary Status)

The same method(s) of disease evaluation and the same technique should be used throughout the study.

All patients: To include diagnostic imaging by CT or MRI of the chest with each evaluation (for disease evaluation where indicated, and to assess for evidence of pulmonary fibrosis) plus abdomen and pelvis, and other sites as indicated based on tumor type and clinical judgment to assess the status of the underlying malignancy. Use of contrast is preferred but is at the discretion of the Investigator, as medically indicated.

*Lymphoma patients: In addition to above, patients will be followed **as indicated and per Investigator discretion** by: fluorodeoxyglucose-positron emission tomography (FDG-PET), X-ray, ultrasound (U/S), and/or BM aspiration/biopsy (Bx).*

For all imaging timepoints, the following will be recorded as per RECIST v1.1 (or other response criteria, as indicated): target lesions including size, location, and type (nodal/non-nodal); sum of diameters of target lesions; any new lesions noted during trial, including size, location, and type (nodal/non-nodal).

- Screening
- EOC2 and every even-numbered cycle thereafter*
- At least 4 weeks following documentation of an OR
- EOT (if > 6 weeks since previous assessment)
- 1M FUP (if PD was not confirmed before or at EOT)
- Long-Term FUP for Response** *(in the event of an ongoing OR or SD at EOT)*
  - Every 2 months

Imaging data (imaging studies and derived assessments) will be stored according to usual practice by the sites and will be available upon request for potential review by the Sponsor or an independent radiology reviewer.

7.4.3 Response Assessment

(To be assessed by the Investigator or qualified designee as per RECIST v1.1 [or other response criteria, as indicated]; to be noted at each evaluation point as CR, PR, SD, PD, or Not Evaluable [NE])

- EOC2 and every even-numbered cycle thereafter*
- At least 4 weeks following documentation of an OR
- EOT (if > 6 weeks since previous assessment)
- 1M FUP (if PD was not confirmed before or at EOT)
- Long-Term FUP for Response** *(in the event of an ongoing OR or SD at EOT)*
  - Every 2 months

**End of Cycle assessments may be conducted at any time during the week prior to Day 1 of the next cycle, including on Day 1 of the next cycle, prior to dosing.*

*** To continue at the intervals specified until disease progression or another therapeutic intervention is initiated, or until the end of trial; documentation may be submitted in writing, an in-person visit will not be required.*

7.5 Immunogenicity Assessment

To assess formation of ADA. All samples must be taken prior to the study drug infusion of that visit. Analysis of ADA and residual serum levels of study drug will be performed at a central laboratory **(Specialty Lab)**. A detailed laboratory manual specifying sample collection, handling, storage, and shipment will be provided to the trial sites; retention time for specimens will be specified therein. If a collected serum sample is inadequate or insufficient for ADA analysis, the analysis of ADA can be done using a PK serum sample from the same timepoint, if available.

7.5.1 Peripheral Blood for Immunogenicity Assessment (Specialty Lab)

(To assess the potential immunogenicity of study drug; serum to be isolated)

ADA samples will be taken according to the schedule shown (**Table 3**; **Appendix 12**).

Note: Whole blood (~ 5 mL) to be collected in serum acquisition tubes at each of the indicated timepoints.

7.6 Pharmacokinetic Assessments

Every effort will be made to collect PK samples at the timepoints specified. Sampling times may be adjusted according to early trial results to optimize evaluation. No additional samples will be collected without formal amendment to this protocol. Analysis will be performed at a central laboratory **(Specialty Lab)**. A detailed laboratory manual specifying sample collection, handling, storage, and shipment will be provided to the trial sites; retention time for specimens will be specified therein. If a collected serum sample is inadequate or insufficient for PK analysis, the analysis of PK can be done using an ADA serum sample from the same timepoint, if available.

7.6.1 Peripheral Blood for Pharmacokinetic Assessment (Specialty Lab)

(To allow for assessment of parameters such as maximum concentration [C_{max}], trough concentration [T_{max}], area under the concentration-time curve [AUC], etc.; serum to be isolated)

PK samples will be taken according to the schedule shown (**Table 3**; **Appendix 12**).

Note: Whole blood (~ 5 mL) to be collected in serum acquisition tubes at each of the indicated timepoints.

Table 3: ADA and PK Sampling Timepoints

Sample	Sampling Time[3]	Window	Cycle 1				Cycle 2		Cycle 3 onward		EOT	1M FUP	Long-Term FUP *if OR/ SD at EOT (or ongoing critical AE); following PD*	As Clinically Indicated
			D1 - D3	D8	D15	D22	D 1	D15	D 1	D15				
ADA	Prior to SOI	- 4h	X		X		X		Odd # cycles		X	X	X[2]	X
PK	Prior to SOI	- 4h	X		X[1]		X[1]	X[1]	X[1]	X[1]				
	EOI	+ 10 min	X		X[1]		X[1]	X[1]	X[1]	X[1]				
	EOI + 2h	±30 min	X											
	EOI + 4h	±30 min	X											
	EOI + 8h[4]	±90 min	X											
	EOI + 24h	±6h	X											
	EOI + 48h	-12h to + 24h	X											
	During Visit	NA		X		X					X	X	X[2]	

Abbreviations (in alphabetical order): 1M FUP, 1-month follow-up; ADA, anti-drug antibody; AE, adverse event; D, day; EOI, end of infusion; EOT, end of treatment; FUP, follow-up; h, hour; min, minutes; NA, not applicable; OR, objective response; PD, progressive disease; PK, pharmacokinetic; SOI, start of infusion

1) If study drug administration is delayed to another day, only one PK sample should be taken during the visit

2) Collection of samples during Long-Term FUP to continue at 2-month intervals for 6 months (for patients who are available for blood collection)
3) Actual collection times to be recorded in the patient's CRF and/or sampling log
4) Comprehensive collection of clinical samples is critical to the conduct of this study. In situations where collection of the EOI + 8h sample is logistically difficult due to clinic staff availability, the observation period may be shortened, and an "end of day" sample may be obtained at the latest practical time. Such an option (if to be routinely employed) is available only after discussion with and approval by the Sponsor.

7.7 Pharmacodynamic and Other Biomarker Assessments (Specialty Lab)

To assess potential pharmacodynamic and other biomarkers; every effort will be made to collect samples as specified. Analyses will be performed at a central laboratory **(Specialty Lab)**. A detailed laboratory manual specifying sample collection, handling, storage, and shipment will be provided to the trial sites; retention time for specimens will be specified therein.

All analyses will be related to and used only in connection with the data collected in the present trial or other Sym023-related trials, and the identity of the patient will remain confidential. The analyses will not have any medical consequences for the patient or their relatives.

7.7.1 Pharmacodynamic Assessments

(To include peripheral blood collection for evaluation of receptor occupancy)

- Cycle 1
  - Day 1 (prior to dosing)
  - Day 1 (24 hours after dosing ± 6 hours, i.e., Day 2)
  - Day 15 (prior to dosing)
- Cycle 2
  - Day 1 (prior to dosing)
  - Day 15 (after dosing + 0 to 7 days) (at the time of biopsy if performed)
- EOC2* (combined with EOT if patient discontinues treatment prior to or at EOC2)
- End of every 4th cycle thereafter* (i.e., EOC6, EOC10, etc.; may be combined with EOT if patient discontinues treatment)
- EOT
- 1M FUP

Note: Whole blood (~ 10 mL) to be collected at each of the indicated timepoints; handling instructions will be provided.

**End of Cycle assessments may be conducted at any time during the week prior to Day 1 of the next cycle, including on Day 1 of the next cycle, prior to dosing.*

7.7.2 Biomarker Assessments

The purpose of biomarker assessments is to develop an approach for the identification and validation of genes or proteins that may predict which patients are likely to respond to Sym023, and that may change with the possible development of acquired resistance.

Analyses may include genes and/or proteins that are unknown or have not been included in the scientific hypotheses of this trial, but that, during the collection of data from this trial, may emerge as new candidate genes and markers related to Sym023 safety, efficacy, or mechanism of action.

All analyses will be related to and used in connection with the data collected in the present trial and the ongoing and future development of Sym023 as a single drug and in combination. The identity of the patient will remain confidential. The analyses will not have any medical consequences for the patient or their relatives.

Residuals from samples collected will be stored for up to 15 years after completion of the trial, where after all samples will be destroyed.

7.7.2.1 Blood Samples for Biomarker Assessments

(To include peripheral blood collection for evaluation of potential biomarkers, including but not limited to ctDNA, RNA, relevant proteins/cytokines, and cellular biomarkers)

- Screening *(after confirmation of eligibility and study enrollment;* may be collected C1/D1 prior to dosing)
- Cycle 2
    - Day 15 (after dosing + 0 to 7 days) (at the time of biopsy if performed)
- EOT

Note: Whole blood (~ 30 mL) to be collected at each of the indicated timepoints; handling instructions will be provided. For those timepoints where both a blood sample and a tumor biopsy are to be obtained, the blood sample is to be collected first.

7.7.2.2 Tumor Sample for Biomarker Assessment *(Biopsies Optional)*

(To include tumor tissue collection for evaluation of potential biomarkers, including but not limited to DNA, RNA, protein, and cellular biomarkers)

- Screening *(after confirmation of eligibility and study enrollment;* may be collected C1/D1 prior to dosing)
- Cycle 2
    - Day 15 (after dosing + 0 to 7 days) (with paired pharmacodynamic and biomarker peripheral blood)
- EOT at the time of PD for patients with a previous OR or prolonged SD (> 16 weeks)

Note: Tumor tissue for formalin-fixed paraffin-embedding (FFPE) to be collected at each of the indicated timepoints; handling instructions will be provided. For those timepoints where both a blood sample and a tumor biopsy are to be obtained, the blood sample is to be collected first.

Tumor biopsies to include core samples of a locally recurrent or metastatic lesion; to be performed with minimal morbidity to the patient by a percutaneous core needle biopsy either with or without the aid of an imaging modality chosen at the discretion of the physician performing the biopsy.

8 MANAGEMENT OF TOXICITY

Comprehensive assessments of any toxicity experienced by the patient will be performed throughout the course of this study. Anticipated toxicities that may be experienced with study drug are detailed in this protocol (**Section 2.4**, **Section 11**), as well as in the IB.

Grades of toxicity (CTCAE v5.0*), as well as clinical judgment, will be used to determine appropriate management of the patient experiencing any AE while participating in this study.

**See < https://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm >*

8.1 Grading and Recording of Toxicity

Any clinical AE, whether observed by the Investigator, or observed or experienced by the patient, will be reported. Any CS change from baseline in a laboratory assessment will be recorded as an AE. All clinical and laboratory AEs must be carefully evaluated for:

- Severity (Grades 1-5; or mild, moderate, severe, life-threatening, fatal) (**Appendix 3**)*
- Duration
- Relationship to study drug (not-related, unlikely, possible, probable, related) (**Appendix 4**)

**In those cases where further definition of an event is provided by the CTCAE v5.0, please refer to those criteria for grading and severity information.*

This information will be documented on the appropriate page of the CRF.

8.2 Evaluation and Treatment of Toxicity

The Principal Investigator, Sub-Investigator, or designated health professional must be available throughout the course of the study to evaluate and treat any AE(s), as well as to evaluate whether continued participation in the trial is warranted or advisable.

If, at any point during the study, significant changes occur in either the patient's clinical status or laboratory assessments, such changes will be followed until the abnormality either resolves, returns to baseline status, or is adequately explained.

8.3 Determination of DLT versus Non-DLT

Patients will be evaluated throughout the course of the trial for evidence of acute as well as delayed and/or cumulative toxicities.

If a significant toxicity thought to be related to study drug is experienced at any point during the patient's participation in the study, the Investigator will determine whether that toxicity meets the protocol criteria for DLT (**Section 6.8.3**).

If the protocol definition of DLT is met, the patient will be discontinued from study treatment, without exception.

Alternatively, the Investigator may determine that the toxicity does not meet the protocol definition for DLT, but nevertheless warrants dose modification, because it is:

- Not controlled by optimal supportive care, or

- Not tolerated due to symptomatology or interference with normal daily activities

For toxicity that does not meet the protocol definition of DLT, the Investigator may, as described below, elect to prolong the infusion duration (for IRRs), or temporarily delay dosing with study drug, to allow for amelioration of the toxicity.

8.4 Premedication

8.4.1 Infusion-Related Reactions

There is an inherent risk for IRRs with the administration of mAbs. An IRR is defined as an AE occurring during the study drug infusion and up to 24 hours after the EOI, which is assessed by the Investigator to be related to the infusion. Signs and symptoms of IRRs may include but are not limited to:

- facial flushing and swelling
- rash including urticaria
- headache
- fever
- chills, rigors
- diaphoresis
- tachycardia
- hypotension
- nausea
- dry mouth
- chest/back/abdominal pain/discomfort
- chest and throat tightness
- shortness of breath
- cough, wheeze, stridor
- hypoxia
- bronchospasm
- laryngeal edema
- angioedema
- shock

The risk of an IRR is highest for the first administration of a mAb and diminishes with subsequent infusions. If an IRR occurs, it should be classified according to the CTCAE v5.0. Guidelines for the grading and management of IRRs of all severities are provided (**Appendix 9**).

8.4.2 Premedication for IRRs (Prior to the First Dose)

Since the mechanism of action of the study drug is to stimulate the immune system premedication with agents such as glucocorticoids which are immunosuppressive is to be avoided. As a result, no premedication is required to be administered prior to patients receiving the first dose of study drug. In patients with a history of IRRs to mAbs or similar products, it is recommended that premedication be administered. In such cases, patients should be

premedicated with a regimen that includes acetaminophen as well as an H1 (e.g., diphenhydramine/hydroxyzine) and an H2-antagonist (e.g., ranitidine/famotidine).

8.4.3 Premedication for IRRs (Following an IRR)

For IRRs while on study, the following premedication instructions are provided:

- For Grade 1 or Grade 2 reactions, premedication prior to subsequent infusions should be considered. Thereafter, if a patient is without recurrence of an IRR, the Investigator may choose to withdraw premedication to determine whether such continued therapy is necessary for that patient. Where practical, it is recommended that withdrawal of premedication be done in a gradual fashion (e.g., by reduction in dose, frequency, or number of agents administered, at the Investigator's discretion). For those patients who experience recurrent signs/symptoms suggestive of an IRR, premedication should be re-instituted for at minimum 2 additional doses before any future attempt to withdraw.
- For Grade 3 reactions, not applicable as this is considered a DLT; therefore, no further treatment with study drug is allowed.
- For Grade 4 reactions, not applicable as no further treatment with study drug is allowed.

If premedication is to be administered, institutional standards may be followed; however, a recommended regimen includes administration of the following approximately 30 minutes prior to the start of infusion (**Table 4**).

Table 4: Recommended Premedication Regimen

	Medication	Dose and Route	Alternative Medication	Dose and Route
1	acetaminophen	1000 mg IV (or PO)		
2	diphenhydramine	50 mg, IV	hydroxyzine	25 mg, PO
3	ranitidine	50 mg, IV	famotidine	20 mg, IV

Abbreviations (in alphabetical order): IV, intravenous; mg, milligrams; PO, per os (orally, by mouth)

Note: Doses may be adjusted based on standard institutional practice. In the event of a Grade 2 IRR, glucocorticoid therapy equivalent to a minimum of 25 mg IV hydrocortisone approximately 0.5 to 2 hours prior to the start of the next infusion may be considered.

8.4.4 Premedication for other Study Drug-Related Toxicities

Following the first dose, should a patient experience symptoms suggestive of other mild-to-moderate study drug-related reactions (e.g., nausea, vomiting, diarrhea, etc.), the patient may be premedicated with standard therapies to reduce the potential for such reactions in the future.

Based on ongoing review of patient safety data, the Sponsor may implement mandatory premedication for all patients treated in this study should a pattern begin to emerge of other mild-to-moderate study drug-related reactions that are amenable to prophylaxis with standard agents. Such action will occur following discussions between the Investigator(s) and the Sponsor's Medical Representative(s).

Any medications administered for either prophylaxis or therapy of signs/symptoms considered to be related to study drug will be documented on the appropriate page of the CRF.

8.5 Dose Modification Options

8.5.1 Prolongation of Infusion Duration

All IRRs that result in infusion prolongation must be reported promptly to the Sponsor (or designee).

8.5.1.1 Instructions for Infusion Prolongation for IRRs

For IRRs, the following infusion prolongation instructions are provided:

- For Grade 1 reactions, the infusion may be slowed to 50% of the prior rate such that the remaining dose to be delivered is administered in 2× longer than the amount of time that was initially scheduled.
- For Grade 2 reactions, the infusion should be interrupted for a minimum of 30 minutes, and at least until there is either amelioration to ≤ Grade 1 severity or return to baseline status. Supportive care should be provided. The infusion should then be restarted and slowed to 50% of the prior rate, as described. Subsequent infusions should be administered at the prolonged rate.
- For Grade 3 reactions, the infusion will be STOPPED and supportive care will be provided. The occurrence will be considered a DLT and the patient will be discontinued from treatment.
- For Grade 4 reactions, the infusion will be STOPPED and supportive care will be provided. The occurrence will be considered a DLT and the patient will be discontinued from treatment.

In all cases, the Investigator should use best clinical judgment in managing such reactions. All infusion interruptions and subsequent prolongations, including modified infusion times, as well as the toxicity that necessitated them, will be clearly documented on the appropriate page of the patient's CRF.

Note: Any assessments to be performed or samples to be collected (e.g., vital signs, PK) at the end of or following the EOI will still be performed or collected beginning at the delayed EOI timepoint. In situations where collection of late day samples, particularly the 8 hours after EOI sample, is logistically difficult due to clinic staff availability, an "end of day" sample may be obtained at the latest practical time on the day of the reaction.

Guidelines for the grading and management of IRRs of all severities are provided (**Appendix 9).**

8.5.1.2 Treatment Following Infusion Prolongation

To enhance patient safety following an infusion prolongation, subsequent infusions will be administered at the prolonged rate. For Grade 1 and Grade 2 IRRs, rechallenge with a shorter duration of infusion (no less than the duration designated by the patient's dose assignment and weight) may be attempted at the Investigator's discretion, after a minimum of 2 doses with no evidence of infusion-related toxicity at the prolonged rate.

8.5.2 Dose Reduction

There is no provision for dose reduction in this study.

8.5.3 Dose Delay

All delays of study drug must be reported promptly to the Sponsor (or designee).

Toxicities may be managed by delay in dosing provided they do not meet the criteria for study discontinuation (**Section 9.1**).

If indicated, the period between any 2 scheduled doses may be extended to allow for amelioration of the toxicity. However, if any observed Grade 3 or Grade 4 toxicity thought to be possibly-, probably-, or related to study drug results in delay of dosing beyond 2 weeks of the next scheduled dose, the event will be considered a DLT.

For toxicities that are to be managed by dose delay, dosing may be restarted at the same dose; however, administration of study drug may only be restarted upon amelioration to ≤ Grade 1, return to baseline status, or resolution of the observed toxicity.

8.5.4 Schedule Alterations

Altered schedules of study drug (i.e., reduced number of treatment days, longer interval between treatment days) may be explored, only after discussion with the Sponsor (or designee), and only during subsequent cycles of treatment (Cycle 2 and beyond).

Patients requiring such schedule alterations during Cycle 1 of the study will be considered to have met the criteria for DLT due to the inability to complete Cycle 1 of study drug treatment.

Note: Any modification of study drug administration, and the reason for such action, must be clearly noted in the patient's CRF. If such a modification impacts a PK sampling interval, the details of such action must also be documented on the appropriate page of the CRF (to aid in the interpretation of PK findings).

9 DISCONTINUING PATIENTS FROM STUDY TREATMENT

Every reasonable effort will be made to keep patients in the study; however, if a patient is discontinued from study treatment, every effort will be made by the Investigator to complete and report the reasons for treatment discontinuation as thoroughly as possible. This includes EOT observations, as required by the protocol at the time of treatment discontinuation, or before initiation of a new treatment, whichever comes first, as well as 1M FUP evaluations to follow (**Section 7**). The reason for treatment discontinuation must be clearly documented on the appropriate page of the CRF. A CRF must be completed for any patient who receives any amount of study drug.

9.1 Criteria for Treatment Discontinuation

Patients will be discontinued from further treatment with study drug in the event of any of the following:

1. **Adverse Events**, including:
    - Any AE or SAE that meets the study DLT criteria at any time during the study
    - Another AE or SAE considered by the Investigator to require treatment discontinuation

        Note: AEs resulting in a patient's permanent discontinuation from study treatment, regardless of seriousness or relationship to study drug, MUST be reported promptly to the Sponsor (or designee).

2. **Progressive Disease:** Confirmed radiographically

    Note: An exception may be made in the case of suspected PSPD. Patients will be permitted to continue treatment beyond initial RECIST v1.1 (or RECIL 2017) defined PD while waiting for confirmation of PD, provided they are clinically stable (per iRECIST).

3. **Clinical Progression:** Treatment failure not meeting the criteria for PD, but considered by the Investigator to require treatment discontinuation

4. **Physician Decision**, including:
    - Use of or requirement for a non-permitted concomitant medication
    - Requirement for a significant surgical procedure

        Note: Patients requiring a minor surgical procedure (e.g., port placement, skin abscess drainage) may continue at the Investigator's discretion following discussion with the Sponsor's Medical Monitor(s). A brief interruption in therapy may be considered.

    - Intercurrent illness which would prevent completion of study-related evaluations
    - Any other reason in the opinion of the Investigator that would justify treatment discontinuation

5. **Withdrawal by Patient:** Withdrawal of consent and election to discontinue treatment (patients may leave the study at any time for any reason if they wish to do so, without consequence)

6. **Protocol Deviation:** Significant deviation/violation from the protocol or eligibility criteria (discontinuation considered only following discussion with the Medical Monitor(s))
7. **Noncompliance with study procedures**
8. **Pregnancy**
9. **Lost to Follow-up**
10. **Death**
11. **Study Terminated by the Sponsor**
12. **Site Terminated by the Sponsor**

9.2 Replacements

Should a patient discontinue treatment with study drug for reasons other than the occurrence of a DLT prior to completing Cycle 1, a replacement patient will be obtained using the original eligibility criteria. Patients discontinued due to DLTs will not be replaced.

Note: Patients must receive their full planned doses of study drug during Cycle 1 to be considered evaluable for tolerability, unless dose delay or discontinuation is the result of a DLT. Patients receiving < 2 full planned study drug doses plus 2 weeks of follow-up during Cycle 1 for reasons other than toxicity will be replaced.

10 ADVERSE EVENTS

10.1 Definitions of Adverse Events

10.1.1 Adverse Event

An AE is any untoward medical occurrence in a patient or a clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an IMP, whether or not considered related to the IMP.

Causality for an AE will be assessed as related, possibly-related, probably-related, unlikely-related, or not-related to IMP. Any AE, regardless of causality, that also meets the seriousness criteria, will be reported as an SAE.

10.1.2 Events Not to be Considered as Adverse Events

A pre-existing condition (i.e., a disorder that is present before the AE recording period starts and is noted on the medical history/physical examination form) should not be recorded as an AE unless the condition worsens or episodes increase in frequency during the AE recording period.

PD will not be captured as an AE as this will be recorded as part of the patient's efficacy evaluation. PD should be reported as an AE if the nature of the PD is different than expected (i.e., signs/symptoms are not typical of PD).

Note: PD may be reported as an AE in the case of patient death, with death being the outcome of the event.

An abnormal laboratory value or an abnormal physiological test finding (e.g., ECG) need not be reported as an AE unless one of the following applies:

- The Investigator considers the abnormality CS
- The event meets the definition of an SAE
- The event requires an intervention
- The event results in an action taken with study drug (e.g., dose-delay and/or discontinuation)

Diagnostic and therapeutic non-invasive and invasive procedures, such as surgery, should not be recorded as AEs. A medical condition for which an unscheduled procedure was performed, should however be recorded if it meets the definition of an AE. For example, acute appendicitis should be recorded as the AE and not the appendectomy.

Procedures to support the treatment regimens, such as insertion of central venous catheters, etc., should not be recorded as AEs, unless the procedures result in complications.

10.1.3 Adverse Events of Medical Interest

Not applicable

10.1.4 Serious Adverse Events

An SAE is an AE that meets one or more of the following regulatory outcome criteria:

- **Results in death**

  In the case of deaths, the event(s) leading to the death should be recorded and reported as SAE(s) with the outcome "Fatal". The death itself will not be reported as an SAE, unless the cause of the death is unknown (e.g., in case of unexplained or sudden death)

- **Is life-threatening**

  The term "life-threatening" refers to an event in which the patient is at immediate risk of death at the time of the event; it does not refer to an event which hypothetically might cause death if it was more severe

- **Requires inpatient hospitalization or prolongation of existing hospitalization**
- **Results in persistent or significant disability/incapacity**

  A disability is defined as any substantial disruption of a person's ability to conduct normal life functions.

- **Is a congenital anomaly/birth defect**
- **Is medically important**

  Medical and scientific judgment must be exercised in deciding whether an AE is believed to be "medically important". Medically important events may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed in this definition.

10.1.5 Events That Do Not Meet the Definition of Serious Adverse Events

PD will not be captured as an SAE unless the nature of the PD is different than expected (i.e., signs/symptoms that are not typical of PD).

Note: PD may be reported as an SAE in the case of patient death, with death being the outcome of the event.

Elective surgery or other scheduled hospitalization periods that were planned before the patient was included in this trial are not to be recorded as SAEs, unless an outcome of the surgery/hospitalization was considered serious.

Hospitalization for observation or convenience prior to or following study drug infusions without an SAE occurring should not be recorded as an SAE, e.g., if a patient is hospitalized merely for observation, or if a patient begins or finalizes the infusion at a time of day requiring a convenience overnight stay in the hospital.

Procedures to support the treatment regimen that require hospitalization should not be recorded as SAEs; however, in cases where a procedure results in complications requiring/prolonging hospitalization, this must be recorded and reported as an SAE.

10.2 Adverse Event Recording and Reporting

All AEs will be recorded from signing of informed consent for participation in the trial. The recording period ends 30 days after receiving the final dose of study drug (at the time of the 1M FUP Visit), unless extended FUP is indicated, per the clinical trial protocol.

Note: Patients who sign informed consent and are subsequently deemed to be screen failures will be followed for the occurrence of SAEs/AEs until it is determined that they will not be participating in the trial.

10.2.1 Information to be Provided for each AE

The Investigator must record all directly observed AEs and all AEs spontaneously reported by the patient. Information regarding the occurrence of AEs should be elicited through open-ended questioning of the patient, review of physical examination findings, and review of laboratory results or other safety information, e.g., ECGs.

All AEs that occur in patients during the AE recording period must be recorded/entered to the AE section of the CRF, whether or not the event is assessed as related to study drug. If the AE is serious, the SAE report forms must also be completed and submitted. The following information will be provided for each AE term reported:

- **Diagnosis**

  A diagnosis should be recorded, if possible. If no diagnosis is available, signs and symptoms should be recorded instead. For fatal AEs, death is an outcome of the AE. The cause of death (rather than the term "death") should be recorded.

- **Severity**

  The Investigator will use the CTCAE version 5.0* to describe the severity of an AE. If the severity of an AE is not specifically graded by the CTCAE guidance document, the Investigator should use the general definitions of Grades 1 to 5 as per the following, and use his/her best medical judgment to describe the severity of the AE (**Appendix 3**):

  - Grade 1: Mild
  - Grade 2: Moderate
  - Grade 3: Severe
  - Grade 4: Life-threatening or disabling
  - Grade 5: Death caused by the event

  Changes in severity of AEs will be recorded.

  Generally, an AE of CTCAE Grade 4 or 5 qualifies for SAE reporting to the Sponsor (or designee). However, a laboratory abnormality of Grade 4 does not need to be reported as an SAE, unless it meets one of the SAE criteria.

  **See < https://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm >*

- **Relationship to IMP/Causality**

  The Investigator will attempt to assess causal relationship of the event to the study drug. Relatedness must be assessed and recorded within the initial report (CRF and SAE report form).

The causal relationship is an assessment of whether the event is related to the use of the IMP. It is not an evaluation of whether the event could hypothetically occur in the investigational patient population.

The causal relationship of an AE to the IMP will be rated using a 5-point causality scale (**Appendix 4**):

- Not-related
- Unlikely-related
- Possibly-related
- Probably-related
- Related

- **Outcome**

  The outcome of the AE must be assessed by the Investigator utilizing one of the following options:

  - Recovered/resolved
  - Recovered/resolved with sequelae
  - Recovering/resolving
  - Ongoing
  - Fatal
  - Unknown

Instructions for reporting changes in an ongoing AE during a patient's participation in the trial will be provided.

10.2.2 Required Follow-up for AEs

Appropriate consultation and follow-up evaluations should be carried out until the event either resolves, returns to baseline status, or has been adequately explained and assessed by the Investigator as chronic and/or stable, and that no long-term deleterious effects have become evident.

This follow-up may extend beyond the 1M FUP Visit, to up to 4 months after the end of treatment if indicated, if the event has not resolved or been adequately explained.

Any patient who develops an immune-mediated event during study or after the end of treatment will be followed for up to 2 years to assess the course of the condition and evaluate potential reversibility of the finding.

Note: Patients who sign informed consent and are subsequently deemed to be screen failures will be followed for the occurrence of SAEs/AEs until it is determined that they will not be participating in the trial.

10.3 Serious Adverse Event Recording and Reporting

10.3.1 Timeframes for Reporting to the Sponsor

All SAEs occurring at any time from signing of informed consent for participation in the trial and until 30 days after receiving the final dose of study drug (at the time of the 1M FUP Visit) must be recorded on the SAE Report Form and recorded as an SAE in the CRF.

Note: Patients who sign informed consent and are subsequently deemed to be screen failures will be followed for the occurrence of SAEs/AEs until it is determined that they will not be participating in the trial.

In case of an SAE, the Investigator must, within 24 hours of awareness of the event, report the SAE to the Sponsor (or designee) by telefax or e-mail transmission. Fax number(s) and e-mail address(es) will be stated on the SAE Report Form and the SAE Report Form Completion Instructions. SAE follow-up information must also be reported to the Sponsor (or designee) within 24 hours of awareness. SAEs, still ongoing after the 1M FUP Visit, should be followed on a regular basis according to the Investigator's clinical judgment, until the event resolves or until the Investigator assesses it as chronic or stable. The Sponsor (or designee) will pursue sufficient information and will return to the trial sites for such information as deemed required.

If the Investigator becomes aware of an SAE that occurred after the 1M FUP Visit and finds it to be related to the IMP (possibly-, probably-, or related to the study drug) or trial conduct, it must be recorded and reported to the Sponsor (or designee) as an SAE.

The Investigator should be aware of local reporting regulations to the IRB/EC. The Sponsor (or designee) will either supply the Investigator with the reports, which should be forwarded to the IRB/EC, or report directly to the IRB/EC depending on local regulations.

10.3.2 Safety Reporting to Health Authorities, Institutional Review Boards/Ethics Committees, and Investigators

Reportability of an SAE as a "Suspected Unexpected Serious Adverse Reaction" (SUSAR) will be determined solely by the Sponsor, based on seriousness, causality, and expectedness criteria.

In addition to SUSARs, the Sponsor or designee is responsible for reporting all relevant safety information regarding SUSARs, or other safety developments, to appropriate Health Authorities and central IRBs/ECs, as well as participating Investigators. Reporting of SUSARs to local IRBs/ECs will be handled either by the Sponsor or designee, or the Investigator depending on local regulations.

The timeline for notification of SUSARs is within 7 calendar days for fatal/life-threatening events and within 15 calendar days for all other SUSARs.

10.4 Pregnancy

If any trial patient becomes pregnant during the trial, the patient must be discontinued from study drug immediately and the pregnancy must be reported to the Sponsor or designee according to the same timelines as an SAE. While pregnancy is not considered an AE, all pregnancies are tracked as SAEs within the safety database to follow-up on exposure to the fetus/infant.

Pregnancies reported in female partners of male trial patients must also be included in the safety database; therefore, a female partner of a male patient on the trial who becomes pregnant will be approached for consent to have the pregnancy followed until term and reported upon to the Sponsor (or designee).

All pregnancies must be followed up every third month and 1-month post-delivery to determine outcome and status of mother and child. Pregnancy complications and elective terminations for medical reasons must be reported as AEs or SAEs as appropriate. Elective terminations for non-

medical reasons should be reported as follow-up, but not as a separate AE/SAE unless complications meet AE/SAE criteria. Spontaneous abortion must be reported as an SAE.

Any SAE occurring in association with a pregnancy brought to the Investigator's attention after the patient has completed the trial and considered by the Investigator as possibly-, probably-, or related to the study drug, must be promptly reported to the Sponsor (or designee).

All pregnancy information including follow-up information must be reported on a designated pregnancy form provided by the Sponsor (or designee).

11 PRECAUTIONS WHEN DOSING WITH STUDY DRUG

11.1 Precautions Regarding Procreation

Studies have not been performed to determine whether this study drug affects reproductive function in males or can cause fetal harm. For this reason, men with partners of childbearing potential must use a highly effective method of contraception while receiving study drug. **"A highly effective method of contraception" is defined as non-hormonal contraception equivalent to a double-barrier method (includes a single-barrier method in combination with a spermicide) or intrauterine device.**

There have been no studies in pregnant females; therefore, it is not known whether study drug can cause fetal harm when administered to a pregnant woman, or whether it can affect reproductive capacity. For this reason, WOCBP should only be administered study drug when highly effective contraceptive measures have been taken and when pregnancy tests are negative.

WOCBP includes any female who has experienced menarche and who has not undergone surgical sterilization (hysterectomy, bilateral tubal ligation, or bilateral oophorectomy), or is not postmenopausal. Post-menopause is defined as:

- Amenorrhea for ≥ 12 months with no other cause
- Irregular menstrual periods, on HRT, with documented FSH level > 35 mIU/mL

Note: Women who are using oral contraceptives, other hormonal contraceptives (vaginal products, transdermal patches, or implanted or injectable products), or mechanical products such as an intrauterine device or barrier methods (diaphragm, condoms, spermicides) to prevent pregnancy, or are practicing abstinence, or where their partner is sterile (e.g., vasectomy), should be considered of childbearing potential.

Women and men of childbearing potential will be informed as to the unknown risk to procreation while participating in this trial and will be advised that they must use highly effective contraception within 2 weeks prior to the first dose and continuing until 6 months after final administration of study drug. A pregnancy test will be performed on each premenopausal female of childbearing potential within ≤ 2 working days prior to first study drug administration, and again at the end of the final treatment cycle.

11.2 Additional Precautions

There are no known contraindications to the administration of study drug, however the following additional precautions are provided:

- Lactating women and children: Use in lactating women or in children has not been evaluated. These patients will be excluded from study entry.
- Drug interactions: No formal drug interaction studies have been performed, therefore no specific guidance can be provided about use of concomitant medications.
- Overdose: There is no experience with clinical overdose. If severe reactions occur in patients, study drug should be discontinued, and all appropriate supportive medical care should be instituted to ameliorate these potential AEs.

- Nonclinical toxicology studies: No adverse events have been observed at the highest dose level of Sym023 tested, which was weekly administration of 100 mg/kg. The highest dose to be administered in this trial is 20 mg/kg administered Q2W.

- Studies of other mAbs: IRRs have been observed, therefore safety in patients with a history of IRRs to mAbs or similar products should be carefully evaluated prior to administration of study drug. It is recommended that premedication to prevent infusion reactions be administered to all patients with a history of such reactions, and facilities and personnel to treat such reactions, if they occur, should be available. In the event of an IRR, the infusion should be slowed/interrupted so that appropriate measures may be taken (**Section 8.5.1**, **Appendix 9**).

- Studies of other anti-TIM-3 antibodies: For a listing of AEs observed with another TIM-3 antibody, see **Section 2.3.1.2**.

- Studies of other antibodies to immune checkpoints: For a listing of AEs observed with anti-PD-1/PDL1 antibodies, see **Appendix 8**. For information on grading and management of immune-mediated toxicities, see **Appendix 10**.

12 SAFETY SURVEILLANCE DURING STUDY

12.1 Safety Review

The Investigator(s) and Sponsor's Medical Representatives will comprise a Study Safety Team. The team will review clinical and laboratory safety data on an ongoing basis throughout the study and make decisions regarding the advisability of continuing accrual to a dose cohort, and/or escalating the dose and allowing accrual to a higher dose cohort. To do so:

- The following will be promptly reported to the Sponsor (or designee):
    - SAEs within 24 hours of Investigator awareness
    - Any immune-related AE of significance, even if not meeting the SAE or DLT definition
    - AEs resulting in permanent discontinuation from study, regardless of seriousness or relationship to study drug
    - DLTs
    - IRRs
    - Dose delays
- AEs will be recorded in the CRF in a timely manner following a patient completing (or being discontinued from) each dosing cycle. Each event will be assessed as to grade and causality.
- The Investigator will make critical laboratory safety data available in a timely manner.
- Patients will be carefully evaluated for evidence of all AEs, including potential cumulative and/or delayed toxicities, throughout the duration of their time on study.
- Biweekly Safety Team Teleconferences will be held between the Investigator(s) and the Sponsor's Representative(s) to discuss ongoing patient status and any emerging safety concerns; frequency may fluctuate based on accrual and study activity, as indicated.

Availability of these data also will enable the Sponsor (or designee) to act promptly in response to safety signals and ensure that governing Health Authorities, as well as Investigators who may be participating at other sites or in other clinical trials of the study drug, are informed of events occurring during the trial.

12.2 Other Safety Surveillance Activities

At least one Medical Monitor will be assigned to review and evaluate relevant clinical/safety information concerning the clinical trial. The responsibilities of the Medical Monitor include, but are not limited to:

- Consultation with Investigator(s) regarding evaluation of patients to be enrolled to the study, treatment delays, restarts, and/or discontinuations
- Ongoing safety monitoring of all patients being treated in the study
- Evaluation of coding and trending of AEs in conjunction with the Drug Safety physician

- Performing surveillance on potential safety signals in conjunction with the Drug Safety physician
- Evaluating abnormal laboratory values and other relevant safety data, e.g., ECGs
- Providing medical support to the Sponsor in answering questions related to the study protocol
- Updating the Safety Team on trial status

A Drug Safety physician will be assigned to review, assess, and approve all SAE cases and associated reports. This physician will also perform the following:

- Assess for safety signals and trends in conjunction with the Medical Monitor
- Assist with questions regarding medical coding of SAEs
- Discuss with the Sponsor's Chief Medical Officer any cases which may present a concern regarding a signal or safety issue.

13 REGULATORY AND ETHICAL CONSIDERATIONS

13.1 Conditions of Testing

In sponsoring this study, it is the intention of the Sponsor to obtain patient safety data for submission to governing Health Authorities. In agreeing to conduct this investigation, the investigative facility agrees to follow all requirements stipulated in this protocol as well as regulations described in the U.S. CFR and/or by governing Health Authorities concerning:

- Responsibilities of Investigators (in the U.S. Title 21 CFR Part 312)
- Informed Consent of Human Subjects (in the U.S. Title 21 CFR Part 50)
- Institutional Review Boards (in the U.S. Title 21 CFR Part 56)

In addition, the Investigator agrees to perform the study in accordance with the principles of the Declaration of Helsinki, and ICH E6(R2) GCP.

13.2 Institutional Review

The Investigator will submit this protocol, any protocol modifications, and the patient ICF to be utilized in this study to the appropriate IRB/EC for review and approval. This committee must operate in accordance with ICH E6(R2) GCP, the U.S. Title 21 CFR Part 56, and/or governing Health Authorities, as appropriate. A letter confirming approval of the protocol and the ICF must be forwarded to the Sponsor (or designee) prior to initiation of this study. The Investigator will not start the study, nor will study drug be shipped to the investigational site, before providing the Sponsor (or designee) with evidence of this approval.

The Investigator is responsible for assuring continuing review and approval of the clinical study. The Investigator must also promptly report all changes in the research activity and all unanticipated problems involving risk to the patients or others to the IRB/EC. The Investigator will not make any changes in the protocol without IRB/EC approval, except where necessary to eliminate apparent immediate hazards to the patients. The Investigator will provide progress reports to the IRB/EC as required by the IRB/EC. If the study remains in progress for more than the IRB/EC-specified approval period, the Investigator must obtain renewal and re-approval from the IRB/EC where appropriate. Documentation of renewal must be submitted to the Sponsor (or designee). The Investigator will provide notice to the IRB/EC of completion of participation in the study.

13.3 Informed Consent

The Investigator agrees to protect the rights, safety, and welfare of the patients entered into the study, including obtaining written informed consent prior to performing any study-related procedures, and informing each patient that the study drug is being used for investigational purposes.

Prior to study start, the Sponsor will provide a sample ICF for modification, as appropriate, by each Investigator. The sample ICF must include all elements required by ICH E6(R2) GCP and must adhere to the IRB/EC requirements and ethical principles that have their origin in the Declaration of Helsinki.

The Investigator's revision to the Sponsor's sample ICF, along with any other written study information to be provided to the patient, must be reviewed and approved by the IRB/EC. A copy of the IRB/EC-approved ICF to be utilized during the study must be submitted to the Sponsor (or designee) prior to study initiation.

Prior to each patient's entry to the study, the Investigator or his/her staff will explain the nature of the study, its purpose and associated procedures, its expected duration, and the potential risks associated with participation. All questions about the trial will be answered to the satisfaction of the patient or the patient's legal representative. The patient will be informed of the right to withdraw from the study at any time without consequence, and without having to provide a reason for this decision. Following the discussion, the patient will be asked if they are willing to personally sign and date the ICF. Only if the patient voluntarily agrees to sign the ICF and has done so, may he/she enter the study.

It is the responsibility of the Investigator to obtain written informed consent from each patient, thereby attesting that consent was given freely in accordance with ICH E6(R2) GCP, the U.S. Title 21 CFR Part 50, or governing Health Authorities, as appropriate. An Investigator listed on the Form FDA 1572 will then co-sign the ICF. A copy of the signed and dated ICF will be provided to the patient. The original executed version must remain in the Investigator's file, per local requirements, and must be available for verification by a representative of the Sponsor (or designee).

13.4 Conditions for Modifying or Terminating the Study

13.4.1 Modification of the Study Protocol

The study is to be conducted as described in this protocol. Departures from either the protocol eligibility criteria or the experimental plan, as outlined herein, will not be allowed. No protocol waivers will be granted.

If modifications in the experimental design, dosages, assessments, patient selection, etc., of the protocol are indicated or required, such changes will only be instituted following consultation between the Sponsor (or designee) and Investigator and will be accomplished through formal amendment(s) to this protocol and approval by the appropriate regulatory authority (as indicated) and review committees, except where necessary to immediately eliminate apparent hazards to patients.

A modification to the protocol will not be made without the express written approval of the Sponsor (or designee). Any amendment prepared by the Sponsor (or designee) will be implemented according to the Sponsor's (or designee's) standard operating procedures (SOPs) and will be reported to the appropriate regulatory authority, the appropriate IRB/EC, and made a formal component of the protocol document.

Protocol changes to eliminate an apparent hazard to a trial patient may be implemented by the Investigator immediately. The Investigator must then, without delay, inform the local IRB/EC, and the Sponsor (or designee) will immediately notify local governing Health Authorities.

13.4.2 Modification of the Informed Consent Form

If modifications to the experimental design, dosages, assessments, patient selection, etc. of the protocol are indicated or required, and if such modifications substantially alter the study design or increase the potential risk to patients, the Sponsor (or designee) will prepare a revision to the existing sample ICF for modification, as appropriate, by each Investigator. Any revision to the sample ICF prepared by the Sponsor (or designee) will be implemented according to the Sponsor's (or designee's) SOPs. Such a revision will be reviewed and approved by the appropriate regulatory authority (as indicated) and IRB/EC.

In addition, all current patients, as well as subsequent study candidates, will be informed of the study design modification or increase in potential risk, and written informed consent for the modification/risk will be obtained as outlined (**Section 13.3**).

13.4.3 Conditions for Termination of the Study or a Study Site

The Sponsor reserves the right to terminate the study, or terminate a clinical trial site's participation in the study, at any time. Should the Sponsor, the Sponsor's designee, and/or the Investigator(s) discover conditions that indicate the study or a study site should be discontinued, an appropriate procedure for termination will be instituted. Reasons for termination may include, but are not limited to, the following:

- Termination of the Study
    - Safety concerns; incidence and/or severity of AEs in the study that indicate a potential health hazard or unexpected, serious, or unacceptable risk caused by the study treatment
    - Discovery of lack of efficacy
    - Unsatisfactory enrollment across the entirety of the trial
    - Drug supply or manufacturing issues
    - The Sponsor's decision to modify or discontinue development of the study drug
    - A request to discontinue the study by a regulatory authority or Health Authority
- Termination of a Study Site
    - Investigator non-compliance with the protocol, ICH E6(R2) GCP, or regulatory requirements
    - Unsatisfactory enrollment at the site with respect to quantity or quality
    - Incomplete data collection; inaccurate or knowingly false data submission

If terminating the study, the Sponsor and Investigator(s) will ensure that adequate consideration is given to the protection of patients' interests. Further, the governing Health Authority and IRB/EC will be notified in writing and the reason for termination will be stated.

13.5 Trial Registration

The trial will be registered in one or more public trial registries (e.g., ClinicalTrials.gov). The trial results will be posted in the same clinical trial registries as the initial registration in

accordance with the latest International Committee of Medical Journal Editors (ICMJE) recommendations (URL: www.icmje.org).

13.6 Insurance and Liability

The Sponsor will obtain Human Clinical Trials Insurance for its legal liability in accordance with laws and regulations, and with limits customary or required by law in the territory in question.

14 INVESTIGATOR RESPONSIBILITIES

14.1 Medical Supervision

An Investigator conducting a clinical study with an investigational agent is required to comply with regulations described in U.S. Title 21 CFR Parts 50, 56, and 312 and/or by governing Health Authorities, as well as ICH E6(R2) GCP.

Medical supervision for the conduct of this protocol is the responsibility of the Principal Investigator. The Principal Investigator must name all Sub-Investigators and may delegate certain day-to-day activities to such Sub-Investigators, but retains overall responsibility for ensuring that the study is conducted properly and in accordance with the design and intent herein. A document outlining the specifics of the delegation will be maintained at the investigational site, in the study files, and will be updated as appropriate.

The Principal Investigator is responsible for ensuring that drugs and devices are available for treating possible medical emergencies. The Principal Investigator is required to ensure compliance with respect to the study drug schedule, visit schedule, and procedures required by the protocol. The Principal Investigator is responsible for ensuring that the study is conducted according to sound medical practices.

14.2 Confidentiality

All goods, materials, information (oral or written) and unpublished documentation provided to the Investigator (or any company acting on their behalf), inclusive of this protocol, the patient CRFs, and the IB, are the exclusive property of the Sponsor. Documents and information provided to the Investigator by the Sponsor may not be given or disclosed by the Investigator or by any person within his/her authority either in part or in totality to any unauthorized person without the prior written formal consent of the Sponsor.

The submission of this protocol and other necessary documentation to the IRB/EC is expressly permitted; the IRB/EC members have the same obligation of confidentiality.

The Investigator shall consider as confidential, and shall take all necessary measures to ensure that there is no breach of confidentiality, all information accumulated, acquired or deduced during the trial, other than that information to be disclosed to a third party mandated by applicable law.

Note: Any language relating to these issues appearing in the clinical trial agreement will supersede that which is outlined in this section.

14.3 Use of Information

All unpublished information relating to this trial and the study drug is considered confidential by the Sponsor and shall remain the sole property of the Sponsor. The Investigator must accept that the Sponsor may use information from this trial relating to the development of the study drug, and therefore, may disclose it as required to Investigators, government-licensing authorities, Health Authorities of other governments, investors, and commercial partners as indicated.

14.4 Publications

The Sponsor acknowledges the Investigators' rights to publish the full results of the trial, regardless of the outcome, in accordance with the latest ICMJE recommendations. Publication of a summary of the results of the study is permissible according to the Sponsor and is not inconsistent with the preceding affirmation regarding confidentiality. Scientific dissemination of the results of this study is encouraged. Any formal publication of data collected from the study will be considered a joint publication by the Investigator and the appropriate personnel of the Sponsor or their designees. Authorship will be determined by agreement.

The Sponsor retains the right to designate one of the authors or someone else involved to be named as the Coordinating Investigator. The Coordinating Investigator and the Sponsor will decide on the publication strategy. The Coordinating Investigator will have the right to publish and present the results and methods as first or last author of multicenter publications. Co-authorship will be decided by the Sponsor and the Coordinating Investigator and will be limited to persons who have contributed substantially to the trial. The Sponsor will have representation in the list of authors.

Publication is subject to the following conditions:

- No publication before the completion of the trial at all participating trial sites without preceding written approval from the Sponsor
- Publications shall not disclose any Sponsor confidential information and property (not including the trial results)
- The Sponsor reserves the right to review results communications prior to public release and can embargo communications regarding trial results for a period that is less than or equal to 60 days. The Sponsor cannot require changes to the communication and cannot extend the embargo.

Note: Any language relating to these issues appearing in the Clinical Trial Agreement will supersede that which is outlined in this section.

14.5 Patient Screening Log

A record listing all patients entered into the study, as well as those considered for entry into the study and subsequently excluded, must be maintained by the Investigator. Patients excluded from the study will have the reason for exclusion recorded on the Patient Screening Log (or similar document).

14.6 Drug Dispensing Inventory

Study site personnel will maintain adequate records of the receipt, dispensing, and disposition of all study drug that the Sponsor ships to the site. Records will be maintained either on a form to be provided by the Sponsor or another similar document authorized for use by the Sponsor, and should include appropriate dates, quantities received, quantities dispensed, lot number (or kit number), disposition details, and the identification code of the patient who received the study drug.

The Investigator agrees to administer study drug only to patients under his/her personal supervision. The Investigator will not supply study drug to any person not authorized to receive it.

14.7 Handling and Disposal of Study Drug

Study drug should be stored in a secure location, under the indicated conditions (**Section 5.2**). Information regarding the number of vials utilized for each patient, as well as the dose of study drug administered to the patient, will be recorded on the appropriate drug inventory form.

Periodically throughout and at the conclusion of the study, vials of study drug will be inventoried by a representative of the Sponsor (or designee). At the completion of the study, all unused study materials MUST be returned to the Sponsor (or designee), unless otherwise authorized in writing.

Information regarding the storage, handling, inventory, and disposition of study drug will be provided by the Sponsor (or designee).

14.8 Recording of Data

Clinical trial data for this study will be captured in an electronic format. Electronic data capture (EDC) services will be provided by a vendor to be determined by the Sponsor. The Investigator agrees to provide all information requested in the CRF in an accurate manner according to instructions provided. CRFs are designed for computer processing and analysis. All data must be carefully entered to permit meaningful interpretation. Corrections to entered data will be identified and tracked by audit trails within the EDC system. Data must be entered into CRFs in a timely fashion.

A CRF is required to be submitted for every patient who receives any amount of study drug. This includes submission of retrievable data on patients who withdraw before completion of the study. Prior to submission, CRFs must be reviewed for completeness and accuracy, and signed and dated where indicated, by either the Principal Investigator or a physician Sub-Investigator whose name is listed on the Form FDA 1572 for this study.

All collected data will be entered into a validated database.

14.9 Source Document Requirements

The Investigator will maintain adequate and accurate records for each patient treated with study drug. Source documents including but not limited to hospital, clinic or office charts, laboratory reports, radiology and pathology reports, pharmacy records, study worksheets, anonymized photographs aimed at documenting study-associated clinical findings, and signed ICFs, must completely reflect the nature and extent of the patient's medical care, must be included in the Investigator's files along with patient study records, and must be available for source document verification against entries in the CRF.

Each trial site will permit authorized representatives of the Sponsor and relevant Health Authorities direct access to (and when required by applicable law, to copy) clinical records for the purposes of quality assurance reviews, audits, and evaluation of the trial safety and progress. The Sponsor (or designee) will check CRF entries against source documents according to the

guidelines of ICH E6(R2) GCP. Data not requiring a separate written record, i.e., data which may be recorded directly in the CRF, will be determined before trial start.

The ICF will include a statement by which patients allow the Sponsor (or designee), as well as authorized regulatory agencies, to have direct access to source data that support data in the CRF (e.g., patient medical files, appointment books, original laboratory records, etc.). The Sponsor (or designee), bound by confidentiality and privacy regulations, will not disclose patient identities or personal medical information.

14.10 Laboratory Reports

Prior to initiation of this study, the Investigator must supply the Sponsor (or designee) with the normal laboratory values for the laboratories to be utilized; specifically, the normal laboratory values for analytes required to be measured, per protocol, are to be supplied.

Laboratory safety evaluations must be performed at the intervals specified. If unexplained laboratory abnormalities occur, corroborative tests will be performed until the laboratory abnormality has resolved, returned to baseline status, and/or adequate explanation of the abnormality has been provided.

Copies of any additional records pertinent to the study (e.g., laboratory data, radiological reports, patient chart summaries, autopsy reports) must be made available to the Sponsor (or designee) or governing Health Authorities, if requested, with due precaution taken to ensure patient confidentiality.

14.11 Record Retention

Regulatory authorities require that the Investigator retain copies of all files pertaining to the study according to local requirements. In addition, the Investigator is responsible for archiving all relevant source documents so that trial data may be compared against source data after completion of the trial, e.g., in case of inspection from authorities. Study records must be stored in a safe and secure location permitting timely retrieval, if necessary. The Investigator must obtain written permission from the Sponsor prior to disposing of any records.

If the Investigator relocates, retires, or withdraws for any reason from the study, trial records may be transferred to an acceptable designee, such as another Investigator within the institution. The Sponsor (or designee), as well as the responsible IRB/EC, must be notified of the identity of the individual assuming responsibility for maintaining the study records and the location of their storage.

14.12 Monitoring of the Study

The Sponsor has responsibility to governing Health Authorities to take all reasonable steps to ensure the proper conduct of the study with respect to trial ethics, protocol adherence, and data integrity and validity.

This study will be closely monitored by representatives of the Sponsor (and/or designee) throughout its duration. Monitoring will be in the form of periodic personal visits with the Investigator and his/her staff as well as any appropriate communications by telephone, telefax, mail, or e-mail transmission. The purpose of these contacts is to review study progress, Investigator and patient adherence to protocol requirements, and any emergent problems

associated with the conduct of the study. The following usually will be assessed during monitoring visits at the site:

- Required regulatory documentation
- Signed ICFs
- Patient accrual and follow-up
- Study drug inventory records
- Investigator and patient compliance to the study protocol
- Concomitant therapy usage
- AE documentation
- Data is accurate, complete, and verifiable when compared to source documents

The Investigator and study staff are expected to cooperate with monitors during such visits and provide them with all relevant study documents. The Investigator must give the Sponsor (and/or designee) direct access to all relevant source documents to confirm consistency with the CRF entries. It is important that the Investigator and relevant personnel are available during monitoring visits and possible audits and that sufficient time is devoted to the process.

In addition, the study may be evaluated by Sponsor auditors (and/or designees) and government inspectors who must be allowed access to CRFs, source documents, and other study files. Sponsor reports will be kept confidential. The Investigator should promptly notify the Sponsor of any audits scheduled by any regulatory authorities, and promptly forward copies of audit reports.

As applicable, in accordance with the Health Insurance Portability and Accountability Act (HIPAA) and associated privacy regulations, patient authorization to use personally identifiable health information may be required from each patient before research activities. This authorization document must clearly specify what parties will have access to a patient's personal health information, for what purpose, and for how long.

14.13 Patient Confidentiality

Every effort will be made to maintain the anonymity and confidentiality of patients during this clinical study. Each participating site will maintain appropriate medical and research records for this trial, in compliance with ICH E6(R2) GCP, regulatory, and institutional requirements for the protection of confidentiality of patients.

Coded patient identifiers will be utilized always (including in any publications) when referring to a patient. However, because of the experimental nature of this treatment, the Investigator agrees to allow representatives of the Sponsor (and/or designee), as well as authorized representatives of the governing Health Authority, to inspect the facilities used in this study and to inspect, for purposes of verification, the hospital or clinic records of all patients enrolled into this study. A statement to this effect should be included in the ICF.

14.14 Financing and Insurance

The study will be supported by the Sponsor. Specifics of the financing and insurance coverage will be addressed in the clinical study agreement between the Sponsor and the Investigator or Institution.

15 HANDLING AND PROCESSING OF DATA

15.1 Data Handling

Study data collection, processing, transfer, and reporting, as well as handling of study personnel information, will be in compliance with ICH E6(R2) GCP and all applicable data protection regulations, including Regulation (EU) 2016/679 of the European Parliament and of the Council of 27 April 2016 on the protection of natural persons with regard to the processing of personal data and on the free movement of such data (General Data Protection Regulation).

15.2 Data Review During this Study

Data obtained from the study will be reviewed in a timely manner throughout by the Sponsor (or designee) and Sponsor's Medical Representative(s) to assess safety and the progress of the project.

15.3 Data Processing

A Data Management Plan (DMP) will be prepared for this trial. The Sponsor (or designee) will be responsible for data processing in accordance with applicable Data Management SOPs and the trial DMP.

Once recorded within the electronic CRF, study data will pass through a set of pre-programmed data validation checks designed to identify inconsistencies and other data errors, and also will undergo an additional study-specific data review process, as stated above in **Section 15.2**. Data issues will be queried via the EDC system and query resolutions will be documented.

Entry and processing of data other than those directly recorded on electronic CRFs by trial sites (e.g., imports of laboratory results) will follow vendor(s) SOPs. Transfer of such data from vendor(s) to Sponsor (or designee) will be handled according to vendor(s) data transfer SOPs and the Sponsor data transfer requirements with full compliance to applicable regulations.

Database Lock will occur upon reaching the pre-defined data cut-off for primary analysis and completion of Sponsor’s (or designee’s) quality control and quality assurance procedures.

Portable Document Format (PDF) files of the electronic CRFs will be provided to the Investigator upon removal of access to the electronic CRFs.

15.4 Clinical Trial Report

Following study completion, a final integrated clinical/statistical Clinical Trial Report (CTR) will be prepared.

15.5 Compliance with the General Data Protection Regulation

The applicable data protection legislation requires that parties enter into a written contract if one party (data processor) processes personal data on behalf of the other party (data controller). This written contract must regulate the subject-matter and duration of the processing, the nature and purpose of the processing, the types of personal data and categories of data subjects, as well as the obligations and rights of the data controller. Accordingly, the parties must enter into a data processing agreement. To the extent the processing of personal data involves transfers of personal data to third countries (e.g., jurisdictions outside of the European Economic Area [EEA]), the parties will enter into the European Commission's standard contractual clauses

between the data controller, the data processor, and all sub-processors, if any. The European Commission's standard contractual clauses ensure an adequate level of protection in relation to transfers of personal data to third countries.

16 STATISTICAL ANALYSIS

16.1 Statistical Considerations

A Statistical Analysis Plan (SAP) that includes a more technical and detailed description (including templates for Tables, Listings, and Figures) of the planned statistical summaries analyses will be prepared and finalized prior to database lock.

Further data-driven and exploratory analyses may be defined and performed and presented in the CTR as appropriate.

16.2 Sample Size Considerations

Approximately 20-48 male and female patients will be enrolled and treated, based on a modified accelerated titration Phase 1 design (more specifically, up to 2 single patient cohorts, followed by a standard 3+3 design), to allow determination of the MTD and/or RP2D. It is assumed that approximately 7 cohorts may be required during the dose-escalation. However, the protocol allows for enrollment of > 7 cohorts, should this be necessary to identify the MTD and/or RP2D. Expansion of the MTD/MAD cohort to treat up to 12 patients may be considered for further evaluation of tolerability.

16.3 Analysis Populations

Two analysis sets will be defined in accordance with the consolidated guidelines, ICH E9 Statistical Principles for Clinical Trials.

The Full Analysis Set (FAS) will comprise all enrolled patients who have received at least a fraction of one dose of study drug. The FAS will be used for evaluation of all endpoints except evaluation of DLTs. The patients in the FAS will contribute to the analyses as allocated to treatment. For the evaluation of PK endpoints, patients, full profiles, or single measurements can be excluded from the analyses. The decision of excluding patients, full profiles, or part of profiles will be described in the CTR.

The DLT Analysis Set will comprise all patients in the FAS enrolled in the dose-escalation, except patients who did not complete Cycle 1 for reasons other than drug toxicity. The DLT Analysis Set will be used for evaluation of DLTs.

16.4 Trial Endpoints

16.4.1 Primary Endpoints

DLTs to establish MTD as defined in **Section 6.9**, and/or the RP2D as defined in **Section 6.6.3**, will be the primary study endpoint. RP2D will be determined by:

- Incidence, severity, and relationship of treatment emergent AEs measured from administration of the first dose of study drug or worsening after taking study drug, to the last dose of study drug plus 30 days
- AEs leading to dose interruption, dose delays, dose reduction, and permanent treatment cessation
- Changes in safety laboratory values from baseline to end of safety follow up

16.4.2 Secondary Endpoints

- Additional safety endpoints, including:
    - Exposure to study medication, including duration, dose reduction and/or delay
    - Changes in vital signs, body weight, and physical examination findings from baseline to end of trial participation
    - ECG Findings
- Occurrence of ADA measured in serum at selected timepoints from baseline to end of trial participation
- Antineoplastic Activity, measured by tumor response to study treatment and tumor shrinkage, time to progression (TTP) based on radiological evident as per RECIST v1.1 and relevant lymphomas assessment criteria.
- PK profile of study drug, derived based on the concentration-time curves after the first infusion

16.5 Statistical Analysis

16.5.1 General Specifications

Statistical analyses will be carried out using Statistical Analysis System (SAS®) Version 9.4 or higher.

All data summaries and statistical analyses will be performed based on the FAS population, unless otherwise specified.

In general, continuous variables, including baseline characteristics, will be summarized using descriptive statistics by reporting the number of observations, mean, standard deviation, median, minimum, and maximum. Categorical/discrete variables will be summarized using frequency distributions showing the number and percentage of patients within a category. Time-to-event data will be summarized using the Kaplan-Meier method, as appropriate.

Unless indicated otherwise, summary statistics will be presented using observed data only. Missing data will not be imputed. If a baseline value is missing, no change from baseline will be calculated. Baseline is defined as the last available observation prior to the first administration of study drug on C1/D1.

16.5.2 Patient Disposition, Baseline and Treatment Characteristics

Patient disposition, including withdrawals of patients from study drug and reason, will be summarized using frequency distributions.

Patient demographics, baseline and disease characteristics such as age, sex, race, cancer type, prior anti-cancer therapies, and ECOG PS, will be presented using descriptive statistics or Frequency distributions, as appropriate.

16.5.3 Study Treatment

Exposure to study drug and the administration profile will be summarized descriptively for each cohort with respect to number of cycles taken, the cumulative dose, the dose intensity, the relative dose intensity, and dose modifications.

16.5.4 Maximum Tolerated Dose

All DLT events will be listed by dose cohort and patient. A summary table of DLTs across dose cohorts by System Organ Class (SOC) and preferred term will be presented, if applicable. The summaries will include number of DLTs, and number and percentages of patients experiencing a DLT.

A table will be presented showing the MTD, if identified, as well as a summary of the dose-escalation.

16.5.5 Adverse Events

AEs will be coded by SOC and preferred term using the most current version of MedDRA. AEs including SAEs will be recorded starting at signing of informed consent* through 30 days following the last dose of study drug (1M FUP Visit), and will be tabulated by maximum severity according to the CTCAE v5.0.

*Patients who sign informed consent and are subsequently deemed to be screen failures will be followed for the occurrence of SAEs/AEs until it is determined that they will not be participating in the trial

AEs will be regarded as TEAEs if they occur after first treatment. Non-treatment emergent AEs (non-TEAEs) are defined as AEs collected before administration of the first dose. If non-TEAEs increase in frequency or severity after treatment, these will be considered TEAEs. TEAEs will be presented by SOC and preferred term unless stated otherwise. The frequencies of TEAEs will be presented including number and percentages of patients having experienced an event and the total number of events.

The calculation of AE incidence will be based on the number of patients per AE category. For each patient who has multiple AEs classified to the same category, that patient will be tabulated under the highest toxicity grade for that AE category. Summary tables will be presented by:

1. AEs, in total and sorted by frequency
2. AEs by relationship
3. AEs by grade and maximum grade
4. SAEs, in total, and by relationship
5. AEs leading to dose interruption, dose delays, dose reduction, and permanent treatment cessation
6. AEs leading to trial drug delay
7. Fatal AEs

During dose-escalation, first-cycle DLTs, AEs leading to death or to discontinuation of study treatment, and SAEs will be evaluated with special attention.

16.5.6 Laboratory Determinations

Biochemistry, hematology, and coagulation parameters will be presented using box plots, if appropriate. In addition, individual patient biochemistry, hematology, and coagulation parameters during the trial will be presented graphically using longitudinal plots. Urinalysis parameters will be summarized using descriptive statistics.

Laboratory measurements will be graded according to CTCAE v5.0, when applicable. The frequencies of the highest CTCAE v5.0 grade observed will be displayed for each AE and for each starting dose level.

Laboratory values outside normal range will be flagged and laboratory values will be listed including grading of abnormal values. Laboratory determinations categorized as in or out of normal range may be summarized in some cases using worst-case shift tables. CS or not clinically significant (NCS) criteria may be applied for out-of-range values.

16.5.7 Vital Signs, Body Weight, Physical Exam Findings

Actual values and change-from-baseline values for VS, body weights, PS, as well as physical examination findings, will be summarized descriptively. Normal and abnormal findings in physical examination will be presented in shift tables by visit, if appropriate.

16.5.8 ECG Findings

Descriptive statistics of ECG observations will be presented. The frequency and percentage of ECG results will be summarized for the following ECG measurements: HR, PR interval, QRS duration, QT interval, and QTc interval. The QTc interval, indicating repolarization time, will be calculated. T-wave and ST-segment ECG abnormalities will be graded based on definitions in the Common Toxicity Criteria (CTC).

Normal and abnormal findings will be presented in shift tables by visit. Additional details regarding the ECG analyses will be provided in the SAP.

16.5.9 Other Safety Data

Concomitant medications and findings in ophthalmology examinations, PFTs, thyroid function tests, and ADA analyses will be summarized in text as recorded in the CRF, and as made available from an independent central assay laboratory, in the case of ADA data.

16.5.10 Antineoplastic Activity

All antineoplastic activity analyses will be descriptive and exploratory in nature. Disease status will be summarized by cycle and dose group, including changes from baseline. As a secondary objective, OR, duration of OR, SD, and TTP will be assessed and calculated, wherever possible, according to standard response criteria.

Response Calculations

In the event of an OR (CR or PR) the duration of the OR will be determined from the day the initial response is observed (using screening/baseline images for comparison) to the day that progression is observed. Number and percentages of patients with documented OR will be presented.

Duration of SD (minimum duration of not less than 16 weeks) will also be assessed using the time from the first dose of study drug to the day that PD is confirmed based on radiological evidence or censored at the last on-study tumor assessment without PD. The number and percentages of patients with SD for more than 16 weeks will be presented.

Best overall response will be summarized by cohort using frequency distribution.

Waterfall plots will be presented for patients with measurable disease.

TTP calculated as from the first dose of study drug to the day that PD is confirmed based on radiological evidence or censored at the last on-study tumor assessment without PD will be presented in a Kaplan-Meier plot, as appropriate.

Other Antineoplastic Assessments

Tumor markers will be listed and summarized, as appropriate.

16.5.11 Pharmacokinetic Analysis

PK analyses will be performed in dose-escalation cohorts on patients who receive any amount of their assigned dose of study drug and have an adequate number of concentration determinations to allow for PK calculation.

The PK profile of study drug will be derived based on the concentration-time curves after the first infusion. $C_{max,}$ C_{EOI}, C_{trough} and T_{max} will be derived from observed data while AUC_{inf}, AUC_{τ}, $AUC_{norm, \tau}$, CL, V_d, and $T_{½}$ will be estimated using non-compartmental methods and actual timepoints. For repeated dosing, C_{EOI} and C_{trough} (equivalent to the concentration at EOI and SOI, respectively) will be assessed.

Individual curves of serum concentration of total study drug versus time after the first infusion will be presented on log- and linear scale for all patients in the PK population. Furthermore, maximum and trough serum concentrations for the period from first dose to EOT will be presented on linear scale individual plots. In addition, mean concentration-time curves will be presented on linear scale using nominal timepoint by cohort and trial part. All PK endpoints will be listed and summarized by trial part and cohort (**Table 5**).

Table 5: PK Endpoint, Definitions, and Derivations	
Symbol	**Definition and Derivation**
C_{trough}	Trough concentration (i.e., concentration of study drug measured pre-infusion)
AUC_{inf}	Area under the concentration-time curve from start of infusion to infinity
AUC_{τ}	Area under the concentration-time curve from start of infusion up to 336 hours.
$AUC_{norm, \tau}$	Dose-normalized area under the concentration-time curve in a dosing interval, calculated as AUC_{τ} divided by the dose infused
C_{max}	Maximum concentration
T_{max}	Time to maximum concentration
C_{EOI}	Concentration at the end of infusion
λ_z	Terminal rate constant (negative of the slope of an ln-linear regression of the un-weighted data considering the terminal phase of the concentration-time curve ≥ limit of quantification). λ_z is not an endpoint, but is used for derivation of endpoints
$T_{½}$	Terminal elimination half-life, calculated as $\ln(2)/ \lambda_z$
CL	Clearance after first dose, calculated as $Dose/AUC_{inf}$ for C1/D1, where AUC_{inf} will be calculated as the sum of the area from time zero to time of last quantifiable concentration, t_z, and the area from t_z to infinity. The second area will be estimated using the observed concentration at t_z and the terminal rate constant
V_d	Volume of distribution during the terminal phase after first dose (CL_S/ λ_z)

16.6 Additional Endpoints and Analyses

16.6.1 Pharmacodynamic and other Biomarker Analyses

Pharmacodynamic and other biomarker assessments, to include collection of peripheral blood, will be conducted in all patients. Tumor biopsies are optional and biomarker analysis of biopsied tumors may be performed on material collected.

Exploratory analysis may be performed. Endpoints may include genes and/or proteins that are unknown or have not been included in the scientific hypotheses at the time of the trial, but that, during the collection of data from this trial, may evolve as new candidate genes and markers related to safety, efficacy, or mechanism of action of the study drug.

Pharmacodynamic and other biomarker analyses will be performed according to standard methodologies and will examine relationships between the pharmacodynamic/biomarker assessments and clinical toxicities observed during the study.

16.7 Modeling of Pharmacokinetic and Pharmacodynamic/Biomarker Data

PK samples will be analyzed on an on-going basis during the trial. All data collected in this trial may be used for modeling of PK, pharmacodynamic and other biomarker assessment to support the planning and dose setting within the current trial as well as for future trials. Preliminary data generated during the trial may be used for exploratory modelling. The final data (i.e., after Database Lock) will be used for the final model and potentially for cross-trial modelling. These modelling activities will be reported separately from the current trial.

16.8 Deviations from the Statistical Plan

Any deviation(s) from the original analysis plan will be described in a protocol amendment and/or in the SAP and/or in the final CTR, as appropriate.

16.9 Interim Analysis

Safety evaluation will be performed prior to each dose-escalation. No other interim analyses are planned.

All relevant safety, PK, and toxicity data will be reviewed on an ongoing basis throughout the trial. Based on an overall evaluation of data collected, the RP2D will be chosen.

17 REFERENCES

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18 APPENDICES

Appendix 1 Performance Status Evaluation

Measures of Performance Status				
Percent	**KARNOFSKY Performance Status Description[1]**		**Level**	**Eastern Cooperative Oncology Group (ECOG) Performance Status Description[2]**
100	Normal; no complaints, no evidence of disease		0	Normal activity
90	Able to carry on normal activity; minor signs or symptoms of disease			
80	Normal activity with effort; some signs or symptoms of disease		1	Symptoms but ambulatory
70	Cares for self; unable to carry on normal activity or do active work			
60	Requires occasional assistance but is able to care for most needs		2	In bed < 50% of time
50	Requires considerable assistance and frequent medical care			
40	Disabled; requires special care and assistance		3	In bed > 50 % of time
30	Severely disabled; hospitalization is indicated although death is not imminent			
20	Very sick; hospitalization is necessary		4	100 % bedridden
10	Moribund; fatal processes progressing rapidly			
0	Death		5	Death

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Appendix 2 New York Heart Association Functional Criteria

New York Heart Association Functional Criteria	
Class I	No limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea, or anginal pain.
Class II	Slight limitation of physical activity. Comfortable at rest, but ordinary physical activity results in fatigue, palpitation, dyspnea, or anginal pain.
Class III	Marked limitation of physical activity. Comfortable at rest, but less than ordinary physical activity results in fatigue, palpitation, dyspnea, or anginal pain.
Class IV	Unable to carry on any physical activity without discomfort. Symptoms of cardiac insufficiency or anginal syndrome may be present even at rest. If any physical activity is undertaken discomfort increases.

The Criteria Committee of the New York Heart Association. *Nomenclature and Criteria for Diagnosis of Diseases of the Heart and Great Vessels*. 9th ed. Boston, Mass: Little, Brown & Co; 1994:253-256

Appendix 3 Clinical Adverse Events: Grading Scale

Severity	CTCAE* Grade	Definition
Mild	1	Awareness of symptom, but easily tolerated. Event is usually transient requiring no special treatment; does not interfere with usual status or activities
Moderate	2	Event may be ameliorated by simple therapeutic measures; may interfere with usual activities
Severe	3	Event results in temporary disability or incapacity; inability to perform usual activities; requires intervention
Life-threatening	4	Event requires immediate intervention; need for emergency treatment; patient is at risk of death at the time of the event
Fatal	5	Event resulting in the subsequent death of the patient

Note: In those cases where further definition of an event is provided by the Common Terminology Criteria for Adverse Events (CTCAE v5.0), please refer to that document for grading and severity information.

*< *https://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm* >

Appendix 4 Clinical Adverse Events: Determining Relationship to Study Drug

NOT-RELATED

This category applies to those AEs which, after careful medical consideration, are clearly felt to be due to extraneous causes (disease, environment, etc.) that are not-related to the administration of study drug.

UNLIKELY-RELATED *(must have first 2)*

This category applies to those AEs which, after careful medical consideration, are felt unlikely to be related to the administration of the study drug. The relationship of an AE to the study drug can be considered unlikely if:

- It does not follow a reasonable temporal sequence from administration of the drug.
- It could readily have been a result of the patient's clinical state, environmental or toxic factors, or other modes of therapy administered to the patient.
- It does not follow a known response pattern to the suspected drug.
- It does not reappear or worsen when the drug is re-administered.

POSSIBLY-RELATED *(must have first 2)*

This category applies to those AEs which, after careful medical consideration, are felt unlikely to be related to the administration of the study drug, but the possibility cannot be ruled out with certainty. The relationship of an AE to the study drug can be considered possible if:

- It follows a reasonable temporal sequence from administration of the drug.
- It could readily have been a result of the patient's clinical state, environmental or toxic factors, or other modes of therapy administered to the patient.
- It follows a known response pattern to the suspected drug.

PROBABLY-RELATED *(must have first 3)*

This category applies to those AEs which, after careful medical consideration, are felt with a high degree of certainty to be related to the administration of the study drug. The relationship of an AE to the study drug can be considered probable if:

- It follows a reasonable temporal sequence from administration of the drug.
- It could not be reasonably explained by the known characteristics of the patient's clinical state, environmental or toxic factors, or other modes of therapy administered to the patient.
- It disappears or decreases upon cessation of drug or reduction in dose (if applicable).*
- It follows a known response pattern to the suspected drug.

RELATED *(must have first 3)*

This category applies to those AEs, which, after careful medical consideration, are felt to be related to the administration of the study drug. The relationship of an AE to the study drug can be considered related if:

- It follows a reasonable temporal sequence from administration of the drug or drug levels have been established in body fluids or tissues.
- It could not be reasonably explained by the known characteristics of the patient's clinical state, environmental or toxic factors, or other modes of therapy administered to the patient.
- It disappears or decreases upon cessation of drug or reduction on dose (if applicable) and appears upon rechallenge.*
- It follows a known response pattern to the suspected drug.

Adapted from: Karch FE and Lasagna L. Adverse drug reactions: a critical review. *JAMA*. 1975 Dec 22; 234 (12):1236-1241.

**There are exceptions when an AE does not disappear upon discontinuation of the drug, yet drug-relatedness clearly exists, e.g., 1) tardive dyskinesia, 2) fixed drug eruptions.*

Appendix 5 Response Evaluation Criteria in Solid Tumors (RECIST v1.1)

Summary of RECIST v1.1 Guidelines

For the purposes of this study, patients should be re-evaluated for response every 8 weeks. In addition to a baseline scan, confirmatory scans should also be obtained ≥ 4 weeks following initial documentation of objective response (OR).

Response and progression will be evaluated in this study using the new international criteria proposed by the revised Response Evaluation Criteria in Solid Tumors (RECIST) guideline (version 1.1) [*Eur J Ca* 45:228-247, 2009]. Changes in the largest diameter (unidimensional measurement) of the tumor lesions and the shortest diameter in the case of malignant lymph nodes are used in the RECIST v1.1 criteria.

A. DEFINITIONS

Evaluable for Toxicity: All patients will be evaluable for toxicity from the time of their first treatment with study drug.

Evaluable for Objective Response: Only those patients who have measurable disease present at baseline, have received at least one cycle of therapy, and have had their disease re-evaluated will be considered evaluable for response. These patients will have their response classified according to the definitions stated below.

Note: Patients who exhibit objective disease progression prior to the end of cycle 1 will also be considered evaluable.

Evaluable Non-Target Disease Response: Patients who have lesions present at baseline that are evaluable but do not meet the definitions of measurable disease, have received at least one cycle of therapy, and have had their disease re-evaluated will be considered evaluable for non-target disease. The response assessment is based on the presence, absence, or unequivocal progression of the lesions.

B. DISEASE PARAMETERS

Measurable Disease: Measurable lesions are defined as those that can be accurately measured in at least one dimension (longest diameter to be recorded) as ≥ 20 mm by chest x-ray, as ≥10 mm with CT scan, or as ≥10 mm with calipers by clinical exam. All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters).

Note: Tumor lesions that are situated in a previously irradiated area might or might not be considered measurable.
If the investigator thinks it appropriate to include them, the conditions under which such lesions should be considered must be defined in the protocol.

Malignant Lymph Nodes: To be considered pathologically enlarged and measurable, a lymph node must be ≥ 15 mm in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). At baseline and at follow-up, only the short axis will be measured and followed.

Non-Measurable Disease: All other lesions (or sites of disease), including small lesions (longest diameter < 10 mm or pathological lymph nodes with ≥ 10 to < 15 mm short axis), are considered non-measurable disease. Bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonitis, inflammatory breast disease, and abdominal masses (not followed by CT or MRI) are considered as non-measurable.

Note: Cystic lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts.

Cystic lesions thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same patient, these are preferred for selection as target lesions.

Target Lesions: All measurable lesions up to a maximum of 2 lesions per organ and 5 lesions in total, 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), be representative of all involved organs, but in addition should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion which can be

measured reproducibly should be selected. A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. If lymph nodes are to be included in the sum, then only the short axis is added into the sum. The baseline sum diameters will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease.

Non-Target Lesions: All other lesions (or sites of disease) including any measurable lesions over and above the 5 target lesions should be identified as **non-target lesions** and should also be recorded at baseline. Measurements of these lesions are not required, but the presence, absence, or in rare cases unequivocal progression of each should be noted throughout follow-up.

C. METHODS FOR EVALUATION OF MEASURABLE DISEASE

All measurements should be taken and recorded in metric notation 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.

Note: The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging-based evaluation is preferred to evaluation by clinical examination unless the lesion(s) being followed cannot be imaged but are assessable by clinical exam.

Clinical Lesions: Clinical lesions will only be considered measurable when they are superficial (e.g., skin nodules and palpable lymph nodes) and ≥ 10 mm diameter as assessed using calipers (e.g., skin nodules). In the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended.

Chest X-ray: Lesions on chest x-ray are acceptable as measurable lesions when they are clearly defined and surrounded by aerated lung. However, CT is preferable.

Conventional CT and MRI: This guideline defines measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm or less. If CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situations (e.g., for body scans).

Use of MRI remains a complex issue. MRI has excellent contrast, spatial, and temporal resolution; however, there are many image acquisition variables involved in MRI, which greatly impact image quality, lesion conspicuity, and measurement. Furthermore, the availability of MRI is variable globally. As with CT, if an MRI is performed, the technical specifications of the scanning sequences used should be optimized for the evaluation of the type and site of disease. Furthermore, as with CT, the modality used at follow-up should be the same as was used at baseline and the lesions should be measured/assessed on the same pulse sequence. It is beyond the scope of the RECIST v1.1 guidelines to prescribe specific MRI pulse sequence parameters for all scanners, body parts, and diseases. Ideally, the same type of scanner should be used and the image acquisition protocol should be followed as closely as possible to prior scans. Body scans should be performed with breath-hold scanning techniques, if possible.

PET-CT: At present, the low dose or attenuation correction CT portion of a combined PET-CT is not always of optimal diagnostic CT quality for use with RECIST v1.1 measurements. However, if the site can document that the CT performed as part of a PET-CT is of identical diagnostic quality to a diagnostic CT (with IV and oral contrast), then the CT portion of the PET-CT can be used for RECIST v1.1 measurements and can be used interchangeably with conventional CT in accurately measuring cancer lesions over time. Note, however, that the PET portion of the CT introduces additional data which may bias an Investigator if it is not routinely or serially performed.

Ultrasound: Ultrasound is not useful in assessment of lesion size and should not be used as a method of measurement. Ultrasound examinations cannot be reproduced in their entirety for independent review later, and, because they are operator dependent, it cannot be guaranteed that the same technique and measurements will be taken from one assessment to the next. If new lesions are identified by ultrasound during the study, confirmation by CT or MRI is advised. If there is concern about radiation exposure using CT, MRI may be used instead of CT in selected instances.

Endoscopy, Laparoscopy: The utilization of these techniques for objective tumor evaluation is not advised. However, such techniques may be useful to confirm complete pathological response when biopsies are obtained or to determine relapse in trials where recurrence following complete response (CR) or surgical resection is an endpoint.

Tumor Markers: Tumor markers alone cannot be used to assess response. If markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response. Specific guidelines for both CA-125 response (in recurrent ovarian cancer) and prostate specific antigen (PSA) response (in recurrent prostate cancer) have been published [*JNCI* 96:487-488, 2004; *J Clin Oncol* 17, 3461-3467, 1999; *J Clin Oncol* 26:1148-1159, 2008]. In addition, the Gynecologic Cancer Intergroup has developed CA-125 progression criteria which are to be integrated with objective tumor assessment for use in first-line trials in ovarian cancer [*JNCI* 92:1534-1535, 2000].

Cytology, Histology: These techniques can be used to differentiate between partial responses (PR) and complete responses (CR) in rare cases (e.g., residual lesions in tumor types, such as germ cell tumors, where known residual benign tumors can remain).

The cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment when the measurable tumor has met criteria for response or stable disease is mandatory to differentiate between response or stable disease (an effusion may be a side effect of the treatment) and progressive disease.

FDG-PET: While FDG-PET response assessments need additional study, it is sometimes reasonable to incorporate the use of FDG-PET scanning to complement CT scanning in assessment of progression (particularly possible 'new' disease). New lesions based on FDG-PET imaging can be identified according to the following algorithm:

a. *Negative FDG-PET at baseline, with a positive FDG-PET at follow-up is a sign of PD based on a new lesion.*

b. *No FDG-PET at baseline and a positive FDG-PET at follow-up:*
   - *If the positive FDG-PET at follow-up corresponds to a new site of disease confirmed by CT, this is PD.*
   - *If the positive FDG-PET at follow-up is not confirmed as a new site of disease on CT, additional follow-up CT scans are needed to determine if there is truly progression occurring at that site (if so, the date of PD will be the date of the initial abnormal FDG-PET scan).*
   - *If the positive FDG-PET at follow-up corresponds to a pre-existing site of disease on CT that is not progressing based on the anatomic images, this is not PD.*

c. *FDG-PET may be used to upgrade a response to a CR in a manner similar to a biopsy in cases where a residual radiographic abnormality is thought to represent fibrosis or scarring. The use of FDG-PET in this circumstance should be prospectively described in the protocol and supported by disease-specific medical literature for the indication. However, it must be acknowledged that both approaches may lead to false positive CR due to limitations of FDG-PET and biopsy resolution/sensitivity.*

Note: A 'positive' FDG-PET scan lesion means one which is FDG avid with an uptake greater than twice that of the surrounding tissue on the attenuation corrected image.

D. RESPONSE CRITERIA

1. Evaluation of Target Lesions

Complete Response (CR): Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to < 10 mm.

Partial Response (PR): At least a 30% decrease in the sum of the diameters of target lesions, taking as reference the baseline sum diameters.

Progressive Disease (PD): At least a 20% increase in the sum of the diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm.

Note: The appearance of one or more new lesions is also considered progressions.

Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.

2. Evaluation of Non-Target Lesions

Complete Response (CR): Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (< 10 mm short axis).

Note: If tumor markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response.

Non-CR/Non-PD: Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits.

Progressive Disease (PD): Appearance of one or more new lesions and/or *unequivocal progression* of existing non-target lesions. *Unequivocal progression* should not normally trump target lesion status. It must be representative of overall disease status change, not a single lesion increase.

Although a clear progression of "non-target" lesions only is exceptional, the opinion of the treating physician should prevail in such circumstances, and the progression status should be confirmed later by the review panel (or Principal Investigator).

3. Evaluation of Best Overall Response

The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for progressive disease the smallest measurements recorded since the treatment started). The patient's best response assignment will depend on the achievement of both measurement and confirmation criteria.

For Patients with Measurable Disease (i.e., Target Disease)				
Target Lesions	**Non-Target Lesions**	**New Lesions**	**Overall Response**	**Best Overall Response when Confirmation is Required***
CR	CR	No	CR	≥ 4 wks. Confirmation**
CR	Non-CR/Non-PD	No	PR	≥ 4 wks. Confirmation**
CR	Not evaluated	No	PR	
PR	Non-CR/Non-PD/Not evaluated	No	PR	
SD	Non-CR/Non-PD/Not evaluated	No	SD	Documented at least once ≥ 4 wks. from baseline**
PD	Any	Yes or No	PD	no prior SD, PR or CR
Any	PD***	Yes or No	PD	
Any	Any	Yes	PD	

* *See RECIST v1.1 manuscript for further details on what is evidence of a new lesion.*
** *Only for non-randomized trials with response as primary endpoint.*
*** *In exceptional circumstances, unequivocal progression in non-target lesions may be accepted as disease progression.*

Note: Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as "*symptomatic deterioration.*" Every effort should be made to document the objective progression even after discontinuation of treatment.

Abbreviations (in alphabetical order): CR, complete response; PD, progressive disease; PR, partial response; SD, stable disease

For Patients with Non-Measurable Disease (i.e., Non-Target Disease)		
Non-Target Lesions	**New Lesions**	**Overall Response**
CR	No	CR
Non-CR/non-PD	No	Non-CR/Non-PD*
Not all evaluated	No	Not evaluated
Unequivocal PD	Yes or No	PD
Any	Yes	PD

* *Non-CR/non-PD is preferred over 'stable disease' for non-target disease since SD is increasingly used as an endpoint for assessment of efficacy in some trials, so to assign this category when no lesions can be measured is not advised.*

Abbreviations (in alphabetical order): CR, complete response; PD, progressive disease; PR, partial response; SD, stable disease

E. DURATION OF RESPONSE
Duration of Overall Response: The duration of overall response is measured from the time measurement criteria are met for CR or PR (whichever is first recorded) until the first date that recurrent or progressive disease is objectively documented (taking as reference for progressive disease the smallest measurements recorded since the treatment started). The duration of overall CR is measured from the time measurement criteria are first met for CR until the first date that progressive disease is objectively documented. **Duration of Stable Disease:** Stable disease is measured from the start of the treatment until the criteria for progression are met, taking as reference the smallest measurements recorded since the treatment started, including the baseline measurements.
F. PROGRESSION FREE SURVIVAL
Progression Free Survival is defined as the duration of time from start of treatment to time of progression or death, whichever occurs first.

Adapted from: Eisenhauer EA, Therasse P, Bogaerts J, et. al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). *Eur. J. Cancer.* 2009; 45:229-247.

<http://www.eortc.be/recist/documents/RECISTGuidelines.pdf >

Appendix 6 Immunotherapeutics RECIST (iRECIST)

1. DEFINITIONS

1.1 Evaluable for adverse events. All patients will be evaluable for adverse event evaluation for the time of their first treatment.

1.2 Evaluable for response. All patients who have received at least one cycle of therapy and have their disease re-evaluated will be considered evaluable for response (exceptions will be those who exhibit objective disease progression prior to the end of cycle 1 who will also be considered evaluable). Patients on therapy for at least this period and who meet the other listed criteria will have their response classified according to the definitions set out below.

Response and progression will be evaluated in this study using the revised international criteria proposed by the Response Evaluation Criteria in Solid Tumors (Version 1.1) (RECIST v1.1) committee as well as the modified iRECIST guidelines. Investigators should note the different requirements for confirmatory scans as well as follow-up for the two criteria.

See below for criteria for continuing treatment past RECIST v1.1 disease progression.

2 RECIST v1.1 RESPONSE AND EVALUATION ENDPOINTS

2.1 *Measurable Disease*. Measurable tumor lesions (nodal, subcutaneous, lung parenchyma, solid organ metastases) are defined as those that can be accurately measured in at least one dimension (longest diameter to be recorded) as ≥ 20 mm with chest x-ray and as ≥ 10 mm with CT scan or clinical examination. Bone lesions are considered measurable only if assessed by CT scan and have an identifiable soft tissue component that meets these requirements (soft tissue component ≥ 10 mm by CT scan). *Malignant lymph nodes* must be ≥ 15 mm in the short axis to be considered measurable; only the short axis will be measured and followed. All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters). Previously irradiated lesions are not considered measurable unless progression has been documented in the lesion.

2.2 *Non-measurable Disease*. All other lesions (or sites of disease), including small lesions are considered non-measurable disease. Bone lesions without a measurable soft tissue component, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonis, inflammatory breast disease, lymphangitic involvement of lung or skin and abdominal masses followed by clinical examination are all non-measurable. Lesions in previously irradiated areas are non-measurable, unless progression has been demonstrated.

2.3 *Target Lesions*. When more than one measurable tumor lesion is present at baseline, all lesions up to a maximum of 5 lesions total (and a maximum of 2 lesions per organ) representative of all involved organs should be identified as target lesions and will be recorded and measured at baseline. Target lesions should be selected based on their size (lesions with the longest diameter), be representative of all involved organs, and should be those that lend themselves to reproducible repeated measurements. Note that pathological nodes must meet the criterion of a short axis of ≥ 15 mm by CT scan and only the short axis of these nodes will contribute to the baseline sum. All other pathological nodes (those with short axis ≥ 10 mm but < 15 mm) should be considered non-target lesions. Nodes that have a short axis < 10 mm are considered non-pathological and should not be recorded or followed. At baseline, the sum of the target lesions (longest diameter of tumor lesions plus short axis of lymph nodes: overall maximum of 5) is to be recorded.

After baseline, a value should be provided on the CRF for all identified target lesions for each assessment, even if very small. If extremely small and faint lesions cannot be accurately measured but are deemed to be present,

a default value of 5 mm may be used. If lesions are too small to measure and indeed are believed to be absent, a default value of 0 mm may be used.

2.4 *Non-target Lesions*. All non-measurable lesions (or sites of disease) plus any measurable lesions over and above those listed as target lesions are considered non-target lesions. Measurements are not required but these lesions should be noted at baseline and should be followed as "present" or "absent".

2.5 *Response*. All patients will have their BEST RESPONSE from the start of study treatment until the end of treatment classified as outlined below:

Complete Response (CR): disappearance of target and non-target lesions and normalization of tumor markers. Pathological lymph nodes must have short axis measures < 10 mm (Note: continue to record the measurement even if < 10 mm and considered CR). Residual lesions (other than nodes < 10 mm) thought to be non-malignant should be further investigated by cytology specialized imaging or other techniques as appropriate for individual cases before CR can be accepted. Confirmation of response is only required in non-randomized studies.

Partial Response (PR): at least a 30% decrease in the sum of measures (longest diameter for tumor lesions and short axis measure for nodes) of target lesions, taking as reference the baseline sum of diameter. Non-target lesions must be non-PD. Confirmation of response is only required in non-randomized studies.

Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum of diameters on study.

Progressive Disease (PD): at least 20% increase in the sum of diameters of measured lesions taking as reference the smallest sum of diameters recorded on study (including baseline) AND an absolute increase of ≥ 5 mm. Appearance of new lesions will also constitute progressive disease (including lesions in previously unassessed areas). In exceptional circumstances, unequivocal progression of non-target disease may be accepted as evidence of disease progression, where the overall tumor burden has increased by at least 73% in volume. Modest increases in the size of one or more non-target lesions are NOT considered unequivocal progression. If the evidence of PD is equivocal (target or non-target), treatment may continue until the next assessment, but if confirmed, the earlier date must be used.

Integration of Target, Non-Target and New Lesions into Response Assessment				
Target Lesions	**Non-Target Lesions**	**New Lesions**	**Overall Response**	**Best Response for this Category Also Requires**
Target lesions + non-target lesions				
CR	CR	No	CR	Normalization of tumor markers, tumor nodes < 10 mm
CR	Non-CR/Non-PD	No	PR	
CR	Not all evaluated	No	PR	
PR	Non-PD/not all evaluated	No	PR	
SD	Non-PD/not all evaluated	No	SD	Documented at least once ≥ 4 weeks from baseline
Not all evaluated	Non-PD	No	NE	
PD	Any	Any	PD	
Any	PD	Any	PD	
Any	Any	Yes	PD	
Non-target lesions ONLY				
No Target	CR	No	CR	Normalization of tumor markers, tumor nodes < 10 mm
No Target	Non-CR/non-PD	No	Non-CR/non-PD	
No Target	Not all evaluated	No	NE	
No Target	Unequivocal PD	Any	PD	
No Target	Any	Yes*	PD	

Note: Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as "symptomatic deterioration". This is a reason for stopping therapy, but is NOT objective PD. Every effort should be made to document the objective progression even after discontinuation of treatment.
*Investigators should record all new lesions; if the new lesion is felt to be equivocal, treatment may be continued pending further assessments.

Abbreviations (in alphabetical order): CR, complete response; NE, not evaluable; PD, progressive disease; SD, stable disease

3 iRECIST RESPONSE ASSESSMENT

Overall response will also be assessed using iRECIST. Immunotherapeutics may result in infiltration of immune cells leading to transient increase in the size in malignant lesions, or undetectable lesions becoming detectable for instance where an increase in tumor burden, or the appearance of new lesions, does not reflect true tumor progression.

Key differences are described below. All responses defined using iRECIST criteria are designated with a prefix "i". iRECIST time-point and best overall responses will be recorded separately.

3.1 Confirming Progression

Unlike RECIST v1.1, iRECIST requires the confirmation of progression and uses the terms iUPD (unconfirmed progression) and iCPD (confirmed progression). Confirmatory scans should be performed at least 4 weeks, but no longer than 8 weeks, after iUPD.

iCPD is confirmed if further increase in tumor burden, compared to the last assessment, is evidenced by one or more of the following:

- Continued increase in tumor burden (from iUPD) where RECIST v1.1 definitions of progression had been met (from nadir) in target, non-target disease or new lesions.
    - Progression in target disease worsens with an increase of at least 5 mm in the absolute value of the sum
    - Continued unequivocal progression in non-target disease with an increase in tumor burden

- Increase in size of previously identified new lesion(s) (an increase of at least 5 mm in the absolute value of the sum of those considered to be target new lesions) or additional new lesions.

- RECIST v1.1 criteria are met in lesion types (target or non-target or new lesions) where progression was not previously identified, including the appearance of additional new lesion.

If iUPD is not confirmed at the next assessment, then the appropriate response will be assigned (iUPD if the criteria are still met, but no worsening, or iSD, iPR, or iCR if those criteria are met compared to baseline). As can be seen in the table below, the prior documentation of iUPD does not preclude assigning iCR, iPR, or iSD in subsequent time-point assessments or as best overall response providing that iCPD is not documented at the next assessment after iUPD.

3.2 New Lesions

New lesions should be assessed and measured as they appear using RECIST v1.1 criteria (maximum of 5 lesions, no more than 2 per site, at least 10 mm in long axis [or 15 mm in short axis for nodal lesions]), and recorded as New Lesion-Target (NLT) and New Lesion-Non-Target (NLNT) to allow clear differentiation from baseline target and non-target lesions.

New lesions may either meet the criteria of NLT or NLNT to drive iUPD (or iCPD). However, the measurements of target lesions should NOT be included in the sum of measures of original lesions identified at baseline. Rather, these measurements will be collected on a separate table in the CRF.

PD is confirmed in the New Lesion category if the next imaging assessment, conducted at least 4 weeks (but not more than 8 weeks) after iUPD confirms further progression from iUPD with either an increase of at least 5 mm in the absolute value of the sum of NLT or an increase (but not necessarily unequivocal increase) in the size of NLNT lesions or the appearance of additional new lesions.

iRECIST Timepoint Response				
Target Lesions*	**Non-Target Lesions***	**New Lesions***	**Timepoint Response**	
			No Prior iUPD**	**Prior iUPD**, *****
iCR	iCR	No	iCR	iCR
iCR	Non-iCR/Non-iUPD	No	iPR	iPR
iPR	Non-iCR/Non-iUPD	No	iPR	iPR
iSD	Non-iCR/Non-iUPD	No	iSD	iSD
iUPD with no change or decrease from last TP	iUPD with no change or decrease from last TP	Yes	NA	NLs confirms iCPD if NLs were previously identified and increase in size (≥ 5 mm in SOM for NLT or any increase for NLNT) or number. If no change in NLs (size or number) from last TP, remains iUPD
iSD	iUPD	No	iUPD	Remains iUPD unless iCPD confirmed based on further increase in size of NT lesion (need not meet RECIST v1.1 criteria for unequivocal PD)
iUPD	Non-iCR/Non-iUPD	No	iUPD	Remains iUPD unless iCPD confirmed based on: • Further increase in SOM of at least 5 mm, otherwise remains iUPD
iUPD	iUPD	No	iUPD	Remains iUPD unless iCPD confirmed based on further increase in: • Previously identified T lesion iUPD SOM ≥ 5 mm and/or • NT lesion iUPD (prior assessment – need not be unequivocal PD)
iUPD	iUPD	Yes	iUPD	Remains iUPD unless iCPD confirmed based on further increase in: • Previously identified T lesion iUPD ≥ 5 mm and/or • Previously identified NT lesion iUPD (need not be unequivocal) and/or • Size or number of NLs previously identified
Non-iUPD/PD	Non-iUPD/PD	Yes	iUPD	Remains iUPD unless iCPD confirmed based on • Increase in size or number of NLs previously identified

*Using RECIST v1.1 principles. If no PSPD occurs, RECIST v1.1 and iRECIST categories for CR, PR, and SD would be the same
**in any lesion category
***previously identified in assessment immediately prior to this TP

Abbreviations (in alphabetical order): CPD, confirmed progressive disease; CR, complete response; NE, not evaluable; NL, new lesion; NLNT, new lesion-non-target; NLT, new lesion-target; NT, non-target; PD, progressive disease; PR, partial response; PSPD, pseudoprogression; SD, stable disease; SOM, sum of measurements; T, target; TP, timepoint; UPD, unconfirmed progressive disease

All patients will have their iRECIST best overall response (iBOR) from the start of study treatment until the end of treatment classified as outlined below.

iRECIST Best Overall Response					
TPR1	**TPR2**	**TPR3**	**TPR4**	**TPR5**	**iBOR**
iCR	iCR, iPR, iUPD, NE	iCR, iPR, iUPD, NE	iUPD	iCPD	iCR
iUPD	iPR, iSD, NE	iCR	iCR, iPR, iSD, iUPD, NE	iCR, iPR, iSD, iUPD, iCPD, NE	iCR
iUPD	iPR	iPR, iSD, iUPD, NE	iPR, iSD, iUPD, NE, iCPD	iPR, iSD, iUPD, iCPD, NE	iPR
iUPD	iSD, NE	PR	iPR, iSD, iUPD, NE	iPR, iSD, iUPD, iCPD, NE	iPR
iUPD	iSD	iSD, iUPD, NE	iSD, iUPD, iCPD, NE	iSD, iUPD, iCPD, NE	iSD
iUPD	iCPD	Anything	Anything	Anything	iCPD
iUPD	iUPD	iCPD	Anything	Anything	iCPD
iUPD	NE	NE	NE	NE	iUPD

- Table assumes a randomized study where confirmation of CR or PR is not required
- NE=not evaluable that cycle
- Designation "i" for BOR can be used to indicate prior iUPD to aid in data interpretation
- For patients with non-target disease only at baseline, only CR or non-CR/non-PD can be assigned at each TPR but is not shown in the table for ease of presentation.

Abbreviations (in alphabetical order): BOR, best overall response; CPD, confirmed progressive disease; CR, complete response; NE, not evaluable; NL, new lesion; PD, progressive disease; PR, partial response; PSPD, pseudoprogression; SD, stable disease; SOM, sum of measurements; TP, timepoint; TPR, timepoint response; UPD, unconfirmed progressive disease

4 RESPONSE AND STABLE DISEASE DURATION (RECIST v1.1 AND iRECIST)

Response duration will be measured from the time measurement criteria for CR/PR or iCR/iPR (whichever is first recorded) are first met until the first date that recurrent or progressive disease is objectively documented, taking as reference the smallest measurements recorded on study (including baseline).

Stable disease duration will be measured from the time of start of treatment until the criteria for progression are met, taking as reference the smallest sum on study (including baseline).

5 METHODS OF MEASUREMENT

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Assessments should be identified on a calendar schedule and should not be affected by delays in therapy. While on study, all lesions recorded at baseline should have their actual measurements recorded at each subsequent evaluation, even when very small (e.g., 2 mm). If it is the opinion of the radiologist that the lesion has likely disappeared, the measurement should be recorded as 0 mm. If the lesion is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned. For lesions which fragment/split, add together the longest diameters of the fragmented portions; for lesions which coalesce, measure the maximal longest diameter for the "merged lesion".

5.1 *Clinical Lesions*. Clinical lesions will only be considered measurable when they are superficial and ≥ 10 mm as assessed using calipers (e.g., skin nodules). For the case of skin lesions, documentation by color photography including a ruler to estimate the size of the lesion is recommended. If feasible, imaging is preferred.

5.2 *Chest X-Ray*. Chest CT is preferred over chest X-ray, particularly when progression is an important endpoint, since CT is more sensitive than X-ray, particularly in identifying new lesions. However, lesions ≥ 20 mm on chest X-ray may be considered measurable if they are clearly defined and surrounded by aerated lung.

5.3 *CT, MRI*. CT is the best currently available and reproducible method to measure lesions selected for response assessment. This guideline has defined measurability of lesions on CT scan based on the assumption that CT

slice thickness is 5 mm or less. If CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situations (e.g., for body scans). Other specialized imaging or other techniques may also be appropriate for individual cases. For example, while PET scans are not considered adequate to measure lesions, PET-CT scans may be used providing that the measures are obtained from the CT scan and the CT scan is of identical diagnostic quality to a diagnostic CT (with IV and oral contrast).

5.4 *Ultrasound*. Ultrasound is not useful in assessment of lesion size and should not be used as a method of measurement. If new lesions are identified by ultrasound during the study, confirmation by CT is advised.

5.5 *Endoscopy, Laparoscopy*. The utilization of these techniques for objective tumor evaluation is not advised. However, they can be useful to confirm complete pathological response when biopsies are obtained or to determine relapse in trials where recurrence following complete response or surgical resection is an endpoint.

5.6 *Tumor Markers*. Tumor markers alone cannot be used to assess objective tumor response. If markers are initially above the upper normal limit, however, they must normalize for a patient to be considered in complete response.

5.7 *Cytology, Histology*. These techniques can be used to differentiate between PR and CR in rare cases if required by protocol (for example, residual lesions in tumor types such as germ cell tumors, where known residual benign tumors can remain). When effusions are known to be a potential adverse effect of treatment (e.g., with certain taxane compounds or angiogenesis inhibitors), the cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment when the measurable tumor has met criteria for response or stable disease is advised to differentiate between response or stable disease and progressive disease.

Adapted from: Seymour L, Bogaerts J, Perrrone A, et. al. iRECIST: guidelines for response criteria for use in trials testing immunotherapeutics. *Lancet*. 2017; 18:143-152. (supplemental materials)

<http://www.eortc.org/recist/irecist/>

Appendix 7 Response Evaluation Criteria in Lymphoma (RECIL 2017)

Response Evaluation Criteria in Lymphoma
International Working Group: Response Criteria Based on Assessment of Target Lesions

Response	% Change from Baseline	FDG-PET	Bone Marrow Involvement	New Lesions
CR	Complete disappearance of all target lesions and all nodes with long axis < 10 mm ≥ 30% decrease in the sum of longest diameter of target lesions (PR) with normalization of FDG-PET	Normalization of FDG-PET (Deauville score 1-3)*	Not involved	No
PR	≥ 30% decrease in the sum of longest diameters of target lesions but not a CR	Positive (Deauville score 4-5)*	Any	No
MR[a]	≥ 10% decrease in the sum of longest diameters of target lesions but not a PR (< 30%)	Any	Any	No
SD	< 10% decrease or ≤ increase in the sum of longest diameters of target lesions	Any	Any	No
PD	20% increase in the sum of longest diameters of target lesions For small lymph nodes measuring < 15 mm post therapy, a minimum absolute increase of 5 mm and the long diameter should exceed 15 mm Appearance of a new lesion	Any	Any	Yes or No

[a] A provisional category

***Deauville Scoring** (for FDG avidity in Hodgkin's or Non-Hodgkin's Lymphoma) (as seen by FDG-PET)
Score 1: No uptake above the background
Score 2: Uptake ≤ mediastinum
Score 3: Uptake > mediastinum but ≤ liver
Score 4: Uptake moderately increase compared to the liver at any site
Score 5: Uptake markedly increased compared to the liver at any site
Score X: New areas of update unlikely to be related to lymphoma

Abbreviations (in alphabetical order): CR, complete response; FDG, fluorodeoxyglucose; mm, millimeter; MR, minor response; PD, progressive disease; PET, positron emission tomography; PR, partial response; SD, stable disease

Adapted from: Younes A, Hilden P, Coiffier B, et. al. International Working Group consensus response evaluation criteria in lymphoma (RECIL 2017). *Annals Oncol*. 2017 Apr 3. doi: 10.1093/annonc/mdx097.

Barrrington SF, Qian W, Somer EJ, et al., Concordance between four European centres of PET reporting criteria designed for use in multicentre trials in Hodgkin lymphoma. *Eur J Nucl Med Mol Imaging.* 2010. 37: 1824-1833.

Fellows GA, Ardeshna KM, Barrington ST, et al. Guidelines for the first line management of classical Hodgkin lymphoma. British J Haemotology, 2014. 166: 34-49.

Appendix 8 Adverse Events Observed with Antibodies to PD-1 and PD-L1

Although the mechanism of action is distinct, inhibitors of TIM-3 have many similarities to blockers of immune checkpoint pathways. Because of these similarities, data on the potential AEs seen after treatment with antibodies to PD-1 and PD-L1 are being included in this CTP.

Immune-mediated and non-immune-mediated AEs reported in the literature and/or prescribing information for PD-1 and PD-L1 pathway inhibitors are listed below, organized by System Organ Class. These data have been collated from the prescribing information of approved products as well as applicable literature and are listed below.

Adverse Events Observed with Antibodies to PD-1 and PD-L1	
Blood and lymphatic system disorders	Anaemia Lymphopenia Haemolytic anaemia Neutropenia Thrombocytopenia Pure red cell aplasia Pancytopenia Eosinophilia Acquired haemophilia A Cryoglobulinemia Disseminated intravascular coagulopathy
Cardiac disorders	Myocarditis Ventricular arrhythmias Hypotension Cardiomyopathy Pericarditis
Ear and labyrinth disorders	Autoimmune inner ear disease (listed below under Immunologic Disorders)
Endocrine disorders	Autoimmune inflammation of pituitary, thyroid, adrenal glands Hypophysitis, hypopituitarism, panypopituitarism Autoimmune thyroid disease (thyroiditis, hypothyroidism, hyperthyroidism) Thyroid disorders Adrenal insufficiency (central or primary) Diabetes mellitus (type 1) Syndrome of inappropriate antidiuretic hormone secretion
Eye disorders (Intraocular inflammation is rare ~1% in patients treated)	Uveitis Iridocylitis Retinal detachment Decreased visual acuity Ocular inflammatory toxicity Iritis Episcleritis Conjunctivitis Orbital inflammation (symptoms include photophobia, dryness of the eye, pain, blurred vision)
Gastrointestinal disorders	Diarrheal colitis (common, presents ~ 6-8 weeks into treatment; Grade 3-4 in 1-2%) Diarrhea Colitis, enterocolitis, gastroenteritis Nausea Vomiting Abdominal pain (abdominal discomfort, upper and lower abdominal pain) Decreased appetite Intestinal perforation Intestinal obstruction

Adverse Events Observed with Antibodies to PD-1 and PD-L1	
	Constipation Pancreatitis (increased amylase and lipase) Stomatitis Dysphagia Hypogeusia Ulcer haemorrhage
General disorders and administration site conditions	Fatigue-includes asthenia and fatigue, decreased activity, malaise Pyrexia IRR (Mild up to 25%, Severe < 2%; composite term includes chills, fever, back pain, flushing, dyspnea, hypotension) Oedema (includes periorbital, face oedema, generalized oedema, localized oedema, gravitational oedema, peripheral oedema, pulmonary oedema, and lymph oedema Weight loss (also listed under investigations) Cachexia secondary to dysphagia
Hepatobiliary disorders	Hepatitis
Immune system disorders (See also endocrine and other classes)	Pneumonitis Inflammatory myositis Myositis Myocarditis Colitis Hepatitis Autoimmune inflammation of pituitary, thyroid, adrenal glands Pancreatitis Myasthenia gravis and other autoimmune neurologic disorders Inflammatory arthritis Bullous pemphigoid Complications after allogeneic HSCT (veno-occlusive disease, graft versus host disease) Vasculitis Arthritis Psoriasis Histiocytic necrotizing lymphadenitis Systemic inflammatory response Polymyositis Pericarditis Dry eye (sicca syndrome) **Defined systemic disease** Sarcoidosis (cutaneous, pulmonary, muscle, neurological) Polymyalgia rheumatica-giant cell arteritis Celiac disease Lupus nephritis Dermatomyositis Autoimmune inflammatory myopathy Psoriasis Polymyositis Myasthenia gravis Sjogren's syndrome Bullous skin diseases (pemphigoid, bullous pemphigus) Autoimmune endocrinopathies (pituitary, thyroid, adrenals) Autoimmune hepatitis Autoimmune pancreatitis Autoimmune haemolytic anaemia Pure red cell aplasia Cryoglobulinemia Acquired Haemophilia A Autoimmune hepatitis

Adverse Events Observed with Antibodies to PD-1 and PD-L1	
	Systemic inflammatory response syndrome Autoimmune colitis Autoimmune pneumonitis
Infections and infestations	Upper respiratory tract infection (rhinitis, viral rhinitis, pharyngitis, nasopharyngitis) Respiratory tract infection Pneumonia/bronchopneumonia (bacterial, mycoplasma, *Pneumocystis jiroveccii* pneumonia) Nasal congestion Urinary tract infection (bacterial, fungal) Severe infections including sepsis, herpes encephalitis, mycobacterial infection leading to retroperitoneal haemorrhage Sepsis
Investigations	Increased ALT Increased AST Increased bilirubin Increased alkaline phosphate Increased GGT Increased creatinine Hyponatremia Hyperkalaemia Hypocalcemia Hypercalcemia Hypomagnesemia Hypermagnesemia Hypophosphatemia Decreased bicarbonate Increased amylase Increased lipase Increased thyroid stimulating hormone (TSH) Decreased weight Anaemia Lymphopenia Leukopenia Thrombocytopenia Increased triglycerides Increased cholesterol Hyperglycaemia Hypoalbuminemia Glomerular filtration rate decreased
Musculoskeletal and connective tissue disorders	Arthralgia Sjogren's syndrome Spondyloarthropathy Myositis Myopathy Rhabdomyolysis Musculoskeletal pain (includes back pain, bone pain, musculoskeletal chest pain, musculoskeletal discomfort, myalgia, pain in jaw, pain in extremities, neck pain, and spinal pain) Inflammatory arthritis-polyarthritis Myalgia Sarcoidosis Dry eye (sicca syndrome)
Nervous system disorders (neurologic syndromes in ~1-3% of patients)	Guillain-Barre syndrome Myasthenia gravis Non-infectious meningitis Transverse myelitis

Adverse Events Observed with Antibodies to PD-1 and PD-L1	
	Peripheral neuropathy and sensory neuropathy (hyperesthesia, hypoesthesia, paraesthesia, dysesthesia, peripheral motor neuropathy, peripheral sensory neuropathy, polyneuropathy); motor and sensory neuropathy Autoimmune encephalitis Encephalitis Dizziness Peroneal nerve palsy Neuritis Headache/migraine headache Partial seizures associated with focal inflammatory foci in brain Dizziness Dysgeusia Confusional state Meningitis/encephalitis Demyelination Encephalopathy Paralysis Polymyositis Insomnia Hypersomnia Recurrent seizures-bradykinesia (Parkinsonism) Polyradiculopathy Necrotizing myelopathy Symmetrical multifocal neuropathy Phrenic nerve palsy Meningoradiculoneuritis Posterior reversible encephalopathy syndrome (PRES) Aseptic Meningitis-Immune related meningitis Enteric neuropathy Autoimmune inner ear disease Multiple sclerosis
Pregnancy, puerperium and perinatal conditions	Embryo-foetal toxicity
Psychiatric disorders	Insomnia
Renal and urinary disorders	Nephritis and renal dysfunction Renal failure Acute kidney injury (rare ~ 1-2% of any grade; Grade 3-4 < 1%; Onset median 91 days; range 21-245 days) Glomerular filtration rate decreased Hematuria Urinary obstruction Tubulointerstitial nephritis-acute granulomatous interstitial nephritis Acute tubular necrosis Immune complex glomerulonephritis Thrombotic microangiopathy Creatinine elevation
Reproductive system and breast disorders	Lymphocytic vasculitis of the uterus
Respiratory, thoracic, and mediastinal disorders	Pneumonitis (uncommon~3%, but potentially severe or life-threatening; median onset 2.8 months) Cough, productive cough Dyspnea, exertional dyspnea Pleural effusion Respiratory failure Respiratory distress Pneumonia Pulmonary embolism Pneumothorax

Adverse Events Observed with Antibodies to PD-1 and PD-L1	
	Hypoxia Acute respiratory distress syndrome Radiation recall pneumonitis
Skin and subcutaneous tissue disorders-Dermatologic (Overall 30-40%; average onset 3.6 weeks	Rash (includes maculopapular rash, erythematous rash, macular rash, popular rash, reticular rash, pustular rash, vesicular rash, acneiform rash, follicular rash, pruritic rash, drug eruption, generalized rash, seborrheic keratosis, lichenoid keratosis, genital rash) Palmar plantar erythrodysesthesia Erythema Vitiligo Pruritus Exfoliative dermatitis Erythema multiforme Pemphigoid Bullous dermatitis Erythema multiforme Toxic epidermal necrolysis Stevens-Johnson syndrome Alopecia Dermatitis Sweet syndrome (neutrophil infiltration of skin) Oral mucositis Xerostomia
Vascular disorders	Venous thromboembolism Hypertension/hypertensive crisis Angiopathy

Adapted from: Opdivo (nivolumab) [package insert]. Princeton, NJ: Bristol-Myers Squibb Company; 2017.

Keytruda (pembrolizumab) [package inset]. Whitehouse Station, NJ: Merck & Co., Inc; 2017.

Tecentriq (atezolizumab) [package insert]. South San Francisco, CA: Genentech, Inc.; 2017.

Bavencio (avelumab) [package insert]. Rockland, MA; EMD Serono, Inc.; 2017.

Imfinzi (durvalumab) [package insert]. Wilmington, DE: AstraZeneca Pharmaceuticals LP; 2017.

Appendix 9 Grading and Management of Infusion-Related Reactions

Grading of Infusion-Related Reactions

The CTCAE v5.0* definition of IRRs (General Disorders and Administration Site Conditions) is shown below. Symptoms occurring during or following infusion of investigational therapy may also be defined according to AE categories such as allergic reaction, anaphylaxis, or cytokine release syndrome. In the setting of symptoms occurring during or following infusion of investigational therapy, investigators are encouraged to use the AE term "Infusion-Related Reaction" and any additional terms (including those not listed here) that best describe the event. Those described should be graded as follows:

Grading of Infusion-Related Reactions

Adverse Event	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Infusion-related reaction	Mild transient reaction; infusion interruption not indicated; intervention not indicated	Therapy or infusion interruption indicated but responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDS, narcotics, IV fluids); prophylactic medications indicated for ≤ 24 hours	Prolonged (e.g., not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for clinical sequelae	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by adverse reaction to the infusion of pharmacological or biological substances.					
Allergic reaction	Systemic intervention not indicated	Oral intervention indicated	Bronchospasm; hospitalization indicated for clinical sequelae; intravenous intervention indicated	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an adverse local or general response from exposure to an allergen.					
Anaphylaxis	-	-	Symptomatic bronchospasm, with or without urticaria; parenteral intervention indicated; allergy-related edema/angioedema; hypotension	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by an acute inflammatory reaction resulting from the release of histamine and histamine-like substances from mast cells, causing a hypersensitivity immune response. Clinically, it presents with breathing difficulty, dizziness, hypotension, cyanosis and loss of consciousness and may lead to death.					
Cytokine release syndrome	Fever with or without constitutional symptoms	Hypotension responding to fluids; hypoxia responding to < 40% O2	Hypotension managed with one pressor; hypoxia requiring ≥ 40% O2	Life-threatening consequences; urgent intervention indicated	Death
Definition: A disorder characterized by fever, tachypnea, headache, tachycardia, hypotension, rash, and/or hypoxia caused by the release of cytokines.					

**See <https://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm >*

Guidelines for Management of Infusion-Related Reactions

Consistent with usual medical practice, selected parenteral medications may be utilized for Grade ≥ 2 allergic/hypersensitivity reactions. The Sponsor should be contacted immediately if questions arise concerning the grade of the reaction. The following are recommended management guidelines for IRRs associated with study drug administration. In all cases the Investigator should use best clinical judgment in managing such reactions.

Management of Infusion-Related Reactions	
Grade 1	• Consider slowing the infusion to 50% of the prior rate • Monitor the patient for worsening condition • If the infusion is extended, administer subsequent infusions at the prolonged rate • Consider premedication or adjustment to premedications for subsequent infusions
Grade 2	• Interrupt the infusion for a minimum of 30 minutes • Administer additional pharmacologic therapy (e.g., diphenhydramine, acetaminophen) and appropriate supportive care (e.g., oxygen), as medically indicated • Resume the infusion at 50% of the prior rate once the infusion-related reaction has resolved or decreased to Grade 1 • Monitor the patient for worsening condition • Administer subsequent infusions at the prolonged rate • Consider premedication or adjustment to premedications for subsequent infusions
≥ Grade 3	• Stop the infusion • Administer additional pharmacologic therapy (diphenhydramine, dexamethasone) and appropriate supportive care (e.g., oxygen), as medically indicated • Administer epinephrine or bronchodilators as medically indicated • Hospital admission for observation may be indicated • Do not resume infusion after a ≥ Grade 3 reaction • Patients who have a Grade 3 infusion-related reaction will be considered to have had a DLT and will be discontinued from treatment. • Patients who have a > Grade 3 infusion-related reaction will be considered to have had a DLT and will be discontinued from treatment

In the Event of Infusion Prolongation

Any assessments to be performed or samples to be collected (e.g., VS, PK) at the end of or following EOI will still be performed or collected beginning at the delayed EOI timepoint. In situations where collection of late day samples, particularly the 8 hours after EOI sample, is logistically difficult due to clinic staff availability, an "end of day" sample may be obtained at the latest practical time on the day of the reaction.

For Grade 1 and Grade 2 reactions, rechallenge with a shorter duration of infusion (no less than the duration designated by the patient's dose assignment and weight) may be attempted at the Investigator's discretion, after a minimum of 2 doses with no evidence of infusion-related toxicity at the prolonged rate.

All infusion interruptions and subsequent prolongations, including modified infusion times, as well as the toxicity that necessitated them, will be clearly documented on the appropriate page of the patient's CRF.

Modification of Infusion Duration for the Trial

The duration of infusion will be prolonged for all subsequent patients entered to the trial in the following situations:

- In the event of a Grade 2 IRR in ≥ two thirds of the patients entered to a cohort, the duration of infusion for subsequent patients entered to the trial will be extended by 30 minutes (or longer, if indicated).
- In the event of a Grade 3 or greater IRR in any patient within a cohort, the duration of infusion for subsequent patients entered to the trial will be extended by 30 minutes (or longer, if indicated). Such a case will also be considered to have met the protocol criteria for a DLT, thus requiring expansion of the cohort.

These same criteria will be applied in the event IRRs occur on the extended 1-hour infusion schedule. In such a case, the duration of infusion for subsequent patients entered to the trial will be further extended by 30 minutes (or longer, if indicated). See **Section 6.5.3.5**.

Appendix 10 Management of Immune-Mediated Toxicities

Instructions for management of immune-mediated toxicities are provided below and are to be implemented as detailed EXCEPT where AEs meet the protocol-specified DLT criteria (**Section 6.8.3**). AEs that meet the protocol definition of DLT will require discontinuation from study treatment, without exception (**Section 6.8.2**); this instruction supersedes those provided below.

Adverse Reaction	Severity*	Dose Modification
Pneumonitis	Grade 2 pneumonitis	Withhold dose^
	Grade 3 or 4 pneumonitis	Permanently discontinue
Myocarditis**	Grade 2 myocarditis	Withhold dose^
	Grade 3 or 4 myocarditis	Permanently discontinue
Adrenal Insufficiency	Grade 2 adrenal insufficiency	Withhold dose^
	Grade 3 or 4 adrenal insufficiency	Permanently discontinue
Encephalitis	New-onset moderate or severe neurologic signs or symptoms	Withhold dose^
	Immune-mediated encephalitis	Permanently discontinue
Nephritis and Renal Dysfunction	Serum creatinine more than 1.5 and up to 6 × ULN	Withhold dose^
	Serum creatinine more than 6 times the ULN	Permanently discontinue
Episcleritis, Uveitis, or Iritis**	Grade 2 episcleritis, uveitis, or iritis	Withhold dose^
	Grade 3 or 4 episcleritis, uveitis, or iritis	Permanently discontinue
Colitis/Diarrhea	Grade 2 or 3 diarrhea or colitis	Withhold dose^
	Grade 4 diarrhea or colitis	Permanently discontinue
Hypophysitis	Grade 2 or 3 hypophysitis	Withhold dose^
	Grade 4 hypophysitis	Permanently discontinue
Type 1 Diabetes Mellitus	Grade 2 or 3 hyperglycemia	Withhold dose^
	Grade 4 hyperglycemia	Permanently discontinue
Inflammatory arthritis	Grade 2 arthritis	Withhold dose^
	Grade 3 arthritis	Permanently discontinue
Myositis**	Grade 2 myositis	Withhold dose^
	Grade 3 myositis	Permanently discontinue
Rash	Grade 2 or 3 rash	Withhold dose^
	Grade 4 rash	Permanently discontinue
Hepatitis	AST or ALT > 3 - 5 × ULN or total bilirubin > 1.5 - 3 × ULN (Grade 2)	Withhold dose^
	AST or ALT > 5 × ULN or total bilirubin > 3 × ULN (≥ Grade 3)	Permanently discontinue
Other	Other Grade 3 adverse reaction: • First occurrence • Recurrence of same event	•Withhold dose^ •Permanently discontinue
	Life-threatening or Grade 4 adverse reaction	Permanently discontinue
	Requirement for 10 mg per day or greater prednisone or equivalent for more than 12 weeks	Permanently discontinue
	Persistent Grade 2 or 3 adverse reactions lasting ≥ 12 weeks	Permanently discontinue

Abbreviations (in alphabetical order): ALT, alanine aminotransferase; AST, aspartate aminotransferase; mg, milligram; ULN, upper limit of normal

* Toxicity graded per Common Terminology Criteria for Adverse Events (Version 5.0) (CTCAE v5.0)

**Adapted from product package inserts to include these reactions; there are no recommended dose modifications for hypothyroidism or hyperthyroidism.

^ May resume treatment when adverse reaction returns to Grade 0 or Grade 1 and glucocorticoid therapy for reaction is discontinued

Appendix 11 Maximum Total Blood Collection Volumes

Maximum Total Blood Collection Volumes												
STUDY ASSESSMENTS	**Vol./ sample** (mL)	**Screening**		**Cycle 1**		**Cycle 2**		**EOT**		**1M FUP**		**TOTAL VOLUME**
		#	**Vol.** (mL)	**#**	**Vol.** (mL)	**#**	**Vol.** (mL)	**#**	**Vol.** (mL)	**#**	**Vol.** (mL)	
Hematology Panel	5	*1*	5	*5*	25	*2*	10	*1*	5	*1*	5	50
Biochemistry Panel	10	*1*	10	*5*	50	*2*	20	*1*	10	*1*	10	100
Coagulation Panel	5	*1*	5	*2*	10	*1*	5	*1*	5	*1*	5	30
Thyroid Function Tests	5	*1*	5	*1*	5	*1*	5	*1*	5	*1*	5	25
Pregnancy Test	5	*1*	5	*1*	5			*1*	5			15
Tumor Markers	5	*1*	5			*1*	5	*1*	5	*1*	5	20
ADA Testing	5			*2*	10	*1*	5	*1*	5	*1**	5	25
PK Studies	5			*11*	55	*4*	20	*1*	5	*1**	5	85
Pharmacodynamic Studies (Receptor Occupancy)	10			*3*	30	*3*	30	*1*	10	*1*	10	80
Biomarker Studies	30	*1*	30			*1*	30	*1*	30			90
Total Volume			65		190		130		85		50	**520**

Abbreviations (in alphabetical order): #, number of samples; 1M FUP, 1-month follow-up; ADA, anti-drug antibody; EOT, end of treatment; mL, milliliter; PK, pharmacokinetic; Vol, volume

*additional samples to be obtained at 2, 4, and 6 months after EOT if patient is available for blood collection

Along with Screening, days with maximum blood volume requirements:

- C1/D1: 100 mL
- Cx/D1: 40 mL (+ 5 mL for odd number cycles)
- EOT: 85 mL
- 1M FUP: 50 mL

Blood volumes for each additional cycle:

- Additional odd number cycles: ~70 mL
- Additional even number cycles: ~ 70 mL

If sites can perform hematology, serum chemistry, and coagulation studies with smaller volumes of blood per sample, they are encouraged to do so. Required PK, ADA, and PD/biomarker volumes are fixed and should not be reduced.

To estimate a patient's total blood collection volume during study participation, maximum estimates are used. During a patient's study participation, the maximum amounts of venous blood that will be collected are listed above. Study duration is based on 8 weeks estimated average patient participation, i.e., an average of Cycle 1 (4 weeks) plus Cycle 2 (4 weeks).

An indwelling venous access device is required for PK blood sample collections on Day 1 of Cycle 1. When an indwelling catheter (or equivalent venous access) is utilized, a blood flush discard of up to 3 mL is to be done before drawing the first blood tube collected on the scheduled day/time for routine laboratory tests and PK samples. **Blood flush discard volumes ARE NOT included in volume calculations in table above and should be considered when summarizing actual blood collection volumes.**

Appendix 12 Schedule of Assessments

STUDY ASSESSMENTS	Screening	CYCLE 1						CYCLE 2			SUBSEQUENT CYCLES			EOT *within 10d after treatment discontinuation*	1M FUP* *30d (+7) after last dose*	Long-Term FUP* *if OR/ SD at EOT, for new-onset or ongoing immune-mediated AEs*	As Clinically Indicated
		D1	D2	D3 (+1)	D8 (±2)	D15 (±2)	D22 (±2)	D1 (±2)	D15 (±2)	End of Cycle 2 (final week)	D1 (±2)	D15 (±2)	End of Even Numbered Cycles (final week)				
CONSENT AND MEDICAL HISTORY																	
Informed Consent[1]/ Eligibility Assessment	x																
Demography	x																
Past Medical History[2]	x	x[a]															
History of Primary Malignancy[3]	x																
SAFETY ASSESSMENTS *(screening assessments within 14 days prior to first dose of study drug unless otherwise specified)*																	
Medication/Procedure Survey[4]	from 14 days prior to 1st dose through 30 days after last dose																
AE Reporting[5]	from signing of informed consent through 30 days after last dose; through 2 months (or 4 months to 2 years) FUP if related critical AEs persist															Q2M[d]	x
DLT Assessment[6]		C1/D1 through C1/D28 (+/- 2 days)															x
ECOG PS Evaluation	x	x[a]						x			x			x	x		x
Vital Signs[7]	x	SOI; EOI; 2h, 4h, 8h after EOI	x	x		SOI, EOI		x			x			x	x		x
Physical Exam (to include weight, pulmonary and cardiac assessments)[8]	x	x[a]						x			x			x	x		x
Hematology Panel[9]	x	x[a]		x	x	x	x	x	x		x	x		x	x		x
Biochemistry Panel[10]	x	x[a]		x	x	x	x	x	x		x	x		x	x		x
Coagulation Panel[11]	x	x[a]				x		x			x			x	x		x
Thyroid Function Tests[12]	x	x[a]						x			x			x	x		x
Urinalysis[13]	x	x[a]				x		x			x			x	x		x
Pregnancy Testing[14]	x	x												x			x
ECG (12-lead)[15]	x	SOI, EOI +15 min						SOI, EOI +15 min						x			x
SAFETY ASSESSMENTS *(results from assessments previously performed as standard of care within 28 days [+2d] prior to 1st dose may be utilized provided no antineoplastic therapy has been delivered between assessment and 1st dose; otherwise within 14 days of 1st dose)*																	
MUGA Scan or ECHO[16]	x													x			x
Ophthalmology Exam[17]	x							EOC1 visual acuity only		x[b]			x[b]	x			x
Pulmonary Function Tests[18]	x													x			x
DISEASE ASSESSMENTS *(screening assessments within 28 days [+2d] prior to first dose of study drug)*																	
Tumor Marker Measurement[19]	x									x[b]			x[b]	x[c]	If no prior PD	Q2M[e]	

STUDY ASSESSMENTS	Screening	CYCLE 1						CYCLE 2			SUBSEQUENT CYCLES			EOT *within 10d after treatment discontinuation*	1M FUP* *30d (+7) after last dose*	Long-Term FUP* *if OR/ SD at EOT, for new-onset or ongoing immune-mediated AEs*	As Clinically Indicated
		D1	D2	D3 (+1)	D8 (±2)	D15 (±2)	D22 (±2)	D1 (±2)	D15 (±2)	End of Cycle 2 (final week)	D1 (±2)	D15 (±2)	End of Even Numbered Cycles (final week)				
Imaging for Disease (and Pulmonary Status)[20]	x									x[b]			x[b]	x[c]	If no prior PD	Q2M[e]	
Lymphoma patients: FDG-PET, X-ray, U/S, BM aspiration/Bx	As indicated									As indicated[b]			As indicated[b]	As indicated	As indicated	Q2M[e]	
Response Assessment (in event of OR or SD)[21]										x[b]			x[b]	x[c]	If no prior PD	Q2M[e]	
ADDITIONAL ASSESSMENTS																	
ADAAssessment[22]		x				x		x			Odd # Cs			x	x	Q2M for 6 months[f]	x
PK Assessment[23]		SOI; EOI; 2h, 4h, 8h after EOI	24h after EOI	-12h to +24h	x	SOI, EOI	x	SOI, EOI	SOI, EOI		SOI, EOI	SOI, EOI		x	x	Q2M for 6 months[f]	
Peripheral Blood for Pharmacodynamic Studies (receptor occupancy)[24]		x	24h			x		x	D15 (+ 0-7)	EOC2 or C3/D1[b]			Q4C (C6, C10, etc.)[b]	x	x		
Peripheral Blood for Biomarker Studies[25]	upon eligibility								D15 (+ 0-7)					x			
Tumor Biopsy for Biomarker Studies (optional)[26]	upon eligibility								D15 (+ 0-7)					Upon PD if prior OR or SD > 16wks			
TRIAL TREATMENT																	
Premedication Administration (if indicated)		x				x		x	x		x	x					
Study Drug Infusion (30 minutes) (+10 min)		x				x		x	x		x	x					
Post-Infusion Monitoring		2h				1h		1h	1h		1h	1h					

Abbreviations (in alphabetical order): 1M FUP, 1-month follow-up; ADA, anti-drug antibody; AE, adverse event; BM, bone marrow; Bx, biopsy; C, cycle: D/d, day; DLT, dose-limiting toxicity; h, hour; ECG, electrocardiogram; ECHO, echocardiogram; ECOG, Eastern Cooperative Oncology Group; EOC, end of cycle; EOI, end of infusion; EOT, end of treatment; FDG, fluorodeoxyglucose; FUP, follow-up; MUGA, multi-gated acquisition; OR, objective response; PET, positron emission tomography; PK, pharmacokinetic; PS, performance status; Q2M, every 2 months; Q4C, every 4 cycles; SD, stable disease; SOI, start of infusion; U/S, ultrasound

[a] Need not be assessed prior to Cycle 1 if ≤ 7 days since screening
[b] End of Cycle assessments may be conducted at any time during the week prior to Day 1 of the next cycle, including on Day 1 of the next cycle, prior to dosing
[c] Conduct only if > 6 weeks since the previous assessment
[d] To be conducted to assess for delayed onset of any post-therapy immune-mediated AE (up to 6 months following last dose), and in the event of an immune-mediated toxicity ongoing at the 1M FUP or noted during the 6-month post-therapy FUP period (up to 2 years). Clinical events may be followed in writing or by telephone; an in-person visit will not be required.

[e] To be conducted in the event of ongoing OR or SD at the end of treatment; continue until confirmed PD or another therapeutic intervention is initiated, or until the end of trial. Documentation may be submitted in writing or by e-mail; an in-person visit will not be required.
[f] Samples to be obtained if patient is available for blood collection

1. Informed Consent: To be signed prior to enrollment and prior to performing any protocol-related procedure, unless such testing was performed previously as part of the routine clinical management of the patient.
2. Past Medical History: To include history of prior/ongoing diseases or conditions as well as prior surgical procedures not related to the underlying malignancy.
3. History of Primary Malignancy: To include details of the primary malignancy, including: diagnosis and histological/cytological classification; date of initial diagnosis; stage of disease at diagnosis and at entry; current sites of metastases; prior surgical procedures for the malignancy and dates; prior antineoplastic therapy, prior radiation therapy, as well as dates of treatments, numbers of cycles, and best response to each therapy; date of most recent disease progression.
4. Medication/Procedure Survey: To include period within 14 days prior to first study drug dose and throughout study for a period of 30 days following last study drug dose.
5. AE Reporting: To detail symptoms that may be present prior to/at the time of first administration. AEs to be assessed from signing of informed consent, throughout study, and for the 1-month period (30 days) following last study drug dose; AEs to continue to be assessed for 2 months (and if necessary 4 months) following last study drug dose if events associated with study drug persist (to confirm that events have resolved, returned to baseline status, or been adequately explained. Investigator discretion may be used with respect to the method of contact for this AE assessment; clinical events may be followed in writing or by telephone, an in-person visit will not be required). Any patient who develops an immune-related toxicity (e.g., pulmonary fibrosis, myocarditis, ocular toxicity, drug-induced hepatotoxicity, etc.) will be followed at approximately 2-month intervals for up to 2 years to assess the course of the condition and evaluate potential reversibility of the finding.
6. DLT Assessment: Beginning on C1/D1 and ending at EOC1 (C1/D28 ± 2 days). To include evaluation for the occurrence of events meeting the trial DLT criteria. Only DLTs occurring during Cycle 1 will be used to make decisions regarding dose-escalation and tolerability. Events occurring after Cycle 1 will also be evaluated and taken into consideration when deciding upon further doses to be assessed as well as establishment of the RP2D.
7. Vital Signs: To include temperature, pulse, respiratory rate, blood pressure, and pulse oximetry. C1/D1 through C1/D3 window allowances align with PK timepoints windows
8. Physical Examination: Complete at screening including height, weight, general appearance, skin, head, eyes, ears, nose, throat, neck/thyroid, chest [includes pulmonary assessment, breasts], cardiovascular [includes heart, peripheral pulses] abdomen, musculoskeletal system, lymph nodes, neurologic and mental status; directed thereafter, must include weight as well as pulmonary and cardiac assessments. Dose adjustments should be made in the event of noted weight change (± 10% [less at the site's discretion or if required by institution procedures]). Pulmonary findings will be evaluated in detail at each visit by the Investigator (or physician designee). Evaluation to include review of pulmonary symptoms including but not limited to: cough, sputum production, hemoptysis, wheezing, dyspnea, dyspnea on exertion, chest pain, and/or chest pain associated with respirations, as well as review of cardiac symptoms including but not limited to chest pain, orthopnea, nocturia, edema, and palpitations.
9. Hematology Panel: To include CBC with hemoglobin, hematocrit, differential, ANC, and platelet count. Evaluation frequency should be increased in the event of hematologic toxicity.
10. Biochemistry Panel (fasting not required): To include Na, K, Cl, bicarbonate or carbon dioxide, BUN or equivalent, creatinine, glucose, bilirubin [total and direct], AST, ALT, ALP, Ca, Mg, phosphorous, albumin, total protein, uric acid, amylase, lipase, and CK (if abnormal, perform isoenzyme analysis to include at minimum CK-MB), serial troponins, and measurement of BNP. Evaluation frequency should be increased in the event of significant serum chemistry abnormalities. Clinically significant electrolyte abnormalities should be corrected prior to dosing.
11. Coagulation Panel: To include PTT (or aPTT), PT and/or INR.
12. Thyroid Function Tests: To include measurement of TSH, fT3, and fT4.
13. Urinalysis: Multi-panel chemical test strips are acceptable and should include assessment of specific gravity, pH, protein, glucose, ketones, leukocytes, nitrite, bilirubin, urobilinogen, and blood. Microscopic examination of sediment, if clinically indicated, to include assessment of cells (WBC and RBC per HPF, and casts).
14. Pregnancy Testing: β-hCG in WOCBP; serum at Screening, serum or urine thereafter; negative test must be confirmed within 2 working days prior to first dose of study drug.
15. ECG (12-Lead): To include measurement of PR interval, QRS duration, QT interval, and QTc interval (msec), as well as HR (BPM); to be performed after patient has been supine

or semi-recumbent for ≥ 10 minutes; repeat subsequent timepoints in triplicate separated by 5 minutes for 4 cycles (Day 1, SOI and EOI) in patients with a Cycle 1 or Cycle 2 QTc that is either: a) > 500 msec; b), increased by 60 msec over baseline; or c) decreased by 20 msec below baseline. If abnormities suggest new evidence of myocardial ischemia, perform isoenzyme analysis (to include at minimum CK-MB), serial troponins, and measurement of BNP.

16. MUGA Scan or ECHO: For measurement of LVEF; to be performed ONLY in patients with a history of CHF, individual patients should be followed with the same testing procedure throughout the study.
17. Ophthalmology Examination: To include funduscopic and slit lamp evaluations for assessment of retinal and corneal integrity, visual acuity as assessed by standardized chart or other appropriate measurement tool (e.g., Snellen chart), and any other noted ocular abnormality. If changes in visual acuity are noted, a thorough ophthalmologic evaluation should be performed within 48 hours (if feasible, based on weekends or holidays) of the initial observation in order to confirm the finding and determine if there is evidence of an immune-mediated AE, or other event that would preclude further treatment with study drug.
18. Pulmonary Function Tests: To include spirometry and diffusing capacity of carbon monoxide [DL_{CO}] to assess for evidence of pulmonary fibrosis. Spirometry assessments to include at minimum: FVC, FEV1, FRC, RV, and TLC. To be repeated if evidence of interstitial pneumonitis, pulmonary fibrosis or other potential evidence of drug-related pulmonary toxicity is documented on imaging studies or if pulmonary symptomatology indicates.
19. Tumor Marker Measurement: As indicated by tumor type.
20. Imaging for Assessment of Disease (and Pulmonary Status): To include diagnostic imaging by CT or MRI of the chest with each evaluation (for disease evaluation where indicated, and to assess for evidence of pulmonary fibrosis) plus abdomen and pelvis, and other sites as indicated based on tumor type and clinical judgment to assess the status of the underlying malignancy. Use of contrast is preferred but is at the discretion of the Investigator, as medically indicated. The same method(s) of disease evaluation and the same technique should be used throughout the study. For all imaging timepoints, the following will be recorded as per RECIST v1.1 (or other response criteria, as indicated): target lesions including size, location, and type (nodal/non-nodal); sum of diameters of target lesions; any new lesions noted during trial, including size, location, and type (nodal/non-nodal).
21. Response Assessment: To be assessed by the Investigator or qualified designee as per RECIST v1.1 (or other response criteria, as indicated).
22. ADA **(Specialty Lab)**: To assess immunogenicity; whole blood (~5 mL at each timepoint) will be collected for serum acquisition. If sampling is on a dosing day, collect prior to infusion. If a collected serum sample is inadequate or insufficient for ADA analysis, the analysis of ADA can be done using a PK serum sample from the same timepoint, if available. A detailed laboratory manual specifying sample collection, handling, storage, and shipment will be provided to the trial sites.
23. PK Sampling **(Specialty Lab)**: See **Section 7.6.1** for window allowances. Whole blood (~5 mL at each timepoint) will be collected for serum acquisition. If a collected serum sample is inadequate or insufficient for PK analysis, the analysis of PK can be done using an ADA serum sample from the same timepoint, if available. A detailed laboratory manual specifying sample collection, handling, storage, and shipment will be provided to the trial sites. PK sampling times may be adjusted according to early trial results to optimize evaluation.
24. Peripheral Blood for Pharmacodynamic Studies (Receptor Occupancy) **(Specialty Lab):** Whole blood (~10 mL at each timepoint) will be collected for assessment of receptor occupancy. C2D15 (+ 0 to 7 days) after dosing; to be collected on the day of tumor biopsy, if performed. End of Cycle sampling may be combined with EOT if patient discontinues treatment. A detailed laboratory manual specifying sample collection, handling, storage, and shipment will be provided to the trial sites.
25. Peripheral Blood for Biomarker Studies **(Specialty Lab):** *To be obtained only after eligibility has been confirmed. (May be collected C1/D1 prior to dosing.)* Whole blood (~30 mL at each timepoint) to be collected. C2D15 (+ 0 to 7 days) after dosing; to be collected on the day of tumor biopsy, if performed. For those timepoints where both a blood sample and a tumor biopsy are to be obtained, the blood sample must be collected first. A detailed laboratory manual specifying sample collection, handling, storage, and shipment will be provided to the trial sites.
26. Tumor Biopsy for Biomarker Studies (optional) (**Specialty Lab**): *To be obtained only after eligibility has been confirmed. (May be collected C1/D1 prior to dosing.)* Tissue for FFPE to be collected. C2D15 (+ 0 to 7 days) after dosing; to be collected with paired peripheral blood for biomarker studies. For those timepoints where both a blood sample and a tumor biopsy are to be obtained, the blood sample must be collected first. EOT sample upon PD only in patients with a prior OR or prolonged SD (> 16 weeks). A detailed laboratory manual specifying sample collection, handling, storage, and shipment will be provided to the trial sites

19 SUMMARY OF CHANGES

19.1 Protocol Amendment 1 dated 04-Apr-2018

- All DLTs will require discontinuation from study treatment, without exception.
- Any treatment delay >2 weeks during Cycle 1 due to toxicity will be considered a DLT, regardless of severity of the event.
- Failure to complete Cycle 1 due to any AE will be considered a DLT, regardless of severity of the event.
- Clarified that immune-mediated toxicity that requires use of glucocorticoids at a dose of ≥ 1 mg/kg/day of prednisone equivalents for treatment of the toxicity will be considered a DLT.
- Any reduction in visual acuity will be considered a DLT, regardless of grade or duration.
- All Grade 4 non-hematologic laboratory changes will be considered a DLT, regardless of rapidity of resolution.
- Any Grade 4 hematologic toxicity (other than those specifically covered which include neutropenia, thrombocytopenia, and anemia) lasting >5 days will be considered a DLT.
- Patients with a history of organ transplantation (e.g., stem cell or solid organ transplant) have been added as an exclusion criterion.
- Added a notation to the retreatment guidelines to indicate that patients may receive standard doses of replacement hormonal therapy for adrenal insufficiency, hypothyroidism, or other endocrine end-organ failure, and may resume study drug once considered by the Investigator to be stable on such therapy. This was added to be consistent with eligibility criteria.
- Tables have been updated based on changes described, including correction to the recommended premedication dose of famotidine from 30mg to 20mg (Table 4).
- Formatting adjustments, outline modifications, cross-reference links and link corrections, and other minor typographical corrections and slight wording changes are included.

Refer to **Table 6** for the changes in Protocol Amendment 1.

Table 6: Protocol Amendment 1		
SECTION	**ORIGINAL TEXT**	**NEW TEXT**
1 Synopsis: Patient Selection: Eligibility 4.3.1 Patients to be Excluded	**Patients to be Excluded** 8. Patients with a clinically significant (CS) cardiovascular disease or condition, including:… • History of acute coronary syndromes (including myocardial infarction [MI] and unstable angina), coronary angioplasty, or stenting within 6 months prior to first study drug administration *Not applicable (new exclusion criterion added, shifting list)*	**Patients to be Excluded** 8. Patients with a clinically significant (CS) cardiovascular disease or condition, including:… • History of acute coronary syndromes (including myocardial infarction [MI] and unstable angina), coronary angioplasty, stenting, or bypass within 6 months prior to first study drug administration 12. Patients with a history of organ transplantation (e.g. stem cell or solid organ transplant)
1 Synopsis: IMP Administration: Doses to be Administered 5.7 Dose Calculation 6.5.3.1.2 Changes in Dose to be Administered	**Changes in Dose to be Administered** *Dose adjustments should be made in the event of noted weight change (± 10%; less at the site's discretion or if required by institution procedures) at visits that require weight measurement. Adjustments may be made in the event of lesser incremental changes in weight and more frequently at the site's discretion.*	**Changes in Dose to be Administered** *Dose adjustments should be made in the event of noted weight change (± 10%; less at the site's discretion or if required by institution procedures) at visits that require weight measurement. Adjustments may be made more frequently at the site's discretion.* *(Text was added to section 5.7)*
1 Synopsis: IMP Administration: Premedication	**Premedication for Infusion-Related Reactions** In the event of an IRR during study: • For Grade 3 reactions, premedication prior to subsequent infusions is required. Patients experiencing a Grade 3 reaction after having received premedication will be discontinued from treatment.	**Premedication for Infusion-Related Reactions** In the event of an IRR during study: • For Grade 3 reactions, not applicable as this is considered a DLT; therefore, no further treatment with study drug is allowed.
1 Synopsis: Continued Treatment: Retreatment Following an Objective Response	This option for retreatment does not apply to patients who previously experienced an immune-mediated toxicity that required permanent discontinuation from study drug (*see Treatment Discontinuation Criteria*).	This option for retreatment does not apply to patients who previously experienced a DLT that required permanent discontinuation from study drug (*see DLT and Treatment Discontinuation Criteria*).
1 Synopsis: AEs and DLTs: Management of DLTs and Other Toxicities	**Management of Dose-Limiting Toxicities** AEs that meet the protocol definition of DLT will be managed by either discontinuing the patient from further participation in the study, or the patient may continue if there is evidence of response or other clinical benefit, but dosing must be delayed, and the patient may not be retreated until retreatment criteria are met.	**Management of Dose-Limiting Toxicities** AEs that meet the protocol definition of DLT will require discontinuation from study treatment, without exception.

Table 6: Protocol Amendment 1		
SECTION	**ORIGINAL TEXT**	**NEW TEXT**
	Patients experiencing certain immune-mediated toxicities may not be retreated and will be discontinued from further participation (*see Treatment Discontinuation Criteria*).	
1 Synopsis: AEs and DLTs: Dose-Limiting Toxicities Definition 6.8.3 Definition of Dose-Limiting Toxicity	Any of the following toxicities occurring during Cycle 1, if judged to be related to study drug (i.e. possibly-related, probably-related, or related), will be considered a DLT for the purposes of this trial. 1. ≥ Grade 3 evidence of any of the following immune-mediated toxicities (patient must be permanently discontinued)… 2. ≥ Grade 3 evidence of any of the following immune-mediated toxicities (if > Grade 3, patient must be permanently discontinued)… 3. ≥ Grade 2… *Not applicable (new bullet point added)* *Not applicable (new toxicity added, shifting list)* 4. Hepatic-related findings consistent with Hy's Law criteria… 5. Any other ≥ Grade 3 or 4 non-hematologic toxicity regardless of duration with the exceptions of… • ≥ Grade 3 asymptomatic electrolyte abnormalities lasting ≤ 3 days that are not clinically complicated, and resolve spontaneously or respond to conventional medical interventions *Not applicable (new toxicity added, shifting list)* 6. Neutropenia that is… 7. Thrombocytopenia that is… 8. Anemia that is Grade 4 and not explained by underlying disease *Not applicable (new toxicity added, shifting list)* 9. Any death where a relationship to study drug cannot be ruled out 10. Inability to complete Cycle 1 at the assigned dose (i.e. receipt of < 2 full planned doses of study drug plus 2 weeks of follow-up) due to ≥ Grade 3 toxicity	Any of the following toxicities occurring during Cycle 1, if judged to be related to study drug (i.e. possibly-related, probably-related, or related), will be considered a DLT for the purposes of tolerability assessment during this trial. 1. ≥ Grade 3 evidence of any of the following immune-mediated toxicities… 2. ≥ Grade 3 evidence of any of the following immune-mediated toxicities… 3. ≥ Grade 2… • Immune-mediated toxicity that requires use of glucocorticoids at a dose of ≥ 1 mg/kg/day of prednisone equivalents for treatment of the toxicity 4. Any reduction in visual acuity, regardless of grade or duration 5. Hepatic-related findings consistent with Hy's Law criteria… 6. Any other ≥ Grade 3 or 4 non-hematologic toxicity regardless of duration with the exceptions of... • Grade 3 asymptomatic electrolyte abnormalities lasting ≤ 3 days that are not clinically complicated, and resolve spontaneously or respond to conventional medical interventions 7. Any Grade 4 non-hematologic laboratory toxicity regardless of duration 8. Neutropenia that is… 9. Thrombocytopenia that is… 10. Anemia that is Grade 4 and not explained by underlying disease 11. Any other Grade 4 hematologic toxicity (other than those specifically excluded) lasting > 5 days 12. Any death where a relationship to study drug cannot be ruled out 13. Inability to complete Cycle 1 at the assigned dose (i.e. receipt of < 2 full planned doses of study drug plus 2 weeks of follow-up) due to any toxicity 14. Treatment delays > 2 weeks from the scheduled next dose during Cycle 1 due to any toxicity

Table 6: Protocol Amendment 1		
SECTION	**ORIGINAL TEXT**	**NEW TEXT**
	11. Treatment delays > 2 weeks from the scheduled next dose during Cycle 1 due to ≥ Grade 3 toxicity	
1 Synopsis: Toxicity Safety Management and Safety Monitoring: IRR Management 8.5.1.1 Instructions for Infusion Prolongation for IRRs	• For Grade 3 reactions, the infusion will be STOPPED and supportive care will be provided. The occurrence will be considered a DLT and the patient will be either discontinued from treatment, or must receive subsequent doses at a prolonged infusion rate (slowed to 50% of the prior rate, or longer). In all cases the Investigator should use best clinical judgment in managing such reactions. For Grade 1 and 2 IRRs, rechallenge with a shorter duration of infusion (no less than 30 minutes) may be attempted at the Investigator's discretion, after a minimum of 2 doses with no evidence of infusion-related toxicity at the prolonged rate. For Grade 3 IRRs, continue administration at the prolonged rate.	• For Grade 3 reactions, the infusion will be STOPPED and supportive care will be provided. The occurrence will be considered a DLT and the patient will be discontinued from treatment. In all cases the Investigator should use best clinical judgment in managing such reactions. For Grade 1 and 2 IRRs, rechallenge with a shorter duration of infusion (no less than 30 minutes) may be attempted at the Investigator's discretion, after a minimum of 2 doses with no evidence of infusion-related toxicity at the prolonged rate.
1 Synopsis: Discontinuation and Follow-Up: Key Treatment Discontinuation Criteria 9.1 Criteria for Treatment Discontinuation	1. Adverse Events, including: • ≥ Grade 3 evidence of any of the following immune-mediated toxicities: o Pneumonitis o Myocarditis o Adrenal insufficiency o Encephalitis o Nephritis, renal dysfunction (serum creatinine elevation) o Episcleritis, uveitis, or iritis • > Grade 3 evidence of any of the following immune-mediated toxicities: o Colitis o Hypophysitis, hyperglycemia o Inflammatory arthritis o Myositis o Rash • Hepatotoxicity characterized by: o AST and/or ALT elevation > 3 × ULN (or > 3 × baseline if elevated at study entry due to hepatic involvement by tumor), with o total bilirubin ≥ 2 × ULN without initial findings of cholestasis (i.e. serum ALP < 2 × ULN), and	1. Adverse Events, including: • Any AE or SAE that meets the study DLT criteria at any time during the study • Another AE or SAE considered by the Investigator to require treatment discontinuation *(All other AEs listed in the original text were removed)*

Table 6: Protocol Amendment 1		
SECTION	**ORIGINAL TEXT**	**NEW TEXT**
	o No explanation for the above findings, such as viral hepatic injury, preexisting or acute liver disease, another drug or condition capable of causing the observed liver injury • > Grade 3 IRR; Grade 3 IRR in a patient who has received premedication • Any DLT considered by the Investigator to require treatment discontinuation • Another AE or SAE considered by the Investigator to require treatment discontinuation	
3.2 Trial Design Summary	Study Assessments …Patients will be evaluated for evidence of immune-mediated toxicities, evidence of certain specified conditions will result in immediate discontinuation from treatment with study drug. Patients will also be evaluated for evidence of antibody formation to study drug. Patients experiencing a DLT regarded as possibly-, probably-, or related to study drug at any point during treatment will either be discontinued from treatment with study drug, or may continue if there is evidence of an OR, SD, or other clinical benefit, but may do so ONLY following discussion with the Sponsor's Medical Monitor(s). Patients may not be retreated following the occurrence of a DLT until there is amelioration to ≤ Grade 1 severity, return to baseline status, or resolution of the toxicity. Only DLTs occurring during Cycle 1 will be used to make determinations regarding dose-escalation and tolerability. Exceptions to continuing on-study include evidence of certain immune-mediated toxicities, as detailed in Section 9.1; in such instances patients must be permanently discontinued from treatment with study drug.	Study Assessments …Patients will be evaluated for evidence of immune-mediated toxicities. Patients will also be evaluated for evidence of antibody formation to study drug. Patients experiencing a DLT regarded as possibly-, probably-, or related to study drug at any point during treatment will be discontinued from study treatment, without exception. Patients may not be retreated following the occurrence of a DLT. Only DLTs occurring during Cycle 1 will be used to make determinations regarding dose-escalation and tolerability.
6.5.3.5 Duration of Infusion	Note: In the event of a Grade 2 IRR, the Investigator may prolong the infusion duration to extend longer than the initially assigned duration (for further instructions see Section 8.5.1, Appendix 9). Study drug will be administered over a longer period for all patients entered to the trial in the following situations: • In the event of a Grade 2 IRR in ≥ two thirds of the patients entered to a cohort, the duration of infusion for subsequent patients entered to the trial will be extended to 1 hour (or longer, if indicated).	Note: In the event of a Grade 2 IRR, see Section 8.5.1, Appendix 9 for further instructions. Study drug will be administered over a longer period for all patients entered to the trial in the following situations: • In the event of a Grade 2 IRR in ≥ two thirds of the patients entered to a cohort, the duration of infusion for subsequent patients entered to the trial will be extended by 30 minutes (or longer, if indicated).

Table 6: Protocol Amendment 1		
SECTION	**ORIGINAL TEXT**	**NEW TEXT**
	• In the event of a Grade 3 or greater IRR in any patient within a cohort, the duration of infusion for subsequent patients entered to the trial will be extended to 1 hour (or longer, if indicated). Such a case will also be considered to have met the protocol criteria for a DLT, thus requiring expansion of the cohort. These same criteria will be applied in the event IRRs occur on the extended 1-hour infusion schedule. In such a case, the duration of infusion for subsequent patients entered to the trial will be extended to 1.5 hours (or longer, if indicated).	• In the event of a Grade 3 or greater IRR in any patient within a cohort, the duration of infusion for subsequent patients entered to the trial will be extended by 30 minutes (or longer, if indicated). Such a case will also be considered to have met the protocol criteria for a DLT, thus requiring expansion of the cohort. These same criteria will be applied in the event IRRs occur on the extended infusion schedule. In such a case, the duration of infusion for subsequent patients entered to the trial will be further extended by 30 minutes (or longer, if indicated).
6.7.1 Retreatment Guidelines	*Not applicable (new text added)*	Note: Patients may receive standard doses of replacement hormonal therapy for adrenal insufficiency, hypothyroidism, or other endocrine end-organ failure, and may resume study drug once considered by the Investigator to be stable on such therapy provided a DLT criterion has not been met.
6.7.6 Retreatment Following an Objective Response	This option for retreatment does not apply to patients who previously experienced an unacceptable toxicity that required permanent discontinuation of study drug (Section 9.1).	This option for retreatment does not apply to patients who previously experienced a DLT that required permanent discontinuation from study drug (Section 6.8.3, Section 9.1).
6.8.2 Management of Dose-Limiting Toxicities and Other Toxicities	If a significant toxicity thought to be related to study drug is experienced at any point during the patient's participation in the study, the Investigator will determine: • Whether that toxicity is dose-limiting (Section 6.8.3), thus requiring either discontinuation from study, or the patient may continue if there is evidence of response or other clinical benefit, but dosing must be delayed and the patient may not be retreated until retreatment criteria are met. Patients experiencing certain immune-mediated toxicities may not be retreated and will be discontinued from further participation (Section 9.1) • Whether the toxicity does not meet the protocol definition of DLT, but nevertheless warrants dose modification, in which case the Investigator may elect to temporarily delay dosing with study drug to allow for amelioration of the toxicity.	If a significant toxicity thought to be related to study drug is experienced at any point during the patient's participation in the study, the Investigator will determine: • Whether that toxicity is dose-limiting (Section 6.8.3), thus requiring discontinuation from study treatment, without exception. • Whether the toxicity does not meet the protocol definition of DLT, but nevertheless warrants dose modification, in which case the Investigator may elect to temporarily delay dosing with study drug to allow for amelioration of the toxicity.
7.1.3 Past Medical History	• Screening • C1/D1 (prior to dosing)	• Screening • C1/D1 (prior to dosing)* * Need not be assessed prior to Cycle 1 if ≤ 7 days since screening

Table 6: Protocol Amendment 1		
SECTION	**ORIGINAL TEXT**	**NEW TEXT**
7.2.8 Electrocardiogram	*(To be evaluated locally; to be performed after patient has been supine for ≥ 10 minutes)*	*(To be evaluated locally; to be performed after patient has been supine or semi-recumbent for ≥ 10 minutes)*
7.3.2 Ophthalmology Examination	*(To include funduscopic and slit lamp evaluations for assessment of retinal and corneal integrity, visual acuity, and any other noted ocular abnormality)* • Screening • EOC2 and every even-numbered cycle thereafter*, ** • EOT** • As clinically indicated	*(To include funduscopic and slit lamp evaluations for assessment of retinal and corneal integrity, visual acuity as assessed by standardized chart or other appropriate measurement tool, and any other noted ocular abnormality)* • Screening • EOC1 (visual acuity only; by Snellen chart or similar measurement tool)* • EOC2 and every even-numbered cycle thereafter*, ** • EOT** • As clinically indicated
7.7.1 Pharmacodynamic Assessments	• Cycle 2 o Day 1 o Day 15 (after dosing + 7 days) (at the time of biopsy if performed)	• Cycle 2 o Day 1 (prior to dosing) o Day 15 (after dosing + 7 days) (at the time of biopsy if performed)
8.3 Determination of DLT versus Non-DLT	If the protocol definition of DLT is met, the patient will be either discontinued from further treatment, or may continue if there is evidence of an OR, SD, or other clinical benefit, but may do so ONLY following discussion with the Sponsor's Medical Monitor(s). Patients may not be retreated following the occurrence of a DLT until there is amelioration to ≤ Grade 1 severity, return to baseline status, or resolution of the toxicity. Exceptions to continuing on study include evidence of certain immune-mediated toxicities as detailed in Section 9.1. In such instances patients must be permanently discontinued from treatment with study drug.	If the protocol definition of DLT is met, the patient will be discontinued from study treatment, without exception.
8.4.3 Premedication for IRRs (Following an IRR)	• For Grade 3 reactions, premedication prior to subsequent infusions will be required (if the patient is to be retreated). Patients experiencing a Grade 3 reaction after having received premedication will be discontinued from treatment.	• For Grade 3 reactions, not applicable as this is considered a DLT; therefore, no further treatment with study drug is allowed.
8.5.1.2 Treatment Following Infusion Prolongation	For Grade 3 IRRs, continue administration at the prolonged rate.	*Text removed*

Table 6: Protocol Amendment 1		
SECTION	**ORIGINAL TEXT**	**NEW TEXT**
10.1.2 Events Not to be Considered as Adverse Events	PD may be reported as an AE/SAE in the case of patient death, with death being the outcome of the event.	Note: PD may be reported as an AE in the case of patient death, with death being the outcome of the event.
10.1.5 Events That Do Not Meet the Definition of Serious Adverse Events	PD may be reported as an SAE in the case of patient death, with death being the outcome of the event.	Note: PD may be reported as an SAE in the case of patient death, with death being the outcome of the event.
10.3.1 Timeframes for Reporting to the Sponsor	In case of an SAE, the Investigator must, within 24 hours of awareness of the event, report the SAE to the Sponsor (or designee) by telefax or e-mail transmission. Fax number(s) and e-mail address(es) will be stated on the SAE Report Form and the SAE Report Form Completion Instructions. Timelines for reporting of SAEs and SAE follow-up information are shown (Table 5).	In case of an SAE, the Investigator must, within 24 hours of awareness of the event, report the SAE to the Sponsor (or designee) by telefax or e-mail transmission. Fax number(s) and e-mail address(es) will be stated on the SAE Report Form and the SAE Report Form Completion Instructions. SAE follow-up information must also be reported to the Sponsor (or designee) within 24 hours of awareness. *Removed Table 5: Timelines for Submission of SAEs and SAE Follow-up*
10.4 Pregnancy	Elective terminations for non-medical reasons should not be reported as AEs.	Elective terminations for non-medical reasons should be reported as follow-up, but not as a separate AE/SAE unless complications meet AE/SAE criteria.
11.1 Precautions Regarding Procreation	Studies have not been performed to determine whether this study drug affects reproductive function in males. For this reason, men with partners with childbearing potential must use a highly effective method of contraception while receiving study drug.	Studies have not been performed to determine whether this study drug affects reproductive function in males or can cause fetal harm. For this reason, men with partners of childbearing potential must use a highly effective method of contraception while receiving study drug.
13.4.2 Modification of the Informed Consent Form	If modifications… the Investigator will prepare a revision to the existing ICF. Such a revision will be reviewed and approved by the appropriate regulatory authority (as indicated) and IRB/EC, and documentation of this approval will be forwarded to the Sponsor (or designee) for submission to the appropriate regulatory body.	If modifications… the Sponsor (or designee) will prepare a revision to the existing sample ICF for modification, as appropriate, by each Investigator. Any revision to the sample ICF prepared by the Sponsor (or designee) will be implemented according to the Sponsor's (or designee's) SOPs. Such a revision will be reviewed and approved by the appropriate regulatory authority (as indicated) and IRB/EC.
14.1 Medical Supervision	An Investigator conducting a clinical study with an investigational agent is required to comply with regulations described in U.S. Title 21 CFR Part 312 and ICH E6(R2) GCP.	An Investigator conducting a clinical study with an investigational agent is required to comply with regulations described in U.S. Title 21 CFR Parts 50, 56, and 312 and/or by governing Health Authorities, as well as ICH E6(R2) GCP.
14.8 Recording of Data	All data must be carefully entered to permit meaningful interpretation. Corrections to entered data will be tracked within the EDC system. Data must be entered into CRFs in a timely fashion.	CRFs are designed for computer processing and analysis. All data must be carefully entered to permit meaningful interpretation. Corrections to

Table 6: Protocol Amendment 1		
SECTION	**ORIGINAL TEXT**	**NEW TEXT**
		entered data will be identified and tracked by audit trails within the EDC system. Data must be entered into CRFs in a timely fashion.
15.1 Data Handling	Data will be handled according to good data management practices, all applicable data protection regulations, and will comply with ICH E6(R2) GCP.	Study data collection, processing, transfer, and reporting as well as handling of study personnel information will be in compliance with ICH E6(R2) GCP and all applicable data protection regulations.
15.3 Data Processing	A Data Management Plan will be prepared for this trial. The Sponsor (or designee) will be responsible for data processing in accordance with applicable Data Management SOPs. Database Lock will occur once quality control procedures and quality assurance procedures (if applicable) have been completed upon reaching the data cut-off for primary analysis. Portable Document Format (PDF) files of the CRFs will be provided to the Investigator before access to the CRF system is revoked.	A Data Management Plan (DMP) will be prepared for this trial. The Sponsor (or designee) will be responsible for data processing in accordance with applicable Data Management SOPs and the trial DMP. Database Lock will occur upon reaching the pre-defined data cut-off for primary analysis and completion of Sponsor's (or designee's) quality control and quality assurance procedures. Portable Document Format (PDF) files of the electronic CRFs will be provided to the Investigator upon removal of access to the electronic CRFs.
Appendix 9: Grading and Management of Infusion-Related Reactions	**In the Event of Infusion Prolongation** For Grade 3 reactions, subsequent infusions must be administered at the prolonged rate. **Modification of Infusion Duration for the Trial** • In the event of a Grade 2 IRR in ≥ two thirds of the patients entered to a cohort, the duration of infusion for subsequent patients entered to the trial will be extended to 1 hour (or longer, if indicated). • In the event of a Grade 3 or greater IRR in any patient within a cohort, the duration of infusion for subsequent patients entered to the trial will be extended to 1 hour (or longer, if indicated). Such a case will also be considered to have met the protocol criteria for a DLT, thus requiring expansion of the cohort. These same criteria will be applied in the event IRRs occur on the extended 1-hour infusion schedule. In such a case, the duration of infusion for subsequent patients entered to the trial will be extended to 1.5 hours (or longer, if indicated). See Section 6.5.3.5.	**In the Event of Infusion Prolongation** *Text removed* **Modification of Infusion Duration for the Trial** • In the event of a Grade 2 IRR in ≥ two thirds of the patients entered to a cohort, the duration of infusion for subsequent patients entered to the trial will be extended by 30 minutes (or longer, if indicated). • In the event of a Grade 3 or greater IRR in any patient within a cohort, the duration of infusion for subsequent patients entered to the trial will be extended by 30 minutes (or longer, if indicated). Such a case will also be considered to have met the protocol criteria for a DLT, thus requiring expansion of the cohort. These same criteria will be applied in the event IRRs occur on the extended 1-hour infusion schedule. In such a case, the duration of infusion for subsequent patients entered to the trial will be further extended by 30 minutes (or longer, if indicated). See Section 6.5.3.5.

Table 6: Protocol Amendment 1		
SECTION	**ORIGINAL TEXT**	**NEW TEXT**
Appendix 10: Management of Immune-Mediated Toxicities	*Not applicable (new text added)*	Instructions for management of immune-mediated toxicities are provided below and are to be implemented as detailed EXCEPT where AEs meet the protocol-specified DLT criteria (Section 6.8.3). AEs that meet the protocol definition of DLT will require discontinuation from study treatment, without exception (Section 6.8.2); this instruction supersedes those provided below.

19.2 Protocol Amendment 2 dated 02-Aug-2018

- Patient exclusion criterion 9 has been added to exclude patients with a significant ocular disease or condition. Patients with non-significant, non-inflammatory disorders (e.g., cataracts, glaucoma) will be allowed.
- DLT criterion 4 has been modified to indicate that study drug-related changes in visual acuity will continue to be considered dose-limiting but changes must now be confirmed by subsequent ophthalmologic exam. In addition, a footnote has been added providing further guidance.
- The Study Safety Committee has been renamed to the Study Safety Team to better align with scope.
- Vital Signs windows have been modified to correspond with PK sampling windows.
- Instructions for ophthalmology reassessment in the event of changes in visual acuity are provided (i.e., within 48 hours, if feasible). The notation also indicates that no patient with a documented decrease in visual acuity may be retreated unless the event is considered unrelated to study drug, and unless the patient is cleared for retreatment by an ophthalmologist.
- Guidelines pertaining to the General Data Protection Regulation have been added.
- Formatting adjustments, minor typographical corrections, outline modifications, and slight wording changes are included.
- The synopsis and tables have been updated based on changes described, where applicable.

Refer to **Table 7** for the changes in Protocol Amendment 2.

Table 7: Protocol Amendment 2

SECTION	ORIGINAL TEXT	NEW TEXT
4.3.1 Patients to be Excluded	*Not applicable (new text added)*	9. Patients with a significant ocular disease or condition, including history of an autoimmune or inflammatory disorder, e.g., episcleritis, uveitis, iritis Note: Patients with a history of dry eye for reasons other than an autoimmune disease or condition may be included if adequately treated. Patients with non-significant, non-inflammatory disorders (e.g., cataracts, glaucoma) will be allowed.
6.8.3 Definition of Dose-Limiting Toxicity	4. Any reduction in visual acuity, regardless of grade or duration	4. Any confirmed reduction in visual acuity, regardless of grade or duration Note: Noted changes in visual acuity must be reevaluated by an ophthalmologist and confirmed within 48 hours *(if feasible, based on weekends or holidays)* of the initial observation; study drug will be held pending evaluation by the ophthalmologist. Changes in visual acuity assessment, if associated with either an immune-related AE, including but not limited to iritis, episcleritis, uveitis, or any

Table 7: Protocol Amendment 2		
SECTION	**ORIGINAL TEXT**	**NEW TEXT**
		other condition that may be considered to be related to therapy with study drug will be considered to be a DLT. Patients in whom a minor fluctuation in visual acuity is due to another known or recently diagnosed underlying condition may continue to be treated once visual acuity fluctuation returns to baseline status, but must be reevaluated by an ophthalmologist prior to each cycle and upon the occurrence of any subsequent ophthalmologic sign or symptom, including but not limited to recurrent changes in visual acuity measurement, in order to reassess for DLT status.
7.2.5 Vital Signs	*(Vital signs [VS] to include temperature, pulse, respiratory rate, blood pressure [BP], and oxygen saturation by pulse oximetry)** • Screening • Cycle 1 o Day 1 ▪ Prior to SOI ▪ End of infusion (EOI) (± 5 min) ▪ 2, 4, 8 hours after EOI (± 15 min) o Day 2 o Day 3 (+ 1 day) o Day 15 ▪ Prior to SOI ▪ EOI (± 5 min) • Each cycle thereafter o Day 1 (prior to dosing) • EOT • 1M FUP • As clinically indicated **Comprehensive assessment of VS is critical to the conduct of this study. In situations where an assessment at 8 hours after EOI is logistically difficult due to clinic staff availability, the observation period may be shortened, and an "end of day" assessment may be obtained at the latest practical time. Such an option (if to be routinely employed) is available only after discussion with and approval by the Sponsor.*	*(Vital signs [VS] to include temperature, pulse, respiratory rate, blood pressure [BP], and oxygen saturation by pulse oximetry)** • Screening • Cycle 1 o Day 1 ▪ Prior to SOI ▪ End of infusion (EOI) (± 10 min) ▪ 2, 4 hours after EOI (± 30 min) ▪ 8 hours after EOI (± 90 min o Day 2 (24 hours after EOI) (± 6 hours) o Day 3 (48 hours after EOI) (- 12 to + 24 hours) o Day 15 ▪ Prior to SOI ▪ EOI (± 10 min) • Each cycle thereafter o Day 1 (prior to dosing) • EOT • 1M FUP • As clinically indicated **Comprehensive assessment of VS is critical to the conduct of this study. In situations where an assessment at 8 hours after EOI is logistically difficult due to clinic staff availability, the observation period may be shortened, and an "end of day" assessment may be obtained at the latest practical time. Such an option (if to be routinely employed) is available only after discussion with and approval by the Sponsor.* Note: C1/D1 through C1/D3 window allowances align with PK timepoints windows

Table 7: Protocol Amendment 2		
SECTION	**ORIGINAL TEXT**	**NEW TEXT**
7.3.2 Ophthalmology Examination	**End of Cycle assessments may be conducted at any time during the week prior to Day 1 of the next cycle, including on Day 1 of the next cycle, prior to dosing.*	**End of Cycle assessments may be conducted at any time during the week prior to Day 1 of the next cycle, including on Day 1 of the next cycle, prior to dosing. Due to inherent variability of Snellen chart assessments, if changes in visual acuity are noted, a thorough ophthalmologic evaluation should be performed within 48 hours (if feasible, based on weekends or holidays) of the initial observation in order to confirm the finding and determine if there is evidence of an immune-mediated AE, or other event that would preclude further treatment with study drug. No patient with any documented decrease in visual acuity will receive further therapy with Sym023 unless the event is considered unrelated to study drug and unless cleared for retreatment by an ophthalmologist.*
7.7.1 Pharmacodynamic Assessments	• Cycle 2 o Day 1 (prior to dosing) o Day 15 (after dosing + 7 days) (at the time of biopsy if performed)	• Cycle 2 o Day 1 (prior to dosing) o Day 15 (after dosing + 0 to 7 days) (at the time of biopsy if performed)
7.7.2.1 Blood Samples for Biomarker Assessments	• Cycle 2 o Day 15 (after dosing + 7 days) (at the time of biopsy if performed)	• Cycle 2 o Day 15 (after dosing + 0 to 7 days) (at the time of biopsy if performed)
7.7.2.2 Tumor Sample for Biomarker Assessment *(Biopsies Optional)*	• Cycle 2 o Day 15 (after dosing + 7 days) (with paired pharmacodynamic and biomarker peripheral blood)	• Cycle 2 o Day 15 (after dosing + 0 to 7 days) (with paired pharmacodynamic and biomarker peripheral blood)
15.1 Data Handling	Study data collection, processing, transfer, and reporting as well as handling of study personnel information will be in compliance with ICH E6(R2) GCP and all applicable data protection regulations.	Study data collection, processing, transfer, and reporting, as well as handling of study personnel information, will be in compliance with ICH E6(R2) GCP and all applicable data protection regulations, including Regulation (EU) 2016/679 of the European Parliament and of the Council of 27 April 2016 on the protection of natural persons with regard to the processing of personal data and on the free movement of such data (General Data Protection Regulation).
15.5 Compliance with the General Data Protection Regulation	*Not applicable (new section and text added)*	The applicable data protection legislation requires that parties enter into a written contract if one party (data processor) processes personal data on behalf of the other party (data controller). This written contract must regulate the subject-matter and duration of the processing, the nature and purpose of the processing, the types of personal data and categories of data subjects, as well as the obligations and rights of the data controller. Accordingly, the parties must enter into a data processing

Table 7: Protocol Amendment 2		
SECTION	**ORIGINAL TEXT**	**NEW TEXT**
		agreement. To the extent the processing of personal data involves transfers of personal data to third countries (e.g., jurisdictions outside of the European Economic Area [EEA]), the parties will enter into the European Commission's standard contractual clauses between the data controller, the data processor, and all sub-processors, if any. The European Commission's standard contractual clauses ensure an adequate level of protection in relation to transfers of personal data to third countries.

19.3 Protocol Amendment 3 dated 18-Mar-2019

- In order to apply more current adverse event grade descriptions and term definitions, the version of the Common Terminology Criteria for Adverse Events (CTCAE) used for this study has been updated from Version 4.03 to Version 5.0. All references to the CTCAE version throughout this protocol have been updated accordingly.
- Grading of infusion-related reactions specified in Appendix 9 have been updated to reflect the use of CTCAE Version 5.0.
- Formatting adjustments, minor typographical corrections, and slight wording changes are included.
- The synopsis and tables have been updated based on changes described, where applicable.

Refer to **Table 8** for the changes in Protocol Amendment 3.

Table 8: Protocol Amendment 3		
SECTION	**ORIGINAL TEXT**	**NEW TEXT**
2.3.2 Clinical Experience with Sym023	No prior studies with Sym023 have been conducted.	The study described in this clinical trial protocol is ongoing. Sym023 is also being studied in a Phase 1 study in combination with Sym021 (anti-PD-1 monoclonal antibody; ClinicalTrials.gov number NCT03311412).
4.3.1 Patients to be Excluded	6. Patients with any of the following coagulation parameter abnormalities at baseline (unless on a stable dose of anticoagulant therapy for a prior thrombotic event, as determined by the Investigator): • Prothrombin time (PT) (as assessed by international normalized ratio [INR]) > 1.5 × ULN for the institution (> 3× ULN for the institution if anticoagulated)…	6. Patients with any of the following coagulation parameter abnormalities at baseline (unless on a stable dose of anticoagulant therapy for a prior thrombotic event, as determined by the Investigator): • Prothrombin time (PT) (or international normalized ratio [INR]) > 1.5 × ULN for the institution (> 3× ULN for the institution if anticoagulated)…

Table 8: Protocol Amendment 3		
SECTION	**ORIGINAL TEXT**	**NEW TEXT**
6.8.3 Definition of Dose-Limiting Toxicity	6. Any other ≥ Grade 3 non-hematologic toxicity regardless of duration, with the exceptions of: • Grade 3 fatigue • Grade 3 nausea, vomiting, or diarrhea lasting ≤ 2 days with best supportive care • Grade 3 asymptomatic electrolyte abnormalities lasting ≤ 3 days that are not clinically complicated, and resolve spontaneously or respond to conventional medical interventions	6. Any other ≥ Grade 3 non-hematologic toxicity regardless of duration, with the exceptions of: • Grade 3 fatigue • Grade 3 nausea, vomiting, or diarrhea lasting ≤ 2 days with best supportive care • Grade 3 asymptomatic electrolyte abnormalities lasting ≤ 3 days that are not clinically complicated, and resolve spontaneously or respond to conventional medical interventions • Other Grade 3 asymptomatic laboratory abnormalities that are clinically non-significant in the investigator's opinion, and that resolve spontaneously or with conventional medical interventions
7.2.7.3 Coagulation Panel	(To include PTT [or aPTT], PT, INR)	(To include PTT [or aPTT], PT and/or INR)

19.4 Protocol Amendment 4 dated 02-May-2019

- Final infusion volumes have been revised and made more granular to accommodate higher doses of drug product as well as patients who have a higher body weight. Additionally, where the amount of IMP is ≥ 40% of the total infusion volume, a larger IV solution bag should be used to prevent the infusion from becoming hypotonic.
- Infusion duration for Sym023 infusion volumes of 500 mL has been specified as 1 hour.
- Formatting adjustments, typographical corrections, and slight wording changes are included.
- The synopsis has been updated based on changes described, where applicable.

Refer to **Table 9** for the changes in Protocol Amendment 4.

Table 9: Protocol Amendment 4		
SECTION	**ORIGINAL TEXT**	**NEW TEXT**
3.2 Trial Design Summary	• On Day 1 of study, patients will receive study drug administered by 30-minute (+10 min) IV infusion in a fixed 50 mL volume for doses < 1 mg/kg, or in a fixed 100 mL volume for doses ≥ 1 mg/kg to ≤ 10 mg/kg, or in a fixed 250 mL volume for doses > 10 mg/kg.	• On Day 1 of study, patients will receive study drug administered by 30-minute (+10 min) or by 60-minute (+ 10 min) IV infusion (depending on dose and body weight) in a fixed 50 mL, 100 mL, 250 mL, or 500 mL volume depending on dose and body weight.
4.3.1 Patients to be Excluded	16. Patients with unresolved > Grade 1 toxicity* associated with any prior antineoplastic therapy except for persistent Grade 2 alopecia,	16. Patients with unresolved > Grade 1 toxicity* associated with any prior antineoplastic therapy except for persistent Grade 2 alopecia,

Table 9: Protocol Amendment 4		
SECTION	**ORIGINAL TEXT**	**NEW TEXT**
	peripheral neuropathy, decreased hemoglobin, hypomagnesemia, and/or end-organ failure being adequately managed by hormone replacement therapy	peripheral neuropathy, decreased hemoglobin, lymphopenia, hypomagnesemia, and/or end-organ failure being adequately managed by hormone replacement therapy
5.6 Administration of IMP	Study drug will be administered by IV infusion via an indwelling catheter. An appropriate dose, based on the patient's cohort assignment, diluted to the total volume specified with 0.9% sodium chloride (NaCl) for IV infusion will be administered initially over 30 minutes (+10 minutes), once every 2 weeks (Q2W; 4 weeks [28 days] equals 1 dosing cycle).	Study drug will be administered by IV infusion via an indwelling catheter. An appropriate dose, based on the patient's cohort assignment, diluted to the total volume specified with 0.9% sodium chloride (NaCl) for IV infusion will be administered initially over: • Approximately 30 minutes (+10 minutes) for infusion volumes ≤ 250 mL • Approximately 60 minutes (+10 minutes) for infusion volumes of 500 mL Dosing will be once every 2 weeks (Q2W; 4 weeks [28 days] equals 1 dosing cycle).
5.8 Dose Preparation	• The total volume of study drug to be delivered will be withdrawn from the study drug vial(s) and added to a prefilled IV bag containing 0.9% NaCl for IV infusion (prior to adding the study drug and an appropriate volume of NaCl solution is removed, such that the final volume to be infused equals: o 50 mL for doses < 1 mg/kg o 100 mL for doses ≥ 1 mg/kg to ≤ 10 mg/kg o 250 mL for doses > 10 mg/kg.	• The total volume of study drug to be delivered will be withdrawn from the study drug vial(s) and added to a prefilled IV bag containing 0.9% NaCl for IV infusion (prior to adding the study drug and an appropriate volume of NaCl solution is removed, such that the final volume to be infused equals: o 50 mL for doses < 1 mg/kg o 100 mL for doses ≥ 1 mg/kg to ≤ 3 mg/kg o 100 mL for doses of > 3 mg/kg to ≤ 10 mg/kg for patients with body weight ≤ 80 kg o 250 mL for doses of > 3 mg/kg to ≤ 10 mg/kg for patients with body weight > 80 kg o 250 mL for doses > 10 mg/kg for patients with body weight ≤ 100 kg o 500 mL for doses > 10 mg/kg for patients with body weight > 100 kg Note: In a case where the amount of IMP is ≥ 40% of the total infusion volume, a larger IV solution bag should be used.
6.5.3.4 Volume of Infusion	Infusions will be delivered in a final volume of: • 50 mL for doses < 1 mg/kg • 100 mL for doses ≥ 1 mg/kg to ≤ 10 mg/kg • 250 mL for doses > 10 mg/kg	Infusions will be delivered in a final volume of: • 50 mL for doses < 1 mg/kg • 100 mL for doses ≥ 1 mg/kg to ≤ 3 mg/kg • 100 mL for doses of > 3 mg/kg to ≤ 10 mg/kg for patients with body weight ≤ 80 kg

Table 9: Protocol Amendment 4		
SECTION	**ORIGINAL TEXT**	**NEW TEXT**
		• 250 mL for doses of > 3 mg/kg to ≤ 10 mg/kg for patients with body weight > 80 kg • 250 mL for doses > 10 mg/kg for patients with body weight ≤ 100 kg • 500 mL for doses > 10 mg/kg for patients with body weight > 100 kg Note: In a case where the amount of IMP is ≥ 40% of the total infusion volume, a larger IV solution bag should be used.
6.5.3.5 Duration of Infusion	Study drug will be administered over 30 minutes (+10 minutes)	Study drug will be administered over: • Approximately 30 minutes (+10 minutes) for infusion volumes ≤ 250 mL • Approximately 60 minutes (+10 minutes) for infusion volumes of 500 mL
6.7.1 Retreatment Guidelines	• Any ongoing study drug-related AE should have either ameliorated to ≤ Grade 1 severity, returned to baseline status, or resolved, with the exceptions of:… o Asymptomatic laboratory abnormalities that are considered clinically insignificant, clinically uncomplicated, and/or that are resolving spontaneously or with conventional medical interventions.	• Any ongoing study drug-related AE should have either ameliorated to ≤ Grade 1 severity, returned to baseline status, or resolved, with the exceptions of:… o Grade 2 asymptomatic laboratory abnormalities that are considered clinically insignificant, clinically uncomplicated, and/or that are resolving spontaneously or with conventional medical interventions.
8.5.1.2 Treatment Following Infusion Prolongation	To enhance patient safety following an infusion prolongation, subsequent infusions will be administered at the prolonged rate. For Grade 1 and 2 IRRs, rechallenge with a shorter duration of infusion (no less than 30 minutes) may be attempted at the Investigator's discretion, after a minimum of 2 doses with no evidence of infusion-related toxicity at the prolonged rate.	To enhance patient safety following an infusion prolongation, subsequent infusions will be administered at the prolonged rate. For Grade 1 and Grade 2 IRRs, rechallenge with a shorter duration of infusion (no less than the duration designated by the patient's dose assignment and weight) may be attempted at the Investigator's discretion, after a minimum of 2 doses with no evidence of infusion-related toxicity at the prolonged rate.
16.5.11 Pharmacokinetic Analysis	Individual curves of serum concentration of total study drug versus time after the first and fourth infusion will be presented on log- and linear scale for all patients in the PK population.	Individual curves of serum concentration of total study drug versus time after the first infusion will be presented on log- and linear scale for all patients in the PK population.
Appendix 9: Grading and Management of Infusion-Related Reactions	For Grade 1 and 2 reactions, rechallenge with a shorter duration of infusion (no less than 30 minutes) may be attempted at the Investigator's discretion, after a minimum of 2 doses with no evidence of infusion-related toxicity at the prolonged rate.	For Grade 1 and Grade 2 reactions, rechallenge with a shorter duration of infusion (no less than the duration designated by the patient's dose assignment and weight) may be attempted at the Investigator's discretion, after a minimum of 2 doses with no evidence of infusion-related toxicity at the prolonged rate.