A Phase 1, Multicenter, Open-label Study to Evaluate the Safety, Tolerability, and Pharmacokinetics of TAB001 in Subjects with Advanced Malignancies

Sponsor Protocol Number: TAB001-01

Application Number: [redacted]

Investigational Product: Toripalimab Injection (TAB001)
Humanized, $IgG_4\kappa$ Monoclonal Antibody Specific for Programmed Cell Death 1 (PD-1)

Sponsor: TopAlliance Biosciences, Inc.
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Medical Monitors: [redacted]
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Contract Research Organization: [redacted]

Protocol History, Date:

Original Protocol,	16 February 2017
Version 2.0	5 December 2017
Version 3.0	2 January 2018
Version 3.1	5 January 2018
Version 4.0	14 August 2018
Version 5.0	14 February 2019
Version 5.1	8 March 2019
Version 6.0	8 October 2019
Version 7.0	25 June 2020

Investigator Agreement

A Phase 1, Multicenter, Open-label Study to Evaluate the Safety, Tolerability, and Pharmacokinetics of TAB001 in Subjects with Advanced Malignancies

I, the undersigned, have reviewed this protocol, and I agree to conduct this protocol in accordance with ethical principles that have their origin in the Declaration of Helsinki and are consistent with the International Conference on Harmonisation (ICH) guidelines on Good Clinical Practice (GCP), any applicable laws and requirements, and any conditions required by a regulatory authority and/or Institutional Review Board/Independent Ethics Committee (IRB/IEC).

I understand that the protocol may not be modified without written approval of the sponsor. All changes to the protocol must be submitted to the applicable regulatory authority and IRB/IEC, and must be approved by the IRB/IEC prior to implementation except when necessary to eliminate immediate hazards to the subjects or when the change(s), as deemed by the sponsor, involves only logistical or administrative changes. Documentation of IRB/IEC approval must be sent to the sponsor immediately upon receipt.

Principal Investigator:

_____

Signature *Date*

_____

Name (please type or print)

_____

Institution

_____

Address

Protocol Synopsis

TITLE

A Phase 1, Multicenter, Open-label Study to Evaluate the Safety, Tolerability, and Pharmacokinetics of TAB001 in Subjects with Advanced Malignancies

HYPOTHESES

The primary research hypothesis is that toripalimab, also known as TAB001 and JS001 will be adequately tolerated following administration in ascending doses to subjects with advanced malignancies.

The secondary research hypothesis is that administration of toripalimab may result in antitumor activity in subjects with advanced malignancies.

OBJECTIVES

Primary Objectives

- Dose-escalation phase: To assess the safety and tolerability of multiple doses of toripalimab and define the maximum tolerated dose (MTD) or the maximum feasible dose (MFD) (highest protocol-defined dose of toripalimab in the absence of exceeding the MTD) in subjects with advanced malignancies.
- Dose-expansion phase: To further characterize the safety profile of toripalimab in subjects with selected advanced malignancies, and to evaluate the recommended Phase 2 dose (RP2D).

Secondary Objectives

- To describe the pharmacokinetic (PK) profile of toripalimab
- To evaluate antitumor activity of toripalimab
- To determine the immunogenicity of toripalimab
- To evaluate overall survival (OS)

[redacted]

STUDY ENDPOINTS

Primary Endpoint

- The primary endpoint is determination of the MTD, which is the highest dose within a cohort in Part A where no more than 1 out of 6 subjects experience dose-limiting toxicities (DLT), or the MFD.
- The primary endpoints for safety assessment include adverse events (AEs), serious adverse events (SAEs), laboratory evaluations, vital signs, physical examinations, and electrocardiogram (ECG) results.

Secondary Endpoints

- The endpoints for assessment of PK of toripalimab include individual toripalimab concentrations in serum and PK parameters including area under the concentration-time curve (AUC), maximum observed concentration (C_{max}), clearance (CL), volume of distribution (V_d), and terminal elimination half-life ($t_{1/2z}$).
- The endpoints for assessment of antitumor activity/efficacy include objective response (OR), disease control (DC), duration of response (DoR), and progression-free survival (PFS), and in Part B only, OS assessed by the Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 as well as the immune-related Response Evaluation Criteria in Solid Tumors (irRECIST) (www.irrecist.com).
- The endpoints for assessment of immunogenicity of toripalimab include the number and percentage of subjects who develop detectable anti-drug antibodies (ADA).

[redacted]

STUDY DESIGN

This is a Phase 1, open-label, 2-part (Part A = dose-escalation, Part B = dose-expansion) study to evaluate the safety, tolerability, PK, immunogenicity, and antitumor activity of toripalimab administered intravenously (IV) on an every 2 week (Q2W) (Part A) or every 3 week (Q3W) (Part B) dosing schedule in adult subjects with advanced solid malignancies who are refractory to standard therapy or for which no standard therapy exists. In Part A, a cycle is 28 days (4 weeks) which includes toripalimab being administered IV Q2W. In Part B, a cycle is 42 days (6 weeks) which includes toripalimab being administered IV Q3W.

In Part A, the study will enroll up to 18 subjects with advanced solid malignancies that are immunotherapy-naïve (no prior exposure to immunotherapy such as but not limited to other anti-CTLA-4, anti-PD-1, or anti-PD-L1 antibodies excluding vaccines). In Part B, up to 280 subjects will be enrolled and prior immunotherapy exclusion will be limited to anti-PD-1, anti-PD-L1, or anti-PD-L2. Enrollment will consist of solid tumors that may include but will not be limited to esophageal carcinoma, gastric carcinoma, cholangiocarcinoma, neuroendocrine tumors (NETs) (excluding lung derived NET), nasopharyngeal carcinoma (NPC), hepatocellular carcinoma (HCC), sarcomas, both chondrosarcoma and soft tissue sarcoma (excluding leiomyosarcoma and including angiosarcoma, undifferentiated pleomorphic sarcoma and alveolar soft part sarcoma), or with agreement of the Sponsor, other tumors that have been treated with at least one line of therapy in the metastatic setting. Patients with MSI-H/dMMR tumors are eligible to enroll. The study will be conducted at up to 30 centers in the United States (U.S.) and up to 15 centers in Europe.

The planned cohorts in Part A are 80 mg, 240 mg and 480 mg. A minimum of three subjects will initially be enrolled at each dose level. Provided there is no DLT in the initial three subjects, escalation to the next cohort may occur. If a DLT does occur, the cohort will be expanded to a total of 6 subjects. A protocol amendment will be submitted to the Food and

Drug Administration (FDA) if there are any changes in dose levels and dosing frequency. Any dose-escalation cohort that has not exceeded the MTD can be expanded up to a maximum of 10 subjects for further evaluation of safety, PK, pharmacodynamics, and clinical activity.

The dose to be evaluated in Part B is 240 mg administered Q3W which was determined after review of safety, PK and pharmacodynamic data from subjects treated with toripalimab (JS001) in studies performed in China (see Section 1.4) as well as safety data from subjects treated in Part A of this study.

All subjects will be evaluated regularly, and their clinical status classified according to RECIST v1.1 and irRECIST. Subjects may continue to receive toripalimab Q2W (± 2 days) in Part A, or Q3W (± 2 days) in Part B, in the absence of confirmed progressive disease (a repeat scan will be conducted in 4 weeks ± 2 days in Part A and in 6 weeks ± 2 days in Part B to confirm disease progression), unacceptable toxicity, withdrawal of consent, intercurrent illness preventing further administration of study drug, or the investigator considers it in the best interest of the subject to discontinue study therapy. If feasible, all subjects will be followed for PFS and OS (Part B only) until the end of the study, defined as the date of the last protocol-specified visit/assessment (including telephone contact), or the date the study is closed by the sponsor, whichever comes first. AEs and SAEs will be followed from the start of the first dose of toripalimab through 90 days after the last dose of toripalimab unless a subject receives another experimental or anticancer therapy, at which time only related AE/SAEs will be collected through 90 days after the last dose of toripalimab.

TARGET SUBJECT POPULATION

Men and women, 18 years or older, with advanced malignancies that are evaluable by RECIST v1.1 and irRECIST criteria, that are refractory to standard therapy or for which no standard therapy exists may be enrolled. Subjects must provide written informed consent, have adequate organ function, and agree to use effective contraception (if relevant). Subjects with certain serious medical conditions would be excluded from participation in the trial.

INCLUSION / EXCLUSION CRITERIA

Eligibility criteria for this study have been carefully considered to ensure the safety of the study subjects. If there is a question about the inclusion/exclusion criteria listed below, the principal investigator (PI) should contact the medical monitor or designee before enrolling the subject.

Inclusion Criteria:

Subjects must meet the following Inclusion criteria:

1. Signed Informed Consent Form
2. Age ≥ 18 years
3. Subject meets the following corresponding requirements for the part of the study they will enroll into:

   During Part A, subjects must have a histologically or cytologically documented, incurable or metastatic solid tumor that has progressed on (or they have been intolerant to) standard systemic therapy options for their tumor type in the metastatic setting or must have a

tumor type for which no such standard systemic option exists.

During Part B, subjects must have a histologically or cytologically documented diagnosis of esophageal carcinoma, gastric carcinoma, cholangiocarcinoma, neuroendocrine tumors (NETs) (excluding lung derived NET), NPC, HCC, sarcomas, both chondrosarcoma and soft tissue sarcoma (excluding leiomyosarcoma and including angiosarcoma, undifferentiated pleomorphic sarcoma and alveolar soft part sarcoma), or with agreement of the Sponsor, other tumors (including NPC and HCC) that have been treated with at least one line of standard systemic therapy for their respective tumor type in the metastatic setting with progressive locally advanced or metastatic disease that is not amenable to definitive local therapy with curative intent. Patients with MSI-H/dMMR tumors are eligible to enroll.

a) Subjects with nasopharyngeal cancer must have received (or been intolerant to) to a platinum-based combination as part of their prior therapy for advanced/metastatic disease.

b) Subjects with soft tissue sarcoma and chondrosarcoma must have radiographic evidence of progression within the previous 6 months and must have received at least 1 line of systemic therapy.

c) Subjects with esophageal cancer must have received (or been intolerant to) a platinum-based combination as part of their prior therapy for advanced/metastatic disease.

d) Subjects with gastric cancer must have received (or been intolerant to) a fluoropyrimidine-platinum combination as part of their prior therapy for advanced/metastatic disease.

e) Subjects with HCC must have received (or been intolerant to) sorafenib as part of their prior therapy for advanced metastatic disease.

4. Measurable disease per RECISTv1.1 and irRECIST
5. Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1
6. Adequate organ and marrow function, as defined below:

a) Hemoglobin ≥ 8.0 g/dL within first 2 weeks prior to first dose of toripalimab

b) Absolute neutrophil count (ANC) ≥ 1.2×10^9/L ($1{,}200/mm^3$)

c) Platelet count ≥ 75×10^9/L ($75{,}000/mm^3$)

d) Total bilirubin ≤ 1.5 × upper limit of normal (ULN) except subjects with documented Gilbert's syndrome who must have a baseline total bilirubin ≤ 3.0 mg/dL

e) Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ≤ 2.5 × ULN; for subjects with hepatic metastases, ALT and AST ≤ 5 × ULN

f) Serum creatinine ≤ 1.5 × ULN OR calculated creatinine clearance (CrCl) or 24-hour urine CrCl ≥ 40 mL/minute

Cockcroft-Gault formula will be used to calculate CrCl (Section 9.4); 24-hour

urine CrCl will be derived using the measured creatinine clearance formula (Section 9.5)

g) International normalized ratio (INR) and activated partial thromboplastin time (aPTT) ≤ 1.5 ×ULN; applies only to subjects who do not receive therapeutic anticoagulation; subjects receiving therapeutic anticoagulation (such as low-molecular weight heparin or warfarin) should be on a stable dose.

7. Willingness to provide consent for biopsy samples (In Part A, fresh pre-treatment biopsies will be requested from subjects with safely accessible lesions. For subjects who cannot provide a fresh pre-treatment biopsy, an archival specimen will be required. In Part B, fresh pre-treatment biopsies will be required from subjects with safely accessible lesions. Archival specimens will be requested).
8. Females of childbearing potential who are sexually active with a nonsterilized male partner must use effective contraception from time of screening, and must agree to continue using such precautions for 90 days after the final dose of toripalimab; cessation of birth control after this point should be discussed with a responsible physician. Periodic abstinence, the rhythm method, and the withdrawal method are not acceptable methods of birth control.

   Females of childbearing potential are defined as those who are not surgically sterile (i.e., bilateral tubal ligation, bilateral oophorectomy, or complete hysterectomy) or postmenopausal (defined as at least 12 months with no menses confirmed by follicle-stimulating hormone [FSH] levels. FSH testing will be conducted at the Screening visit to confirm post-menopausal status).

   Subjects must use effective contraception as described in Table 1-1.
9. Nonsterilized males who are sexually active with a female partner of childbearing potential must use effective contraception (see Table 1-1) from Day 1 and for 90 days after receipt of the final dose of toripalimab.

Table 1-1: Highly Effective Methods of Contraception

Barrier Methods	Hormonal Methods
• Male condom plus spermicide • Copper T intrauterine device • Levonorgestrel-releasing intrauterine system (e.g., Mirena®) [a]	• Implants • Hormone shot or injection • Combined pill • Minipill • Patch

[a] This is also considered a hormonal method.

Exclusion Criteria:

Any of the following would exclude the subject from participation in the study:

1. Concurrent enrollment in another clinical study, unless it is an observational (non-interventional) clinical study or the follow-up period of an interventional study.

2. Any concurrent chemotherapy, radiotherapy, immunotherapy, or biologic therapy for cancer treatment. Concurrent use of hormones for non-cancer-related conditions (e.g., insulin for diabetes and hormone replacement therapy) is acceptable. NOTE: Local treatment of isolated lesions for palliative intent is acceptable (e.g., by local surgery or radiotherapy).
3. Receipt of any investigational anticancer therapy within 4 weeks prior to the first dose of toripalimab.
4. Current or prior use of immunosuppressive medication within 2 weeks prior to the first dose of toripalimab, with the exception of intranasal and inhaled corticosteroids or systemic corticosteroids not to exceed 10 mg/day of prednisone or equivalent.
5. In Part A: Prior exposure to immunotherapy such as but not limited to other anti-CTLA-4, anti-PD-1, or anti-PD-L1 antibodies excluding vaccines. In Part B: Exclusion of prior immunotherapy exposure will be limited to anti-PD-1, anti-PD-L1, or anti-PD-L2.
6. Prior allogeneic bone marrow transplantation or prior solid organ transplantation.
7. Major surgery (as defined by the investigator) within 4 weeks prior to first dose of toripalimab or still recovering from prior surgery.
8. Unresolved toxicities from prior anticancer therapy, defined as having not resolved to baseline or to NCI-CTCAE v4.03 Grade 0 or 1, or to levels dictated in the inclusion / exclusion criteria with the exception of alopecia. Subjects with irreversible toxicity that is not reasonably expected to be exacerbated by toripalimab may be included (e.g., hearing loss) after consultation with the medical monitor.
9. Active or prior documented autoimmune disease within the past 2 years. NOTE: Subjects with vitiligo, Grave's disease not requiring systemic treatment other than thyroid hormone replacement (within the past 2 years) , or psoriasis not requiring systemic treatment are not excluded. Subjects with a history of autoimmune hypothyroidism requiring only thyroid hormone replacement therapy will not be excluded.
10. Known history of tuberculosis.
11. Subjects who are known to be human immunodeficiency virus (HIV) positive.
12. Subjects with evidence of hepatitis B or C virus infection, unless their hepatitis is considered to have been cured. (Note that subjects with prior hepatitis B virus [HBV] infection must have HBV viral load [VL] <100 IU/mL before study enrollment, and must be treated according to local standards; hepatitis C virus [HCV] infection must have, before study enrollment, no detectable VL and must be treated according to local standards).
13. Active or prior documented inflammatory bowel disease (e.g., Crohn's disease, ulcerative colitis).
14. History of primary immunodeficiency.
15. Uncontrolled intercurrent illness including, but not limited to, ongoing or active infection, symptomatic congestive heart failure according to New York Heart Association (NYHA) Functional Classification ≥ 3, uncontrolled hypertension, unstable angina pectoris, cardiac arrhythmia, active peptic ulcer disease or gastritis, or psychiatric illness/social situations that would limit compliance with study requirements, substantially increase risk of

incurring AEs from toripalimab, or compromise the ability of the subject to give written informed consent.

16. Symptomatic or untreated central nervous system metastases requiring concurrent treatment, inclusive of but not limited to surgery, radiation, and/or corticosteroids. Subjects with previously treated brain metastases may participate provided they are clinically stable for at least 4 weeks prior to study entry, have no evidence of new or enlarging metastases, and are off steroids.
17. Receipt of live attenuated vaccination within 4 weeks prior to study entry or within 4 weeks of receiving toripalimab.
18. Any condition that, in the opinion of the investigator or sponsor, would interfere with evaluation of toripalimab or interpretation of subject safety or study results.
19. Pregnant or breastfeeding women.

INVESTIGATIONAL PRODUCT, DOSAGE, AND MODE OF ADMINISTRATION

Toripalimab is a humanized, $IgG_4\kappa$ monoclonal antibody specific for PD-1. Toripalimab will be administered IV over a minimum of 60 minutes in Cycle 1. In subsequent cycles, the infusion time may be reduced to a minimum of 30 minutes depending upon subject tolerance. The infusion duration may be increased at any time at the discretion of the investigator. Refer to Section 3.1.7.3 Management of Toripalimab-related Toxicities.

STATISTICAL ANALYSIS

Statistical Considerations: All statistical analyses will be performed using SAS Version 9.3 or higher, unless otherwise noted. In general, analysis of categorical variables will include counts and percentage of subjects in each category observed. For continuous variables, the sample size (n), mean, standard deviation (SD), mean, median, minimum, and maximum will be presented. No formal comparisons among dose groups (escalation) or treatment cohorts(in Part B expansion cohorts) are planned. Missing data will not be imputed unless otherwise stated. Subject demographics, baseline characteristics, and disposition will be characterized using descriptive statistics. PK data will be presented descriptively, with accompanying figures.

No formal interim analysis is planned for this study. However, a review of safety data and available PK data will be performed after completion of each dose escalation cohort. In addition to ongoing safety data review in Part B, a periodic cumulative review of safety will be performed. A statistical analysis plan (SAP) will fully describe the planned analyses for this study.

Sample Size Considerations: It is assumed that 3 cohorts will be required to determine the MTD or the MFD; therefore, up to 18 subjects will be enrolled in the dose escalation (Part A) portion of the study. Up to 280 subjects will be enrolled in the expansion phase (Part B) at a dose determined from the safety, clinical responses, PK and pharmacodynamics found in Part A and other pertinent data, for a total of up to approximately 298 subjects. Assuming a 10% drop out rate, a total of up to approximately 327 subjects are expected to be enrolled. Six expansion cohorts may include 5 disease-specific cohorts and, at the discretion of the Sponsor, another tumor cohort, to a maximum of 40 subjects enrolled in each cohort with the exception of the sarcoma cohort in which a maximum of 80 subjects can be enrolled. After 40

subjects have been enrolled in the sarcoma cohort, a further 40 subjects will be enrolled and will be limited to angiosarcoma, undifferentiated pleomorphic sarcoma and alveolar soft part sarcoma.

Safety Analyses: The results from AEs, concomitant medications (CMs), vital signs, ECGs, safety laboratory results, and physical examinations will be provided in listings. AEs and medical history will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) version 19.1 or higher. CM will be coded using WHODrug version September 2016 or higher. Summaries of AEs and other parameters will be provided in summary tables to assess frequency of incidence. A list of preferred terms designated as adverse events of special interest (AESI) will be provided in the SAP.

Efficacy Analyses: Frequency counts and percentages will be presented for Objective Response Rate (ORR) and Disease Control Rate (DCR) for each dose cohort in Part A and for the expansion cohort(s) in Part B. For analysis of PFS and OS in Part B, the median time-to-event and 95% confidence intervals (CI) will be calculated using the Kaplan-Meier method.

Pharmacokinetic Analyses: The PK profile of toripalimab will be determined for each subject by noncompartmental analysis using standard PK software (e.g., Phoenix WinNonlin). Parameters will include AUC, C_{max}, CL, V_d, and $t_{1/2z}$. Serum concentrations as well as PK parameters will be reported and summarized. Population PK analysis may also be performed. The relationship between PK and pharmacodynamics, safety and efficacy will be assessed if data allow.

Immunogenicity Analyses: the number and percentage of subjects who develop detectable ADA will be reported.

Pharmacodynamic Analyses: [redacted] At a minimum, all relevant pharmacodynamic data of all data will be reported in data listings. PD-1 receptor occupancy (RO) and T cell subsets in the peripheral blood will be analyzed by flow cytometry and correlated with PK results.

SIGNATURE PAGE

Product Name: **Toripalimab Injection**

Protocol Number: **TAB001-01**

The signatures of the representatives below constitute their approval of this protocol and provide the necessary assurances that this study will be conducted according to all stipulations stated in the protocol, including all statements as to confidentiality. It is also agreed that the study will not be initiated without the approval of an appropriate Institutional Review Board or Independent Ethics Committee.

Signatures:

[redacted] **Senior Vice President of Oncology and Cellular Therapy**

[redacted] 25 June 2020
Date

[redacted] **Medical Monitor, Consultant**

[redacted] 25 JUNE 2020
Date

[redacted] **Clinical Operations Consultant**

[redacted] 25 June 2020
Signature Date

TABLE OF CONTENTS

LIST OF IN-TEXT TABLES

List of Abbreviations

Abbreviation or Specialized Term	Definition
ADA	anti-drug antibodies
ADR	adverse drug reaction
AE	adverse event
AESI	adverse events of special interest
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANA	anti-nuclear antibody
ANC	absolute neutrophil count
aPTT	activated partial thromboplastin time
ASPS	alveolar soft part sarcoma
AST	aspartate aminotransferase
AUC	area under the concentration-time curve
$AUC_{(0\text{-}inf)}$	AUC to time infinity
$AUC_{(0\text{-}t)}$	AUC to time of last measurable concentration
$AUC_{(t\text{-}inf)}$	AUC from time of last measurable concentration to time infinity
$AUC_{(t\text{-}inf)\%}$	percentage of $AUC_{(t\text{-}inf)}$ of $AUC_{(0\text{-}inf)}$
AUC TAU	AUC to the end of the dosing period
BOR	best overall response
BP	blood pressure
BSA	body surface area
BUN	blood urea nitrogen
C_{avg}	average observed concentration
CBC	complete blood count
CI	confidence interval
CL	Clearance
CL_{ss}	clearance at steady state
cm	centimeter
CM	concomitant medications
C_{max}	maximum observed concentration
CPK	creatine phosphokinase
CR	complete response
CrCl	calculated creatinine clearance
CRO	Clinical Research Organization
CT	computed tomography

Abbreviation or Specialized Term	Definition
DC	disease control
DCO	data cutoff
DCR	disease control rate
dL	deciliter
DLT	dose-limiting toxicity
dMMR	mismatch repair deficient
DNA	deoxyribonucleic acid
DoR	duration of response
EC_{50}	half-maximal effective concentration
EC	esophageal cancer
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
ELISA	enzyme-linked immunosorbent assay
EOI	end of infusion
ETBR	endothelin-B receptor
FAAN	Food Allergy and Anaphylaxis Network
FAS	full analysis set
FDA	Food and Drug Administration
FFPE	formalin fixed paraffin embedded
FIH	first-in-human
FSH	follicle-stimulating hormone
g	gram
G-CSF	granulocyte colony-stimulating factor
GC	gastric cancer
GCP	Good Clinical Practice
GEC	gastroesophageal junction cancer
γ-GGT	gamma-glutamyltransferase
GLP	Good Laboratory Practice
GM-CSF	granulocyte-macrophage colony-stimulating factor
GMP	Good Manufacturing Practice
HBV	hepatitis B virus
HCC	hepatocellular carcinoma
HCG	Human chorionic gonadotropin
HCT	hematocrit
HCV	hepatitis c virus

Abbreviation or Specialized Term	Definition
HED	human equivalent dose
HepB cAb	hepatitis B core antibody
HepB SA	hepatitis B surface antigen
HepC Ab	hepatitis C antibody
HepC RNA	hepatitis C ribonucleic acid
HGB	hemoglobin
HIV	human immunodeficiency virus
HR	hour or heart rate
IB	Investigator's Brochure
IBW	ideal body weight
IC_{50}	half-maximal inhibitory concentration
ICF	informed consent form
ICH	International Conference on Harmonisation
IDO	dioxygenase
IEC	Independent Ethics Committee
IgG_{4K}	Immunoglobulin gamma 4, kappa
IgM	Immunoglobulin M
IHC	Immunohistochemistry
ILD	Interstitial lung disease
IMP	investigational medicinal product
INR	international normalized ratio
IP	intraperitoneal
irAE	immune-related adverse event
IRB	Institutional Review Board
irBOR	immune-related best overall response
irCR	immune-related complete response
irNE	immune-related NE
ir-NN	irNon-CR/Non-PD
irPD	immune-related progressive disease
irPR	immune-related partial response
irRC	immune-related Response Criteria
irRECIST	immune-related Response Evaluation Criteria in Solid Tumors
irSD	immune-related stable disease
IU	international units
IV	intravenous
IWG	International Working Group

Abbreviation or Specialized Term	Definition
kDa	kilodalton
Kel	elimination rate constant from the central compartment
Kg	kilogram
L	liter
LDH	lactate dehydrogenase
LLOQ	lower limit of quantitation
μg	microgram
mAb	monoclonal antibody
MABEL	minimally-anticipated biological effect level
mDOR	median duration of overall response
MedDRA	Medical Dictionary for Regulatory Activities
MFD	maximum feasible dose
mg	milligram
mL	milliliter
mm	millimeter
MMR	mismatch repair
MOA	mechanism of action
mPFS	median progression free survival
MRI	magnetic resonance imaging
MRSD	maximum recommended safe dose
MRT_{inf}	mean residence time extrapolated to infinity
MSI	microsatellite instability
MSI-H	microsatellite instability-high
MSS	microsatellite stable
MTD	maximum tolerated dose
n	sample size
NAb	neutralizing antibody
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Events
NET	neuroendocrine tumor
ng	Nanogram
NHP	non-human primate
NIAID	National Institute of Allergy and Infectious Diseases
NK	natural killer
NKT	natural killer T
nM	nanomolar

Abbreviation or Specialized Term	Definition
NOAEL	no-observed-adverse-effect level
NPC	nasopharyngeal carcinoma
NS	no sample
NSCLC	non-small cell lung carcinoma
NYHA	New York Heart Association
OR	objective response
ORR	objective response rate
OS	overall survival
PBMC	peripheral blood mononuclear cell
PD	progressive disease
PD-1	programmed cell death 1
PD-L1	programmed death ligand 1
PD-L2	programmed death ligand 2
PEF	peak expiratory flow
PET	positive emission tomography
PFS	progression-free survival
PI	principal investigator
PK	pharmacokinetic(s)
PPS	per-protocol set
PR	partial response
PT	prothrombin time
Q1W	every 1 week
Q2W	every 2 weeks
Q3W	every 3 weeks
Q4W	every 4 weeks
Q8W	every 8 weeks
Q9W	every 9 weeks
Q12W	every 12 weeks
QTcF	QT interval corrected by Fridericia's formula
RBC	red blood cell
RCC	renal cell carcinoma
RECIST	Response Evaluation Criteria in Solid Tumors
RES	response-evaluable set
RNA	ribonucleic acid
RO	receptor occupancy
RP2D	recommended phase 2 dose

Abbreviation or Specialized Term	Definition
SAE	serious adverse event
SAP	statistical analysis plan
S_{cr}	serum creatine
SD	study day, stable disease or standard deviation
SID	subject identification number
SS	safety set
SUSAR	suspected unexpected serious adverse reactions
$t_{1/2}$	terminal half-life
$t_{1/2z}$	terminal elimination half-life
T4	thyroxine
TEAE	treatment emergent adverse event
T_{max}	time to observed maximum serum concentration
T_{min}	total collection time
TMB	tumor mutational burden
TMTB	total measured tumor burden
TNF	tumor necrosis factor
TNFα	tumor necrosis factor alpha
Treg	regulatory T cells
TSH	thyroid stimulating hormone
TTR	time to response
U_{cr}	urine creatinine
ULN	upper limit of normal
UPS	undifferentiated pleomorphic sarcoma
U.S.	United States
U_{vol}	urine volume
V_d	volume of distribution
VEGF	vascular endothelial growth factor
VL	viral load
V_{ss}	apparent volume of distribution at equilibrium determined after intravenous administration
Vz	volume of distribution during terminal phase after intravenous administration
WBC	white blood cell
WBDC	web based data capture
w/v	Weight per volume

1 INTRODUCTION

1.1 Disease Background

Genetic and epigenetic changes occurring in cancer cells result in tumor-associated antigens that can be recognized by the immune system (Pardoll 2012). To produce immunity against tumors, three major steps are important (Mellman, et al., 2011). First, to initiate the immune response, dendritic cells need to encounter antigens, such as protein products of mutated genes, from the tumor, and process them. Second, in lymphoid organs, the dendritic cells that are processing the antigens have to generate T-cell responses, such as the production of CD8+ effector cells with cytotoxic capabilities. In addition, the dendritic cells may evoke antibody responses, or natural killer (NK) or natural killer T (NKT) cell responses. Third, tumor-specific T cells must enter the tumor environment and attack the tumor. However, tumors have multiple means of evading the immune response. Among these are that tumors may facilitate a local increase in regulatory T cells (Treg) that suppress the activity of effector T cells, decrease expression of MHC class I molecules on the surface of tumor cells, decrease expression of tumor antigens targeted by the immune system, or express molecules, such as programmed death ligand 1 (PD-L1) or programmed death ligand 2 (PD-L2), on their surfaces that interact with molecules on the surface of activated T cells. The latter results in T-cell exhaustion or anergy. Tumors may also produce molecules such as 2,3-dioxygenase (IDO) that suppress T cell function. Myeloid-derived cells entering the tumor may also produce molecules that suppress effector T cell function. Hypoxia may result in production of CCL28 that facilitates movement of Treg cells into the tumor. Tumor stroma cells may block proliferation and function of effector T cells and tumor vascular cells may inhibit T cell adhesion and thereby interfere with homing of such cells into tumors, partly mediated by vascular endothelial growth factor (VEGF) and endothelin-B receptor (ETBR).

An important mechanism by which tumors thwart immune resistance is through immune checkpoint pathways, which normally mediate tolerance and lessen collateral tissue damage. Immune checkpoints may be stimulatory or inhibitory (Mellman, et al., 2011, Pardoll 2012, Ribas 2012). The potential T cells targets for immunoregulatory treatments with monoclonal antibodies include those that stimulate activating receptors and those that block the action of inhibitory receptors. Activating receptors on the T cell include: HVEM, CD27, CD137, GITR, OX40, and CD28. Inhibitory receptors include: LAG-3, VISTA, BTLA, TIGIT, TIM-3, PD-1, and CTLA-4.

1.2 Toripalimab Background

Toripalimab is briefly described below. Refer to the current Toripalimab Investigator's Brochure (IB) for details.

Toripalimab injection (also known as JS001 and TAB001) is a humanized IgG_{4K} (immunoglobulin gamma 4, kappa) monoclonal antibody (mAb) specific for human programmed death-1 (PD-1), a co-inhibitory receptor expressed on T cells and is being evaluated for the treatment of cancer. Toripalimab contains serine228 to proline substitution to minimize Fab arm exchange.

As with other anti-PD-1 antibodies, toripalimab has a high affinity and blocks interaction between PD-1 and its ligand, PD-L1. However, toripalimab differs from other such antibodies in that the binding to PD-1 is more prolonged, as measured by the dissociation coefficient. Based on the results of nonclinical pharmacology studies performed to date, toripalimab binds to human PD-1, and blocks the interaction between PD-1 and its ligands. Toripalimab inhibits the inhibitory signaling cascade that is triggered by interactions between PD-1 and its ligands. In primary cell-based assays using cells obtained from healthy donors and cancer patients, toripalimab increases T cell proliferation, effector cytokine production, and survival following stimulation with a variety of antigens.

1.3 Summary of Nonclinical Experience

Toripalimab binds both human and cynomolgus monkey PD-1 with similar affinity by enzyme-linked immunosorbent assay (ELISA) and flow cytometry, but does not bind mouse or rat PD-1. The cynomolgus monkey is thus selected because it is a relevant toxicology species.

Single, 4-week repeat-dose (every 2 weeks over 4 weeks [total of 3 doses]) and 26-week pivotal repeat-dose (every week over 26 weeks [total of 27 doses]) toxicology studies of toripalimab was performed in cynomolgus monkeys.

Following a single intravenous (IV) infusion of toripalimab for 30 minutes at doses up to 203 mg/kg to male and female cynomolgus monkeys (Smithers Avanza study no. 2352-13085), there was no effect on mortality, physical examinations, cageside observations, body weights, body weight changes, food consumption, or clinical pathology (clinical chemistry, hematology, coagulation, and urinalysis).

The terminal half-life ($t_{1/2}$) of toripalimab following the single IV dose was approximately 108 and 116 hours in male and female monkeys, respectively, dosed with 1 mg/kg and 256 hours in a female monkey dosed with 203 mg/kg toripalimab. At Study Day (SD) 28, all

animals had antibodies to toripalimab and a confirmatory assay showed antibodies in all animals except a high dose female. The presence of antibodies did not appear to affect the serum toripalimab levels as $t_{1/2}$ was long in all animals.

The no-observed-adverse-effect level (NOAEL) is 203 mg/kg when administered once via IV infusion for 30 minutes to male and female cynomolgus monkeys.

Following 30 minute IV infusions every 2 weeks (Q2W) over four weeks (total of three doses) of toripalimab at doses up to 100 mg/kg to male and female cynomolgus monkeys (Smithers Avanza study no. 2352-13086), there was no effect on mortality, physical examinations, cageside observations, body weights, body weight changes, food consumption, ophthalmic examination findings, electrocardiogram (ECG) evaluations, clinical pathology (clinical chemistry, hematology, coagulation, and urinalysis), gross pathology findings, absolute and relative organ weights, and histopathology findings. Serum concentration-time profiles of toripalimab were characterized by a bi-phasic decline with time. The serum concentration of toripalimab declined very slowly from serum following dosing, both on SD 1 and 29. No gender difference was observed in the rate of decline; however, a dose-dependent slowing was observed with mostly higher maximum observed concentrations (C_{max}) values on SD 15 and 29 indicating some accumulation at the higher doses from multiple dosing, consistent with higher residual serum concentrations in samples collected prior to dosing on SD 15 and SD 29. Anti-drug antibodies (ADA) were observed in most 1 and 10 mg/kg monkeys and persisted to the end of recovery while antibodies were only observed in 2/10 monkeys at 100 mg/kg and did not persist to recovery. The NOAEL of toripalimab in male and female cynomolgus monkeys is 100 mg/kg when administered via 30 minute IV infusions Q2W over four weeks (total of three doses).

Following IV infusions once a week over 26 weeks (total of 27 doses) of toripalimab at doses of 10, 30, and 100 mg/kg to male and female cynomolgus monkeys (InnoStar study no. 1348RD2), there was no toripalimab-related adverse effects on in-life parameters, ophthalmic examination findings, safety pharmacology, clinical pathology (clinical chemistry, hematology, coagulation, urinalysis and analysis and fecal occult blood test), immune function parameters (immune-phenotype, complements, immunoglobulin and immune histological examination of the kidney), hormone analysis, macroscopic and microscopic findings. At 100 mg/kg level, the mean C_{max} and $AUC_{0\text{-}168h}$ following the 26^{th} dosing phase were 4.4 mg/mL and 431 mg•h/mL for males, and 5.03 mg/mL and 602 mg•h/mL for females, respectively. The dose of 100 mg/kg (every 1 week [Q1W] for 27 doses, mean $AUC_{0\text{-}168.5h}$ = 525944 μg•h/mL) was considered the NOAEL. The Maximum Recommended Safe Dose (MRSD) is considered to be 10 mg/kg (1/10 of NOAEL). The proposed human starting dose is 80 mg, about 1 mg/kg given an 80 kg average body weight of a patient, a

dose that is 10-fold lower than the MRSD. Furthermore, two FDA approved PD-1 blocking mAbs, Pembrolizumab (KEYTRUDA®) and Nivolumab (Opdivo®), were included as a positive control and compared with toripalimab in binding affinity assays and cytokine release assays. The study results showed none of the three agents induced cytokine release in unstimulated and pre-activated human peripheral blood mononuclear cells (PBMCs), indicating a possible comparable safety profile.

1.4 Summary of Clinical Experience

As of December 16, 2019, toripalimab has been administered to approximately 1241 subjects participating in a total of 27 Phase I-III clinical trials in China. In the United States, toripalimab has been administered to 109 subjects in 1 Phase I clinical trial. Refer to Section 5 of the IB for information on the effect of toripalimab in humans.

Toripalimab was approved in China on 17 December 2018 for the treatment of patients with locally progressive or metastatic melanoma that have progressed after receiving standard treatment. The approved dose is 3 mg/kg Q2W.

This update is based on the currently available pharmacokinetic (PK), efficacy and safety data of toripalimab, as well as on the types of adverse drug reactions (ADRs) obtained from summarization of safety data. This update covers the latest experience in clinical use of toripalimab to support its further clinical development.

Clinical trials of subjects with advanced solid tumors are ongoing or have been completed in China and include those for progressive or metastatic melanoma, mucosal melanoma, gastric adenocarcinoma, esophageal squamous carcinoma, nasopharyngeal carcinoma (NPC) and head-and-neck squamous cell carcinoma, recurrent refractory malignant lymphoma, NSCLC, triple-negative advanced breast cancer, locally progressive or metastatic urothelial bladder carcinoma, advanced renal carcinoma, advanced neuroendocrine neoplasms, and high-risk recurrent hepatic carcinoma after radical surgery.

Several trials are also investigating combination therapy with toripalimab and: GP regimen (gemcitabine and cisplatin) in the treatment of advanced NPC; axitinib in subjects with advanced renal carcinoma and melanoma who failed standard care; pemetrexed and carboplatin for treating advanced or recurrent non-small-cell lung carcinoma. For further details see the IB.

1.4.1 Summary of Safety from Trials Performed in China

Summary of the safety of monotherapy in Chinese subjects was based on 12 company sponsored studies. There were a total of 985 subjects, including melanoma (N=322), nasopharyngeal cancer (N=200), urothelial carcinoma (N=160), esophageal squamous cell carcinoma (N=65), adenocarcinoma gastric (N=63), squamous cell carcinoma of head and

neck (N=34), non-small cell lung cancer (N=33), triple negative breast cancer (N=20), malignant lymphoma (N=24), soft tissue sarcoma (N=12), renal carcinoma (N=6), neuroendocrine tumor (N=40), pancreatic cancer (N=2) and other types of tumors (N=4). The administered doses were: 0.3 mg/kg (N=3), 1 mg/kg (N=39), 3 mg/kg (N=851), 10 mg/kg (N=31) and 240 mg (N=61).

In the 985 subjects, 964 subjects (97.9%) had at least one adverse event (AE), 928 subjects (94.2%) had study related AEs (if judged by investigators as positively related, probably related, possibly related or possibly unrelated, the causal relationship of the AE/serious adverse event [SAE] with the study drug was classified as related). The majority of subjects reported AEs of CTCAE grade 1-2. The study drug related AEs with the reporting rate ≥10% were anemia, elevated alanine aminotransferase (ALT), elevated aspartate aminotransferase (AST), fever, hypothyroidism, weakness, elevated thyroid stimulating hormone (TSH), cough, rash, decreased appetite, pruritus, increased blood glucose, decreased white blood cell count and urine protein detected. The reporting rate of the AEs leading to termination of study drug was 13.6% (134 subjects), and 15.6% (154 subjects) for AEs leading to dose interruption of study drug. The reporting rate of Common Terminology Criteria for Adverse Events (CTCAE)≥ grade 3 AE was 40.3%; 302 subjects (30.7%) had CTCAE≥ grade 3 AE related to the study drug, where the reporting rate ≥1% was seen in anemia, hyponatremia, pulmonary infection and abnormal hepatic function. The reporting rate of SAEs was 22.9%; 161 subjects (16.3%) had study drug related SAEs, where the reporting rate ≥1% was seen in pulmonary infection and abnormal hepatic function.

In the 985 subjects, systematic immune-related adverse events (irAE) adjudication had been made in the 741 subjects receiving the recommended therapeutic dose (3 mg/kg or 240 mg) (not including CT8, CT14 and CT17). In the 741 subjects, 236 subjects (31.8%) had at least one category of irAE, the majority of which were grade 1-2. The most common irAE was hypothyroidism that occurred in 13.6% subjects. 1 subject died of interstitial pneumonia.

Overall, the AEs observed in the pooled safety data were mainly abnormalities in various examinations, mostly grade 1-2 in severity, or consistent with the characteristics of underlying disease. The irAE profile was consistent with that reported for similar products and showed good tolerability. Overall, the AEs were manageable.

Refer to IB for detailed safety and clinical efficacy data on studies performed in China as well as the summary table of ADRs determined by company.

1.4.2 Safety Summary of Phase 1 Study in the United States (TAB001-01; NCT03474640)

Currently, one phase I study is ongoing for toripalimab in the United States (U.S.) (TAB001-01: a multicenter, open label, phase I clinical study to evaluate the safety, tolerability and pharmacokinetics (PK) of TAB001 in the subjects with advanced malignancies). The study includes two parts. Part A, the dose escalation phase, has been completed. A total of three

dose groups of 80 mg (3 subjects), 240 mg (8 subjects) and 480 mg (7 subjects) IV Q2W were set up, 18 subjects were enrolled, and 1 dose-limiting toxicity (DLT) event (grade 3 myocarditis) occurred; Part B is the dose extension phase using the therapeutic dose of 240 mg IV Q3W, 280 subjects are expected to be enrolled. A total of 109 subjects were enrolled in Part A and Part B by 16 December 2019.

The DLT of myocarditis was also an SAE. A blood test showing elevated troponin T was consistent with myocarditis. The subject had received 2 doses of 480 mg toripalimab, the highest dose in the study. Magnetic resonance imaging (MRI) of the heart showed no evidence of myocarditis and a heart muscle biopsy did not show inflammation. The event was considered to be immune related and possibly related to toripalimab.

Summary of safety from the phase I study in the U.S. was based on the 109 subjects who had received at least one dose of toripalimab. 104 (95.4%) subjects reported at least one AE during treatment, and 59 (54.1%) subjects reported AEs that were related to study drug. 56 (51.4%) subjects reported AEs with CTCAE ≥ grade 3, of which 17 (15.6%) were related to the study drug. For 5 (4.6%) subjects, the investigational product was interrupted due to an AE. For treatment emergent adverse events (TEAE) reported in ⩾10% of subjects, see Table 1.4.2-1.

Table 1.4.2-1: TEAEs Reported in ≥10% of Subjects in Phase I Studies in the United States

Preferred Term (PT)	Frequency (%)	Frequency (%)
	All CTCAE grades	CTCAE ≥ Grade 3
Subjects reporting at least 1 TEAE (N=109)	104 (95.4)	56 (51.4)
Fatigue	29 (26.6)	4 (3.7)
Nausea	23 (21.1)	3 (2.8)
Constipation	20 (18.3)	2 (1.8)
Anemia	19 (17.4)	8 (7.4)
Diarrhea	19 (19.3)	0
Dyspnoea	18 (16.5)	5 (4.6)
Abdominal pain	17 (15.6)	3 (2.8)
Blood alkaline phosphatase increased	15 (13.8)	4 (3.7)
Decreased appetite	15 (13.8)	0
AST increased	14 (12.8)	1 (0.9)
ALT increased	13 (11.9)	1 (0.9)
Peripheral edema	13 (11.9)	0
Pyrexia	13 (11.9)	2 (1.8)
Vomiting	13 (11.9)	4 (3.7)
Hyponatremia	12 (11.0)	8 (7.4)
Upper respiratory tract infection	12 (11.0)	0
Hypokalaemia	11 (10.1)	4 (3.7)
Cough	11 (10.1)	1 (0.9)

82 treatment emergent SAEs were reported in 47 (43.1%) subjects of which 9 (8.3%) were considered related to the study drug (see Table 1.4.2-2). 5 (4.6%) subjects reported SAEs with death outcome.

Table 1.4.2-2: Treatment Related Serious Adverse Events in a Phase 1 Trial Conducted in the United States (N=109)

System Organ ClassSystem Organ Class Preferred Term	CTCAE All Incidence (%)	CTCAE ≥ Grade 3 Incidence (%)
Cardiac disorders	**1 (0.9)**	**1 (0.9)**
Myocarditis	1 (0.9)	1 (0.9)
Gastrointestinal disorders	**2 (1.8)**	**2 (1.8)**
Large intestine preforation	1 (0.9)	1 (0.9)
Vomiting	1 (0.9)	1 (0.9)
General disorders and administration site conditions	**2 (1.8)**	**1 (0.9)**
Asthenia	1 (0.9)	1 (0.9)
Pyrexia	1 (0.9)	0
Immune system disorders	**2 (1.8)**	**2 (1.8)**
Immune-mediated adverse reaction	1 (0.9)	1 (0.9)
Serum sickness	1 (0.9)	1 (0.9)
Respiratory, thoracic and mediastinal disorders	**1 (0.9)**	**0**
Pneumonitis	1 (0.9)	0
Vascular disorders	**1 (0.9)**	**1 (0.9)**
Orthostatic hypotension	1 (0.9)	1 (0.9)

The spectrum of AEs for toripalimab, including SAEs, is generally similar to approved drugs in the same class without novel safety signals. The incidence of AEs does not appear to be dose related. The subjects will be continuously treated and monitored for safety and efficacy readouts (duration of response [DoR] and progression free survival[PFS]) until disease progression or intolerable toxicity.

In addition to the specific risks identified in the current toripalimab studies in China and the United States, trials of other immune checkpoint inhibitors most frequently report iRAEs of the gastrointestinal tract (e.g., colitis), endocrine glands (e.g., autoimmune thyroid and adrenal disease), hypophysitis, skin, and liver (e.g., autoimmune hepatitis) (Postow, et al., 2018). To a lesser extent, iRAEs involve the central nervous system (e.g., aseptic meningitis, transverse myelitis) and cardiovascular (e.g., myocarditis), pulmonary (e.g., pneumonitis), musculoskeletal (e.g., myositis and myasthenia gravis), and hematologic systems are involved (Postow, et al., 2018; Spain, et al., 2019). Because of the number of systems that may be involved, it is important to maintain a high index of suspicion for iRAEs and to refer subjects to the relevant specialists, such as a pulmonologist, cardiologist, endocrinologist, dermatologist, or rheumatologist.

Refer to IB for detailed safety data from the TAB001-01 study performed in the U.S.

1.4.3 Summary of Pharmacokinetic Analyses

A pooled PK analysis was performed by pooling the sample data of toripalimab in various dose groups (doses 0.3-10 mg/kg, as well as a fixed dose of 240 mg, Q2W) in three phase I dose- escalation clinical studies (CT1, CT2 and CT3). See Table 1.4.3-1 for the detailed parameters. The study results showed that after IV infusion of 1, 3 and 10 mg/kg to the clinical subjects, toripalimab basically presented linear PK characteristics and that after the dose increased to 10 mg/kg, the drug presented certain non-linear PK characteristics. The study results revealed that toripalimab showed an obvious "long-acting" characteristic of antibody drugs, with the plasma drug concentrations basically reaching a steady state after about 3 to 4 consecutive IV infusions of toripalimab to the clinical subjects, with mean half-life of 222.98±61.92 hours (9.29±2.58 days), Cmax of 77.17±47.3 μg/mL, and AUC(0-t) of 11635.89±7204.64, respectively, after multiple administrations in the 3 mg/kg group (n=37).

Table 1.4.3-1: Summary of PK Parameters after Multiple Intravenous Infusions of Toripalimab

PK Parameters	Units	Toripalimab									
		0.3 mg/kg		1 mg/kg		3 mg/kg		10 mg/kg		240 mg / subject	
Kel	1/hr	0.004±0.000	n=2	0.003 ±0.001	n=14	0.002 ±0.001	n=27	0.002 ±0.001	n=10	0.001	n=1
t1/2	hr	188.322 ±4.934	n=2	242.52 ±42.69	n=14	302.91 ±88.48	n=27	430.3 ±193.82	n=10	525.106	n=1
Tmax	hr	0-2	n=2	2 (0.5, 12)	n=14	2 (0.5, 24)	n=27	2 (0, 24)	n=10	0	n=1
Cmax	μg/mL	6.577 ±2.193	n=2	30.42 ±11.03	n=14	93.31 ±30.55	n=27	305.97 ±97.01	n=10	152.628	n=1
AUC(0-t)	hr*μg/mL	1099.367 ±448.421	n=2	4538.23 ±1541.22	n=14	18180.89 ±6101.07	n=27	62833.57 ±24694.62	n=10	34212.001	n=1
AUC(0-inf)	hr*μg/mL	1583.594 ±717.532	n=2	7895.14 ±2051.06	n=14	34529.42 ±12671.64	n=27	157946.58 ±81099.1	n=10	95199.868	n=1
AUC(t-inf)%	%	29.785 ±3.498	n=2	37.87 ±6.88	n=14	46.09±9.07	n=27	54.72 ±13.45	n=10	64.063	n=1
Vd	mL/kg	57.017 ±24.486	n=2	66.58 ±18.73	n=14	54.1 ±27.26	n=27	69.64 ±54.5 6	n=10	1909.836	n=1
CL	mL/hr/kg	0.211 ±0.096	n=2	0.19 ±0.05	n=14	0.13 ±0.06	n=27	0.12 ±0.08	n=10	2.521	n=1
MRTinf	hr	264.836 ±11.921	n=2	341.12 ±58.95	n=14	435.8 ±125.05	n=27	609.1 ±259.74	n=10	755.415	n=1

Kel = elimination rate constant from the central compartment; t1/2 = terminal half-life; Tmax = time to observed maximum serum concentration; Cmax = maximum observed concentration; AUC(0-t) = area under the curve (AUC) to time of last measurable concentration; AUC(0-inf) = AUC to time infinity; AUC(t-inf)% = percentage of $AUC_{(t\text{-}inf)}$ of $AUC_{(0\text{-}inf)}$; vd = volume of distribution; CL = clearance; MRTinf = mean residence time extrapolated to infinity

The minimum steady-state plasma concentration was about 20~40 μg/ml when toripalimab was administered IV at 3 mg/kg Q2W. In vitro experiments demonstrated that when the

plasma concentration of toripalimab was >20 nM or 3 μg/ml, PD-1 receptors on the surface of T-cells could be saturated, and that given the limitation of the antibody's macromolecules to enter the tumor microenvironment, the concentration of toripalimab in the peripheral blood was maintained at 20 μg/ml in order to ensure complete occupancy of lymphocyte PD- 1 in the tumor microenvironment. All Phase I studies showed that complete occupancy of PD-1 receptors could be maintained during the whole course of treatment in different dosage groups (0.3, 1, 3 and 10 mg/kg Q2W). The results of PK studies mentioned above and the resulting receptor occupancy (RO) data supported 3 mg/kg IV Q2W to be selected as the dose for the CT4 phase II key study (see Section 5.4 of the IB detailed information about the safety and efficacy of toripalimab). Two early studies explored a fixed dose of 240 mg IV every 3 weeks (Q3W). Of these two studies, a preliminary PK study involving 14 subjects revealed the peak steady-state plasma concentration and minimum steady-state plasma concentration at the dose of 240 mg Q3W (85 μg/mL and 21 μg/mL, respectively) are similar with those of 3 mg/kg Q2W (77 μg/mL and 25 μg/mL), which showed similar drug exposure and steady concentration and sufficient PD-1 RO. Those above results of toripalimab's PK/RO and Phase II key studies about melanoma, support the fixed dose of toripalimab 240 mg IV Q3W to be used as the recommended dose in Part B of this study and in Phase III clinical studies.

1.4.4 Immunogenicity of toripalimab

Use of any recombinant protein is associated with potential induction of local and systemic immune responses. Additional tests, for example, autoimmune serology or biopsies, should be used to monitor the production of ADA carefully to determine the probability of possible immunogenicity and the effect on subjects.

As of 1 May 2018, the pooled analysis on 518 subjects had shown the observation of ADA in subjects at the dose of 0.3-10 mg/kg and individual ADA positive rate of 15.4% in the subjects. The ADA positive rate observed was 18% in the 128 subjects with melanoma who received 3 mg/kg toripalimab injection. In accordance with PK and exposure-effect analysis, currently no evidence of loss of efficacy, change in the toxicity profile, or change in the PK profile was observed in the presence of ADA. No difference was observed in the efficacy and safety profile between the subjects with positive and negative ADA test results.

Based on the guideline for immunogenicity released by the U.S. FDA in January 2019, the serum matrix before administration from the subjects in the two phase II registration clinical studies for nasopharyngeal carcinoma (CT-5) and urothelial carcinoma (CT-12) and the blank matrix in humans constructed by the previous ADA test to validate the ADA positive threshold using analytical procedure were statistically analyzed in September 2019. The results showed a statistically significant difference in the response value between the two populations, thus the ADA positive threshold was reset for the serum matrix from the tested

subjects prior to administration in October 2019, and all the tested samples for relevant items were analyzed.

As of March 2020, in accordance with the new method for setting the ADA threshold, the ADA positivity rate observed in 190 subjects with nasopharyngeal carcinoma who received 3 mg/kg toripalimab injection was 3.7% and the ADA positivity rate was 6.6% in 151 subjects with urothelial carcinoma. The pooled analysis showed an ADA positivity rate of 5.0% in the 341 subjects with nasopharyngeal carcinoma and urothelial carcinoma who received 3 mg/kg toripalimab injection. Currently, from the PK and exposure-effect analysis, no evidence of loss of efficacy, change in toxicity profile or change in the PK profile was observed in the presence of ADA, and no difference was observed in the efficacy and safety between the subjects with positive and negative ADA test results.

A neutralizing antibody (NAb) assay is currently being developed to evaluate the neutralizing activity of ADA positive samples.

1.4.5 Pharmacodynamics study of toripalimab in NCT03316144

The pharmacodynamic effect of toripalimab was evaluated by PD-1 RO on the target cell over the course of treatment using the flow cytometry analysis. Toripalimab bound to the target molecule PD-1 on activated T lymphocytes (CD3+ CD45RA-) with full occupancy in all subjects from three cohorts after the initial dose. The full RO (>80% RO) was maintained in all subjects throughout the study period of 84 days.

1.5 Rationale for the current Study

A brief summary of the rationale for targeting PD-1 in oncology is provided below. For a more comprehensive review of toripalimab pharmacology, PK, and toxicology data, please refer to the toripalimab IB.

Blockade of the interaction between PD-1/PD-L1 has been demonstrated in non-clinical and clinical studies to enhance specific responses against tumors. In murine studies of melanoma, breast, ovarian, lung, liver, pancreatic and colon cancers, blockade of PD-1/PD-L1 reduced tumor burden and improved survival (Blank, et al., 2004; Curiel, et al., 2004; Hirano, et al., 2005). In humans, such blockade enhanced T cell responses against melanoma and leukemia (Fourcade, et al., 2010; Norde, et al., 2011). A number of clinical trials have demonstrated that monoclonal anti-PD-1 antibodies show evidence of efficacy and adequate safety in melanoma, non-small cell lung cancer (NSCLC), renal cell carcinoma (RCC), and mismatch repair deficient tumors, including colorectal cancer (Ansell, et al., 2015; Asaoka, et al., 2015; Berger, et al., 2008; Borghaei, et al., 2015; Brahmer, et al., 2010; Brahmer, et al., 2015; Le, et al., 2015; Garon, et al., 2015; Hamid, et al., 2013; Larkin, et al., 2015; Motzer, et

al., 2015; Nghiem, et al., 2016; Robert, et al., 2015; Topalian, et al., 2012; Wolchok, et al., 2013).

While toripalimab has a high affinity and blocks interaction between PD-1 and its ligand, PD-L1, it differs from other such antibodies by demonstrating more prolonged binding to PD-1 (Refer to the IB for more details). This raises the possibility of prolonged action of the drug in the tissues.

1.6 Rationale for Tumor Selection

Blockade of PD-1 pathway by mAbs has been demonstrated in non-clinical and clinical studies to enhance specific T cell responses against a broad spectrum of human malignancies. Solid tumors have thus been selected for this dose-escalation study on the basis of unmet medical need. Selected cancer patients, including but not limited to advanced gastric cancer (GC), esophageal cancer (EC), cholangiocarcinoma, hepatocellular cancer (HCC), sarcomas, both chondrosarcoma and soft tissue sarcoma (excluding leiomyosarcoma and including angiosarcoma, undifferentiated pleomorphic sarcoma and alveolar soft part sarcoma), neuroendocrine tumors (NETs) (excluding lung derived NET), NPC, or with the agreement of the Sponsor, other tumors will be enrolled for the expansion phase of the study, because of unmet medical need and evidence supporting the potential benefits to anti-PD-1 treatment.

Patients with GC, EC, or gastroesophageal junction cancer (GEC) often present with advanced and metastatic stage disease, which has poor prognosis, limited treatment options and represent an important unmet medical need.

Preliminary data from the phase I/II open-label study NCT01928394 for patients with GC/GEC receiving nivolumab monotherapy revealed an objective response rate of 12% (n = 7/58; 1 CR, 6 PR) and 12 patients (21%) with SD demonstrating antitumor activity in these disease settings. (http://meetinglibrary.asco.org/content/160127-173). Subsequent publication of the trial results confirmed the response rate: “Of 160 treated patients (59 with nivolumab 3 mg/kg, 49 with nivolumab 1 mg/kg plus ipilimumab 3 mg/kg, 52 with nivolumab 3 mg/kg plus ipilimumab 1 mg/kg), 79% had received two or more prior therapies. At the data cutoff, investigator-assessed objective response rates were 12% (95% confidence interval [CI], 5% to 23%), 24% (95% CI, 13% to 39%), and 8% (95% CI, 2% to 19%) in the three groups, respectively” (Jainjigian YY, et al., 2019). Since toripalimab differs from other such antibodies in that the binding to PD-1 is more prolonged, as measured by the dissociation coefficient, GC/GEC continues to be investigated to gather more experience in the U.S. and is planned in Europe.

NETs are heterogeneous and show diverse biologic and clinical behaviors, reflect primary tumor origin, type of neuroendocrine cell, and pathologic features (Kim, et al., 2016). NETs in the GI tract appear to be associated with different anatomical distributions in Western versus Eastern populations of the world. Most commonly NETs in the GI tract in the U.S. involve small intestine (38%), followed by the rectum (34%), colon (16%), stomach (11%), and unknown sites (1%). The average annual incidence of GI NETs in the U.S. is 2.5 cases per 100 000 per year, and an apparent recent increase in incidence may reflect increased identification of gastric and rectal NET cases. In Korea, the rectum (48%) is the most common location of GI tract NETs, followed by stomach (15%), pancreas (9%), colon (8%), small intestine (8%), liver (7%), appendix (3%), and biliary tract (2%). Everolimus, mammalian target of rapamycin (mTOR) inhibitor, and sunitinib, a multiple receptor tyrosine kinase (RTK) inhibitor were approved for treatment of advanced, progressive, well-differentiated pNETs in 2011 (Liu, et al., 2016). In 2016. for everolimus, the indication was expanded to encompass advanced, well-differentiated, non-functional gastrointestinal and lung NETs. Ongoing trials for NETs continue to investigate the clinical activity and therapeutic potential of other drugs, including other RTK and mTOR pathway inhibitors, and immune checkpoint inhibitors. Evidence from several clinical trials suggests some response to anti-PD-1 monotherapy in terms of Karnofsky Functional Status (KFS) scores and stable disease, and a number of trials are investigating combination therapies (Chauhan, et al., 2017). A trial of toripalimab (Title: A Trial of JS001 in Patients with Advanced Neuroendocrine Tumors; ClinicalTrials.gov Identifier: NCT03167853) enrolled chemotherapy refractory NET patients in China (Lu M, et al., 2020). Of 40 patients, 8 partial responses and 6 with stable disease were observed with a 20% objective response rate (ORR) and a 35% disease control rate (DCR). The median DOR was 15.2 months. Patients with PD-L1 expression (≥10%) or high tumor mutational burden (TMB) had better ORR than PD-L1 <10% (50.0% vs. 10.7%, P ¼ 0.019) and TMB-low patients (75.0% vs. 16.1%, P ¼ 0.03). Three of 8 (37.5%) responders had ARID1A mutations, whereas only 1 of 27 nonresponders had mutations (P ¼ 0.03). Notably, 1 exceptional responder with TMB-L, microsatellite stable (MSS), and PD-L1–negative had multiple genomic arrangements with high prediction score for neoantigens. The authors concluded that toripalimab showed antitumor activity and had acceptable safety in treating recurrent or metastatic NETs. Patients with positive PD-L1 expression, TMB-H (top 10%), and/or microsatellite instability (MSI-H) might preferentially benefit from the treatment. The genomic mutation of ARID1A and high genomic rearrangements might be correlated with clinical benefit.

Based on some evidence of response to anti-PD-1 monotherapy, the results of the clinical trial in China and differences in the spectrum of disease in Asia versus the U.S., and the sparsity of data for the treatment of NETs further investigation is planned with toripalimab.

Hepatobiliary malignancies represent 13% of cancers worldwide, and 3% of cancer mortality in the United States. Cholangiocarcinoma is the second most common primary hepatic cancer and the most frequent among biliary tract cancers and has a very poor prognosis (Blechacz, 2017). Only surgery appears to have the potential curative outcomes, but the disease tends to be diagnosed late, and recurrences are frequent after resection. Liver transplantation alone is not recommended because of high recurrence rates and 20% survival rate, but neoadjuvant radiation and chemotherapy decreases recurrence rates and increases 5 year survival. While cholangiocarcinoma has tended to be considered resistant to chemotherapy, the addition of cisplatin and erlotinib to gemcitabine therapy has been associated with better responses. Immune checkpoint inhibitors are being investigated as treatments for cholangiocarcinoma, and pembrolizumab has been approved for all refractory mismatch repair (MMR)–deficient cancers, including cholangiocarcinoma (Le, et al., 2017). In the KEYNOTE 028 study, cholangiocarcinomas showed a 17% response rate with a median response duration of 40 weeks. While there is a high unmet medical need for treatments for cholangiocarcinoma, data on immune checkpoint inhibitors for this disease are still sparse, and further investigations are warranted to clarify the role of anti-PD-1 therapy.

HCC is a major health problem and worldwide is the second leading cause of cancer-related death. Immunotherapy seems suitable as a possible treatment for HCC since it is seen in the setting of chronic hepatic inflammation, such as in individuals infected with hepatitis B or C and those with non-alcoholic fatty liver disease (Brown, et al., 2017). This inflammation encourages oncogenesis and often results in immunogenic lesions. Specific gene mutations result in the expression of tumor-associated antigens and neo-antigens which become targets for the immune system. Several clinical trials showed that immune checkpoint inhibitors have promise in the treatment of HCC. Adverse events from checkpoint inhibitors are associated with induction of autoimmunity, including hepatitis and transaminitis. Although patients with HCC treated with immune checkpoint inhibitors show increased AST/ALT in comparison with melanoma and NSCLC patients, a safety study by Brown, et al., found that this was not associated with patients discontinuing therapy or deaths attributed to drug toxicity.

Patients with unresectable, recurrent, and/or metastatic high grade soft-tissue sarcoma and chondrosarcoma who progress after systemic therapy have limited treatment options. In the phase II open-label study NCT02301039, sarcoma patients received pembrolizumab after failure of prior systemic therapy (Tawbi, et al., 2017). In this 86-patient single-arm study, there were two cohorts, soft-tissue sarcoma or bone sarcoma. In each cohort, pembrolizumab which is a mAb to target PD-1 was received by 42 patients of whom 40 were evaluable. Median follow-up was 17·8 months (IQR 12·3-19·3). Of 40 patients with soft-tissue sarcoma, 7 (18%) showed an OR, including 4 (40%) of 10 patients with undifferentiated

pleomorphic sarcoma, 2 (20%) of 10 patients with liposarcoma, and 1 (10%) of 10 patients with synovial sarcoma. No patients with leiomyosarcoma (n=10) had an OR. Of 40 patients with bone sarcoma, 2 (5%) had an OR, including 1 (5%) of 22 patients with osteosarcoma and 1 (20%) of 5 patients with chondrosarcoma. Of 13 patients with Ewing's sarcoma, none had an OR. The authors concluded that while the primary endpoint of overall response was not met for either cohort, pembrolizumab appeared to show activity in patients with undifferentiated pleomorphic sarcoma or dedifferentiated liposarcoma. In addition, as seen for leiomyosarcoma in the above study by Tawbi, et al., in a phase 2, single center, single agent study of 12 patients, nivolumab which is a human immunoglobulin G_4 (IgG_4) monoclonal antibody to target PD-1 did not demonstrate benefit in a cohort of previously treated advanced uterine leiomyosarcoma patients (Ben-Ami, et al., 2017).

As of May 2020, in the current TAB001-01 study, responses for `undifferentiated pleomorphic sarcomas and to a greater extent angiosarcoma have been encouraging. Of 6 subjects with angiosarcoma, 5 were evaluable, and the best responses for 3 of those subjects were partial response (PR) (60%). Four subjects with undifferentiated pleomorphic sarcoma were evaluable and 1 had an initial PR (25%) and was still in follow up. Angiosarcoma is rare, accounts for less than 2% of all soft tissue sarcomas, and mainly affects adult and elderly patients (Cao J, et al., 2019). It is an aggressive malignant tumor that arises from lymphatic or vascular endothelial cells. Angiosarcomas most frequently occur as cutaneous lesions (about 60% of cases), particularly the head and neck, may present within the soft tissues, visceral organs, bone and retroperitoneum. Angiosarcoma has a high rate of local recurrence and metastasis. Advanced/metastatic disease at presentation occurs in 16 to 44% of patients, and overall survival (OS) ranges from 6 to 16 months. Risk factors include chronic lymphoedema, history of radiation, environmental carcinogens and certain familial syndromes. Conventional options of treatment include surgery, radiotherapy and chemotherapy. Targeted therapeutic agents and immunotherapy have been studied as promising treatments of angiosarcoma.

A Phase 1 clinical trial of toripalimab conducted in China, included 12 patients with chemo-refractory advanced alveolar soft part sarcoma (ASPS) and responses were promising (Yang, et al., 2020). Of these patients, 1 showed a complete response (CR), 2 showed PRs, and 8 showed SD. The ORR was 25.0% (3/12) and the DCR was 91.7% (11/12). The responses were durable, as the median progression free survival (PFS) and the median overall survival (OS) were 11.1 month and 34.7 month, respectively. Alveolar soft part sarcoma is rare (Jaber, et al., 2015). Mostly it arises in lower limb soft tissues in adults and in children in the head and neck region. Usually it presents as a slowly growing mass or as metastatic disease. ASPS is a rare neoplasm, about 0.2% to 0.9% of all soft tissue sarcomas occurring mostly in those between ages 15 to 35 years; it is rare in patients less than 5 years of age those older

than 50 years. Females are more frequently affected than males with a 2:1 ratio in the first 3 decades of life but after that a slight male predominance is seen (Jaber, et al., 2015).

ASPS has a high frequency of metastasis that may occur before the primary tumor is noted (Jaber, et al., 2015). In 20% to 30% of patients the tumor recurs locally. Prognosis depends on whether the initial presentation is localized or metastatic, as well as age and tumor size. The 5-year survival rate for localized disease at presentation is 71%, compared with 20% for patients with metastatic disease at time of diagnosis. Large tumors are most likely to be associated with metastasis at the time of diagnosis.

Given the safety profile of toripalimab is similar to that of other anti-PD-1 monoclonal antibodies, the responses seen for angiosarcoma and undifferentiated pleomorphic sarcomas in the current trial and the promising results of another toripalimab clinical trial showing a high response rate for subjects with ASPS, the sarcoma cohort was expanded to enroll an additional 40 subjects focusing on these sarcoma subtypes. In addition, there is a high unmet medical need for treatments of these rare tumors.

Patients with unresectable and/or recurrent NPC who progress after radiation therapy have limited treatment options and represent an important unmet medical need. NPC patients have been reported to have a high percentage of PD-L1 expression (>60%) by multiple studies, indicating potential implication of PD-1 blockade in treating these patients (Zhang, et al., 2015; Chang, et al., 2017; Zhang, et al., 2008).

As a result, patients with GC, EC, cholangiocarcinoma, NETs (excluding lung derived NET), sarcomas, both chondrosarcoma and soft tissue sarcoma (excluding leiomyosarcoma and including angiosarcoma, undifferentiated pleomorphic sarcoma and ASPS), HCC, and NPC, as well as other indications where PD-1 is thought to play a role in tumor immune evasion, may be enrolled in this toripalimab clinical trial.

1.7 Rationale for Dose

The rationale for the proposed Phase 1 starting dose has taken into account all relevant preclinical pharmacology and toxicology data, including calculated and experimentally measured receptor occupancy, dose-response in human cell-based assays, and pharmacodynamic evaluations conducted in conjunction with the toxicology studies, as well as the safety profiles and Food and Drug Administration (FDA) approved clinical dose of similar drugs targeting the same molecule.

As a starting point, the guidelines presented in the FDA Guidance for Industry Estimating the Maximum Safe Starting Dose in Initial Clinical Trials for Therapeutics in Adult Healthy Volunteers were used. The NOAEL determined in the Good Laboratory Practice (GLP)-

compliant repeat-dose toxicology study in cynomolgus monkeys was 100 mg/kg (the highest dose level tested). Toripalimab is not pharmacologically active in rodent species and therefore rodent toxicology studies were not performed. Since toripalimab is a protein administered IV with a molecular weight > 100 kDa, mg/kg scaling was used, and the human-equivalent dose (HED) was determined to be 100 mg/kg. A default safety factor of 10 is appropriate, as there are no considerations indicating a safety concern that warrants increasing the safety factor. Based on this analysis, the MRSD is considered to be 10 mg/kg (1/10 of NOAEL). The proposed human starting dose is 80 mg, about 1 mg/kg given an average patient weight of 80 kg, a dose that is 10-fold lower than the MRSD.

Furthermore, commercially purchased Pembrolizumab (KEYTRUDA®) and Nivolumab (Opdivo®) had been included as positive controls and compared with toripalimab in binding affinity assays and *in vitro* cytokine release assays. The study results showed none of the three agents induced cytokine release in unstimulated and pre-activated human PBMCs, indicating a possible comparable safety profile.

Based on literature reports and data obtained from other anti-PD-1 products, there is no clear relationship between body size and PK or efficacy/safety at the therapeutic dose. Given the clinical experience, the proposed starting dose of 80 mg, about 1 mg/kg, would not pose unreasonable risk on patients. We therefore propose a flat starting dose of 80 mg in this study.

Toripalimab has been administered to humans in 26 trials in China and 1 trial (TAB001-01) in the United States as of Dec 2019. One phase I study (NCT03316144) conducted at Institute of Hematology & Blood Diseases Hospital, Chinese Academy of Medical Science, was a 3+3 dose-escalation study treating Malignant Lymphoma. The dose-escalation cohorts are 1, 3 and 10 mg/kg biweekly (Q2W) via IV infusion. Any dose-escalation cohort that did not exceeded the MTD could be expanded up to a maximum of 3 subjects at each dose level for further evaluation of safety, PK, pharmacodynamics, and efficacy. The first subject was enrolled on 5 Sep 2017 and last subject enrolled on 2 Dec 2017. The study has enrolled a total of 13 subjects, 4 subjects in the 1 mg/kg cohort, 3 subjects in the 3 mg/kg cohort and 6 subjects in the 10 mg/kg cohort. See Section 1.4 for details regarding study NCT03316144.

From the Phase I toripalimab dose escalation study (NCT03316144), toripalimab was well tolerated in up to 10 mg/kg Q2W. No DLT or death has occurred. 100% of subjects had TEAEs, but the majority of AEs were of Grade 1 or 2. The spectrum of AEs is similar to approved drugs in the same class without novel safety signals. The observed serum half-life of toripalimab was 16.4 to 18.1 days after five consecutive Q2W doses of 1, 3, or 10 mg/kg. 1 out of 13 subjects had an ADA positive sample(s) identified after dosing. The trough concentration of toripalimab after 6 doses were 10.08±5.69, 40.09±26.95 and 209.24±23.73

ug/mL for 1, 3 and 10 mg/kg cohorts respectively. Previous in vitro study has shown that the saturation binding and blocking effect on PD-1 was achieved when toripalimab concentration was no less than 2.9 μg/mL (See IB, page 30 for details). Consistent with the in vitro blocking study, toripalimab bound to the target molecule PD-1 on PBMC with full occupancy in all subjects from three cohorts after the initial dose. The full receptor occupancy (>80% RO) was maintained in all subjects throughout the study period of 84 days, indicating the PD-1 receptor was fully saturated in three dose cohorts.

Additionally, objective clinical response was observed in all three cohorts. The incidence of AEs or clinical response does not appear to be dose related. Given the favorable safety and efficacy profile of the Phase I toripalimab study NCT03316144 and observed long half-life of toripalimab, upon the completion of the current dose escalation study (TAB001-01) at 80 mg, 240 mg and 480 mg fixed dose Q2W, we plan to explore the intermediate dose of 240 mg Q3W in the expansion phase for further safety and efficacy evaluation.

2 OBJECTIVES AND ENDPOINTS

2.1 Objectives

2.1.1 Primary Objectives

- Dose-escalation phase: To assess the safety and tolerability of multiple doses of toripalimab and define the MTD or the maximum feasible dose (MFD) (highest protocol-defined dose of toripalimab in the absence of exceeding the MTD) in subjects with advanced malignancies.
- Dose-expansion phase: To further characterize the safety profile of toripalimab in subjects with selected advanced malignancies, and to evaluate the recommended Phase 2 Dose (RP2D).

2.1.2 Secondary Objectives

- To describe the PK profile of toripalimab
- To evaluate antitumor activity of toripalimab
- To determine the immunogenicity of toripalimab
- To evaluate OS

2.1.3 [redacted]

[redacted]

- [redacted]

[redacted]

[redacted]

2.2 Study Endpoints

2.2.1 Primary Endpoint

- The primary endpoint is determination of the MTD, which is the highest dose within Part A where no more than 1 out of 6 subjects experience a DLT, or the MFD.
- The primary endpoints for safety assessment include AEs, SAEs, laboratory evaluations, vital signs, physical examinations, and ECG results.

2.2.2 Secondary Endpoints

- The endpoints for assessment of PK of toripalimab include individual toripalimab concentrations in serum and PK parameters including area under the concentration-time curve (AUC), C_{max}, clearance (CL), volume of distribution (V_d), and terminal elimination half-life ($t_{1/2z}$).
- The endpoints for assessment of antitumor activity/efficacy include OR, disease control (DC), DoR, PFS and OS assessed by the Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 as well as the immune-related Response Evaluation Criteria in Solid Tumors (irRECIST) (www.irrecist.com).
- The endpoints for assessment of immunogenicity of toripalimab include the number and percentage of subjects who develop detectable ADA.

2.2.3 [redacted]

[redacted]

[redacted]

3 STUDY DESIGN

3.1 Description of the Study

3.1.1 Overview

This Phase 1, open-label, 2-part (Part A = dose-escalation, Part B = dose-expansion) study to evaluate the safety, tolerability, PK, immunogenicity, and antitumor activity of toripalimab administered IV on a Q2W (Part A) or Q3W (Part B) dosing schedule in adult subjects with advanced solid malignancies that are refractory to standard therapy or for which no standard therapy exists. In Part A, a cycle is 28 days (4 weeks) which includes toripalimab being administered IV Q2W. In Part B, a cycle is 42 days (6 weeks) which includes toripalimab being administered IV Q3W.

3.1.2 Part A – Dose Escalation

Part A will use a 3+3 design and will enroll cohorts of 3-6 subjects sequentially at escalating doses of 80 mg, 240 mg and 480 mg. Subjects will receive their assigned dose Q2W (± 2 days) in the absence of confirmed progressive disease, unacceptable toxicity, withdrawal of consent, intercurrent illness preventing further administration of toripalimab, or the investigator considers it in the best interest of a subject to discontinue study treatment. A protocol amendment will be submitted to the FDA if there are any changes in dose levels and dosing frequency.

Dose escalation will continue up to a flat dose of 480 mg or until identification of a MTD or the MFD. Up to a total of 18 immunotherapy-naïve subjects (no prior exposure to immunotherapy such as but not limited to other anti-CTLA-4, anti-PD-1, or anti-PD-L1 antibodies excluding vaccines) may be enrolled in Part A.

3.1.3 Part B – Dose Expansion

In Part B, up to 280 subjects with solid tumors including but not limited to esophageal or gastric carcinoma, cholangiocarcinoma, NETs (excluding lung derived NET), sarcomas, both chondrosarcoma and soft tissue sarcoma (excluding leiomyosarcoma and including angiosarcoma, undifferentiated pleomorphic sarcoma and ASPS), or with agreement of the Sponsor, other tumors, including NPC and HCC, that have been treated with at least one line of therapy in the metastatic setting will be enrolled. Patients with microsatellite instability-high (MSI-H)/ mismatch repair deficient (dMMR) tumors are eligible to enroll.

The dose(s) to be evaluated in Part B will be 240 mg administered IV Q3W after review of safety, PK and pharmacodynamic data from subjects treated with TAB001. A maximum of 40 subjects can be enrolled in each cohort with the exception of the sarcoma cohort, in which

a maximum of 80 subjects can be enrolled. Enrollment will consist of solid tumors that may include but will not be limited to esophageal and gastric carcinoma, cholangiocarcinoma, NETs (excluding lung derived NET), sarcomas, both chondrosarcoma and soft tissue sarcoma (excluding leiomyosarcoma and including angiosarcoma, undifferentiated pleomorphic sarcoma and ASPS), or with agreement of the Sponsor, other tumors, including NPC and HCC, that have been treated with at least one line of therapy in the metastatic setting. After 40 subjects have been enrolled in the sarcoma cohort, a further 40 subjects will be enrolled and will be limited to angiosarcoma, undifferentiated pleomorphic sarcoma and alveolar soft part sarcoma. Patients with MSI-H/dMMR tumors are eligible to enroll. Subjects will receive their assigned dose IV Q3W until confirmed disease progression, unacceptable toxicity, withdrawal of consent, intercurrent illness preventing further administration of toripalimab, or the investigator considers it in the best interest of a subject to discontinue study therapy.

3.1.4 Treatment Regimen

All subjects will be evaluated regularly, and their clinical status classified according to RECIST v1.1 and irRECIST (http://www.irrecist.com/). If feasible, all subjects will be followed for PFS and OS (Part B only) until the end of the study, defined as the date of the last protocol-specified visit/assessment (including telephone contact), or the date the study is closed by the sponsor, whichever comes first. AEs and SAEs will be followed from the start of the first dose of toripalimab through 90 days after the last dose of toripalimab. For subjects who receive another experimental or anticancer therapy, only related AE/SAEs will be collected through 90 days after the last dose of study drug.

In Part A, radiological assessment of tumor response status must be performed approximately every 8 weeks (± 10 days) for the first 12 months and approximately every 12 weeks (± 10 days) thereafter, unless the Investigator determines it is more appropriate to continue the radiological assessments on an approximately 8 week frequency.

In Part B, radiological assessment of tumor response status must be performed approximately every 9 weeks (± 10 days) for the first 12 months and approximately every 18 weeks (± 10 days) thereafter, unless the Investigator determines it is more appropriate to continue the radiological assessments on an approximately 9 week frequency.

Subjects will be monitored for safety, PK, anti-toripalimab antibodies and clinical activity as outlined in Section 4.2. Serum samples will be collected to screen for changes in markers of immune response and determine whether changes in serum markers are predictive of response and/or reflective of pharmacodynamic response. In Part A, fresh pre-treatment biopsies will be requested from subjects with safely accessible lesions. For subjects who

cannot provide a fresh pre-treatment biopsy, an archival specimen will be required. In Part B, fresh pre-treatment biopsies will be required from all subjects with safely accessible lesions. Archival specimens will be requested. Biopsies results from materials specifically obtained for the study will not affect eligibility. However, the biopsy report upon which the diagnosis was based should be in the subject's medical record.

The study will be conducted at up to 30 centers in the U.S..

3.1.5 Treatment Regimen

Subjects will be treated in either Part A or Part B of the study. Subjects will receive toripalimab IV Q2W (Part A) or Q3W (Part B) until confirmed disease progression, unacceptable toxicity, withdrawal of consent, intercurrent illness preventing further administration of toripalimab, or the investigator considers it in the best interest of a subject to discontinue study therapy.

Toripalimab will be administered IV over a minimum of 60 minutes. In subsequent cycles, the infusion time may be reduced to a minimum of 30 minutes depending upon subject tolerance. The infusion duration may be increased at any time at the discretion of the investigator.

Refer to Section 4.8 for a description of toripalimab dose calculation, preparation, and administration.

Toripalimab may be administered in the setting of progressive disease (PD) as long as all of the following criteria are met:

- Absence of clinical symptoms or signs indicating clinically significant disease progression
- No decline in Eastern Cooperative Oncology Group (ECOG) performance status from baseline
- Absence of rapid disease progression or threat to vital organs or critical anatomical sites (e.g., CNS metastasis, respiratory failure due to tumor compression, spinal cord compression) requiring urgent alternative medical intervention; no significant, unacceptable or irreversible toxicities related to study treatment.

These subjects would continue on to the next regulatory scheduled visit and thereafter as per the Schedule of Evaluations. However, a repeat scan to assess for true disease progression in 4 weeks ± 2 days in Part A and in 6 weeks ± 2 days in Part B is required. It is also required that any subject with pending organ compromise be discontinued from the toripalimab treatment.

If feasible, all subjects will be followed for PFS and OS (Part B only) until the end of the study, defined as the date of the last protocol-specified visit/assessment (including telephone contact), or the date the study is closed by the sponsor, whichever comes first.

3.1.6 Dose-escalation Design

3.1.6.1 General Dose Escalation and De-escalation Rules

Rules for dose escalation and de-escalation are as follows:

1. A minimum of 3 subjects will be enrolled in each dose cohort.
2. The administration of toripalimab to the first and second subjects of each cohort will be separated by at least 24 hours.
3. All safety data will be reviewed by a study-specific dose-escalation committee (including, but not limited to, the sponsor medical monitor or designee, and participating principal investigator's or designees) before proceeding with an escalation or de-escalation decision. All decisions from the committee will be documented and shared with each participating principal investigator.
4. A 3+3 dose-escalation design will be followed as summarized below:
    a. If 0 out of the 3 subjects in a dose cohort experience a DLT during the DLT evaluation period, dose escalation may proceed to the next planned cohort with approval of the dose-escalation committee.
    b. If 1 of the 3 subjects in any dose cohort experiences a DLT during the DLT evaluation period, that dose cohort will be expanded to a total of 6 subjects. If no more than 1 of 6 subjects in the dose cohort experiences a DLT, dose escalation may proceed to the next planned dose cohort(s) with the approval of the dose-escalation committee.
    c. If 2 or more subjects in a dose cohort experience a DLT during the DLT evaluation period, the MTD will have been exceeded and no further subjects will be enrolled into that dose cohort. A previous lower-dose cohort or an intermediate-dose cohort may be explored based on the recommendation of the dose-escalation committee.
5. Any cohort that has not exceeded the MTD can be expanded up to a maximum of 10 subjects for further evaluation of safety and efficacy.
6. Intrasubject dose escalation will not be allowed.

3.1.6.2 Dose-limiting Toxicity

DLTs will be evaluated in each cohort in Part A. The period for evaluating DLTs will be defined as the time period starting with the first dose of toripalimab until the planned administration of the third dose of toripalimab. Subjects are considered evaluable for DLT if they receive the protocol-assigned dose(s) of toripalimab and complete the safety follow-up through the end of the DLT evaluation period, or experience a DLT during the DLT evaluation period. Any subject who experiences a DLT will receive no further toripalimab (see Section 4.1.5 Withdrawal Criteria). Subjects who do not remain on the study up to this time for reasons other than DLT will be replaced with another subject at the same dose level. Grading of DLTs will be according to the National Cancer Institute-Common Terminology Criteria for Adverse Events (NCI-CTCAE) v4.03.

A DLT will be defined as all Grade 3 or higher adverse events that occur during the DLT evaluation period that are at least possibly related to toripalimab, including but not limited to:

- Neutropenic fever, regardless of grade
- Grade 4 neutropenia lasting > 7 days
- Increase in ALT or AST to > 3 x ULN with concurrent increase in bilirubin to > 2 x ULN
- Any Grade ≥ 3 enterocolitis
- Grade 4 thrombocytopenia of any duration
- Grade 3 thrombocytopenia associated with bleeding
- Any Grade 4 irAE or non-irAE irrespective of duration
- Any Grade 3 or 4 noninfectious pneumonitis irrespective of duration
- Any Grade 3 irAE including rash, pruritus, or diarrhea that does not downgrade to ≤ Grade 2 within 7 days after onset of the event despite maximal supportive care including systemic corticosteroids
- Any ≥ Grade 2 pneumonitis that does not resolve to ≤ Grade 1 within 14 days of the initiation of maximal supportive care

The definition excludes the following conditions:

- Grade 3 fatigue or nausea for ≤ 7 days

- Grade 3 decrease in lymphocyte count that downgrades to ≤ Grade 2 within 7 days after onset of the event and resolves to ≤ Grade 1 or baseline within 14 days, unless not clinically significant (e.g., fungal nail infections or thrush)
- Grade 3 endocrinopathy that is managed with or without systemic corticosteroid therapy and/or hormone replacement therapy and the following criterion is met:
  - The subject is asymptomatic
- Grade 3 inflammatory reaction attributed to a local antitumor response (e.g., inflammatory reaction at sites of metastatic disease, lymph nodes, etc.) that resolve to ≤ Grade 1 within 30 days

While the rules for adjudicating DLTs in the context of dose escalation/cohort expansion are specified above, an AE not listed above, or an AE meeting the DLT criteria above but occurring outside of the DLT period may be defined as a delayed DLT following the procedures outlined below.

Delayed DLTs will be evaluated on a case-by-case basis upon consultation between the sponsor and the PI. At minimum, a review and discussion of potential delayed DLTs will take place at each safety review prior to a dose escalation decision (i.e., approximately every 6-8 weeks). Factors taking into account whether these AEs constitute a delayed DLT include the emerging safety profile of toripalimab, whether the AE meets the definition of a DLT as defined above including duration of the event and response to intervening therapy, and clear determination of whether there is a well-documented alternative explanation for the toxicity observed. In the event that the delayed DLT constitutes a laboratory based toxicity not associated with clinical signs or symptoms, confirmation of the laboratory results will be obtained and DLT determination will be evaluated in light of the clinical benefit of toripalimab to the subject.

Once the documented AE has been designated a delayed DLT, by the sponsor and PI, the same rules of reporting as that for DLTs described in Section 5.7.1 will be followed.

The impact of a delayed DLT on the dose-escalation cohort will follow the rules outlined in Section 3.1.6. If a higher dose is under evaluation (relative to the dose cohort where a delayed DLT was noted), further enrollment in the higher dose cohort will be held pending outcome of the evaluation of the lower dose cohort. Subjects who are tolerating study drug at the higher dose level may be allowed to continue treatment provided the PI believes there is a favorable benefit-risk and there is agreement with the sponsor.

All subjects will be evaluated regularly, and their clinical status classified according to RECIST v1.1 and irRECIST (http://www.irrecist.com/). If feasible, all subjects will be

followed for PFS and OS (Part B only) until the end of the study, defined as the date of the last protocol-specified visit/assessment (including telephone contact), or the date the study is closed by the sponsor, whichever comes first. AEs and SAEs will be followed from the start of the first dose of toripalimab through 90 days after the last dose of toripalimab unless a subject receives another experimental or anticancer therapy, at which time only related AE/SAEs will be collected through 90 days after the last dose of toripalimab. The endpoints to be measured in this study are described in Section 2.2.

3.1.7 Management of Study Related Toxicities

Management of study related toxicities will be the same for Part A and Part B of this study.

3.1.7.1 Toripalimab Dose Modifications

Following the first dose of toripalimab, subsequent administration of toripalimab can be modified based on toxicities observed as described in Table 3.1.7-1. All toxicities will be graded according to NCI-CTCAE v4.03.

Dose modifications will not be required for AEs that are clearly not attributed to toripalimab (such as an accident) or for laboratory abnormalities that are not deemed to be clinically

Table 3.1.7-1: Toripalimab Dose Modification Due to Toxicity

Severity	Immune-related Adverse Events (irAEs) [a]	All Other Events [b]
Grade 1	None	**For infusion-related reactions:** • The infusion rate of toripalimab may be decreased by 50% or temporarily interrupted until resolution of the event • Acetaminophen and/or antihistamines may be administered per institutional standard at the discretion of the investigator • Refer to Section 4.10.1.2 for use of corticosteroids • Consider premedication prior to subsequent doses **All other AEs:** No dose adjustment is required

Severity	Immune-related Adverse Events (irAEs) [a]	All Other Events [b]
Grade 2	**For endocrinopathy:** • Hold toripalimab dose • When endocrinopathy is controlled, resume toripalimab dosing **For dermatologic irAEs:** • Do not hold toripalimab dose **For pneumonitis:** • Hold toripalimab until resolution to ≤ Grade 1 • If resolution to ≤ Grade 1 occurs within 3 days of the initiation of maximal supportive care (including corticosteroids), resume toripalimab administration at next scheduled dose. Otherwise, discontinue toripalimab **For all other irAEs:** • Hold toripalimab until resolution to ≤ Grade 1 • If resolution to ≤ Grade 1 does not occur within 30 days, discontinue toripalimab	**For infusion-related reactions:** • The infusion rate of toripalimab may be decreased by 50% or temporarily interrupted until resolution of the event • Acetaminophen and/or antihistamines may be administered per institutional standard at the discretion of the investigator • Refer to Section 4.10.1.2 for use of corticosteroids • Consider premedication prior to subsequent doses **All other AEs:** • Hold toripalimab until resolution to ≤ Grade 1 or baseline • If resolution to ≤ Grade 1 does not occur within 30 days, discontinue toripalimab

Severity	Immune-related Adverse Events (irAEs) [a]	All Other Events [b]
Grade 3	**For endocrinopathy:** • Hold toripalimab dose. • When endocrinopathy is controlled, resume toripalimab) administration at next scheduled dose **For dermatologic irAEs:** • Hold toripalimab until resolution to ≤ Grade 1 or baseline • If resolution to ≤ Grade 1 or baseline does not occur within 30 days, discontinue toripalimab **For elevations in transaminases:** • For elevations in transaminases ≤ 8 × upper limit of normal (ULN), hold toripalimab until resolution to ≤ Grade 1 or baseline • If elevations downgrade to ≤ Grade 2 within 7 days or resolve to ≤ Grade 1 or baseline within 14 days, resume toripalimab administration at next scheduled dose. Otherwise, discontinue toripalimab • For elevations in transaminases > 8 × ULN, discontinue toripalimab **For elevations in total bilirubin:** • For elevations in total bilirubin ≤ 5 × ULN, hold toripalimab until resolution to ≤ Grade 1 or baseline • If elevations downgrade to ≤ Grade 2 (< 3 × ULN) within 7 days or resolve to ≤ Grade 1 or baseline within 14 days, resume toripalimab administration at next scheduled dose. Otherwise, discontinue toripalimab • For elevations in total bilirubin > 5 × ULN, discontinue toripalimab **For all other irAEs:** • Discontinue toripalimab	**For hypersensitivity and infusion-related reactions:** • Discontinue toripalimab **All other AEs:** • Hold toripalimab until resolution to ≤ Grade 1 or baseline • For AEs that downgrade to ≤ Grade 2 within 7 days or resolve to ≤ Grade 1 or baseline within 14 days, resume toripalimab administration at next scheduled dose. Otherwise, discontinue toripalimab
Grade 4	• Discontinue toripalimab	• Discontinue toripalimab

a. Management of irAEs may require administration of immunosuppressive medications (and/or hormone replacement therapy for endocrinopathies; see Section 3.1.7.2 for management of irAEs). Resolution of irAEs managed in this manner in the timeframes specified is acceptable.

b See Section 3.1.7.3 for management of toripalimab-related toxicities.

3.1.7.2 Management of Immune-related Adverse Events

Based on the mechanism of action (MOA) of toripalimab leading to T-cell activation and proliferation, there is the possibility of observing irAEs during the conduct of this study.

Optimal strategies to monitor the immune related toxicities are evolving, and therefore, subjects receiving toripalimab should be carefully monitored for signs and symptoms of irAEs. In the absence of alternate etiology (e.g., infection or PD), signs or symptoms of enterocolitis, pneumonitis, transaminitis, dermatitis, hepatitis, and endocrinopathies should be considered immune-mediated.

The management guidelines summarized in Table 3.1.7-2, Management of Immune-related Adverse Events will provide guidance to investigators on the management and recommended interventions to prevent morbidity and mortality of these rare immune-related toxicities.

Immune-Related Colitis

Toripalimab can cause immune-mediated colitis, defined as requiring use of corticosteroids with no clear alternate etiology. Immune-related colitis shares some characteristics with inflammatory bowel disease but with little specificity. Signs and symptoms of colitis may include diarrhea (loose stools) or more bowel movements than usual, blood in stools or dark, tarry, sticky stools.

The investigator will handle AEs (diarrhea and colitis) according to local standard procedure or follow the recommendations listed in Table 3.1.7-3.

Immune-Related Hepatitis

Toripalimab can cause immune-mediated hepatitis, defined as requiring use of corticosteroids and no clear alternate etiology. Signs and symptoms of hepatitis may include transaminase elevation, total bilirubin elevation, jaundice, severe nausea or vomiting, right upper quadrant abdominal pain, drowsiness, dark urine (tea colored), bleeding or bruising more easily than normal, and decreased appetite. The investigator will handle immune-related hepatic AEs according to local standard procedure or follow the recommendations listed in Table 3.1.7-4.

The administration of any recombinant protein has the potential to induce local and systemic immunologic reactions. Subjects will be carefully monitored for the formation of ADA.

Table 3.1.7-2: Management of Immune-related Adverse Events

1	Subject evaluation to identify any alternative etiology
2	In the absence of a clear alternative etiology, all events of an inflammatory nature should be considered to be immune-related
3	Symptomatic and topical therapy should be considered for low-grade event
4	Systemic corticosteroids (e.g., prednisone or IV equivalent should be considered for a persistent low-grade event or for a severe event)
5	If symptoms recur of worsen during corticosteroid tapering, increase the corticosteroid dose until stabilization or improvement of symptoms, then resume corticosteroid tapering at a slower rate
6	More potent immunosuppressives – tumor necrosis factor (TNF) antagonist class (e.g., infliximab) or mycophenylate should be considered for events not responding to systemic steroids after discussion with the medical monitor

Table 3.1.7-3: Management of Gastrointestinal irAEs.

Grade 1	• Symptomatic treatment (for example, loperamide) according to institutional standards; • Close monitoring; instruct subject to report worsening immediately and treat as Grade ≥2
Grade 2	• ≤5 days: Symptomatic treatment according to institutional standards • >5 days or recurrence: 0.5–1.0 mg/kg/d methylprednisolone; consider prophylactic antibiotics; • Persistence or worsening despite steroids >3 days: treat as Grade 3/4 • Improvement to ≤Grade 1: taper steroids over at least 4 weeks, consider prophylactic antibiotics for opportunistic infections, resume study therapy per protocol
Grade 3-4 Should discontinuation from treatment be warranted	• Immediately: 1.0–2.0 mg/kg/d methylprednisolone IV; consider prophylactic antibiotics and lower colonoscopy • Persistence >3 days or recurrence: add infliximab 5 mg/kg (if no contraindication such as perforation or sepsis) • Improvement to ≤Grade 2 within ≤3 days: taper steroids over at least 4 weeks

Table 3.1.7-4: Management of Hepatic irAEs.

Grade 1	• Continue liver function monitoring • If worsens: Treat as Grade ≥2
Grade 2	• Monitor every 3 days; • Returning to baseline: resume per protocol monitoring • LFT elevation >5 days or worsening: 0.5-1.0 mg/kg/d methylprednisolone IV or oral equivalent; consider prophylactic antibiotics • LFT return to ≤Grade 1 or baseline: taper steroids over at least 4 weeks; resume routine monitoring and resume study treatment per protocol
Grade 3-4 Should discontinuation from treatment be warranted	• Monitor every ≤2 days; • Immediately: 1.0-2.0 mg/kg/d methylprednisolone IV or IV equivalent; start prophylactic antibiotics; consult gastroenterologist • Persistence >3 days or recurrence: add mycophenolate mofetil 1g bid; if no response within ≤5 days, consider other immunosuppressants per local guidelines • LFT return to Grade 2: stop immunosuppressants • LFT return to ≤Grade 1: taper steroids over at least 4 weeks

3.1.7.3 Management of Toripalimab-related Toxicities

Infusion-related Reactions

Infusion-related reactions may manifest with symptoms such as fever, chills, rigors, headache, rash, pruritus, arthralgia, hypo- or hypertension, bronchospasm, or other symptoms.

In order to promptly treat infusion-related reactions, it is recommended that treatment medications be prepared prior to the start of the infusion and placed within easy access of the bedside along with standing orders for the treatment of infusion related reactions.

Once symptoms of an infusion reaction occur (e.g., sense of feeling cold, chills, rigors, fever, neck pain, nausea), the infusion should be interrupted, and the subject should be assessed for other signs or symptoms (e.g., hypotension, hypoxia, wheezing, urticaria) suggestive of a more serious reaction.

Medications used to treat an infusion reaction will be at the discretion of the investigator. Sites should follow the guidelines in Table 3.1.7-1 for medical management of the actual infusion (i.e., reducing the infusion rate or stopping the infusion based on symptoms the subject is eliciting).

As with any antibody, allergic reactions to dose administration are possible. Therefore, appropriate drugs and medical equipment to treat acute anaphylactic reactions must be immediately available, and study personnel must be trained to recognize and treat anaphylaxis. See Table 3.1.7-1 for management guidelines by event severity.

Liver Chemistry Testing Procedures

The procedures listed below are to be followed if a subject meets the criteria for treatment discontinuation based on elevations in transaminases or total bilirubin as defined in Table 3.1.7-1 or any of the other criteria defined below. They do not apply if a subject develops liver chemistry abnormalities as a result of progressive disease.

Medical Management of Liver Chemistry Event

If a subject meets any of the criteria for treatment discontinuation based on elevations in transaminases or total bilirubin as defined in Table 3.1.7-1, do the following:

- Immediately withdraw the subject from further administration of toripalimab.
- Within 24 hours of learning of its occurrence, report the event to TopAlliance Biosciences Patient Safety representative as a SAE, notify the medical monitor of the

abnormality, confirm the subject has discontinued toripalimab, and appropriate follow-up has been arranged.

- Complete the Liver Event Follow-up Assessments listed below, especially the autoimmune work-up.
- Upon completion of the safety follow-up, permanently withdraw the subject from treatment and do not rechallenge with toripalimab.
- Follow procedures for stopping the study (See Section 3.1.8).

In addition, for subjects experiencing ALT ≥ 3 × ULN and bilirubin ≥ 2 × ULN (> 35% direct bilirubin) (or ALT ≥ 3 × ULN and international normalized ratio (INR) > 1.5) that was not present at baseline because of existing liver metastases or HCC which allow for ALT≤5) and is not attributable to tumor progression:

- Make every reasonable attempt to have subjects return to the clinic within 24 hours for repeat liver chemistries and additional testing.
- Close monitoring including specialist or hepatology consultation is recommended.
- Monitor subjects until liver chemistries (ALT, AST, alkaline phosphatase, bilirubin) resolve, stabilize or return to within baseline values.

Liver Event Follow-up Assessments

For subjects that meet study stopping criteria based on liver function abnormalities (Section 3.1.8), make every attempt to carry out the **liver event follow-up assessments** described below:

- Anti-nuclear antibody (ANA), anti-smooth muscle antibody, and Type 1 anti-liver kidney microsomal antibodies.
- Obtain viral hepatitis serology testing including:
  - Hepatitis A Immunoglobulin M (IgM) antibody
  - Hepatitis B surface antigen and Hepatitis B core antibody (IgM)
  - Hepatitis C ribonucleic acid (RNA)
- Assess eosinophilia
- Liver imaging (ultrasound, magnetic resonance, or computerized tomography) to evaluate liver disease.

In addition to the above, for subjects meeting any of the study stopping criteria, make every attempt to carry out the following additional **liver event follow-up assessments** described below:

- Viral hepatitis serology including:
  - Cytomegalovirus IgM antibody
  - Epstein-Barr viral capsid antigen IgM antibody (or if unavailable, obtain heterophile antibody or monospot testing)
  - Hepatitis E IgM antibody (if subject resides outside the U. S. or Canada, or has traveled outside the U.S. or Canada in past 3 months)
- All End of Treatment Central Laboratory Assessments (PK and pharmacodynamic blood draws) should be collected as described in Sections 4.3.4, and 4.4.
- Serum creatine phosphokinase (CPK) and lactate dehydrogenase (LDH).
- Fractionate bilirubin, if total bilirubin ≥ 2 × ULN.
- Record the appearance or worsening of clinical symptoms of hepatitis, or hypersensitivity, fatigue, decreased appetite, nausea, vomiting, abdominal pain, jaundice, fever, or rash as relevant on the AE electronic case report form (eCRF).
- Record use of concomitant medications, acetaminophen, herbal remedies, other over the counter medications, or putative hepatotoxins on the Concomitant Medications (CM) eCRF.
- The Liver Imaging and/or Liver Biopsy reports are also to be provided to the Sponsor if these tests are performed.

3.1.8 Study Stopping Criteria

If the following occurs, administration of toripalimab will be stopped and no additional subjects will be entered into the study:

- Any safety finding assessed as related to toripalimab that, in the opinion of the sponsor in consultation with the medical monitor and investigator(s), contraindicates further dosing of study subjects.
- Refer to Section 3.1.7.3 Management of toripalimab-related toxicities

If any such safety findings occur, further administration of toripalimab will be stopped and no further subjects will be entered into the study. Thereafter the regulatory authorities and

Institutional Review Boards (IRBs)/Independent Ethics Committees (IECs) will be notified and a prompt cumulative review of safety data and the circumstances of the event in question will be conducted. The findings will be shared with the regulatory authorities and the IRBs/IECs. If it is deemed appropriate by the sponsor after review by the medical monitor and investigator(s), justification for stopping the study will be sent to the regulatory authorities and the IRBs/IECs as required.

Any subjects who have already received toripalimab and are currently in the study at the time study-stopping criteria are met will continue to be followed through 90 days after the last dose of toripalimab unless a subject receives another experimental or anticancer therapy, at which time only related AE/SAEs will be collected through 90 days after the last dose of toripalimab.

Withdrawal criteria for individual subjects are provided in Section 4.1.5.

4 MATERIALS AND METHODS

4.1 Subjects

4.1.1 Number of Subjects

This study is expected to enroll up to 18 subjects (not including replacement subjects) in Part A. Additional subjects may be enrolled depending on the number of dose levels and toxicity profile observed. Part B will enroll up to 280 subjects, maximum of 80 subjects in a sarcoma cohort and 40 subjects for the other 5 cohorts. After 40 subjects have been enrolled in the sarcoma cohort, a further 40 subjects will be enrolled and will be limited to angiosarcoma, undifferentiated pleomorphic sarcoma and alveolar soft part sarcoma. Men and women, 18 years or older, with advanced malignancies that are evaluable by RECIST v1.1 and irRECIST, that are refractory to standard treatment or for which no standard therapy exists may be enrolled.

Additional subjects may be required, depending on the number of dose levels explored and toxicity profile observed.

4.1.2 Inclusion Criteria

Eligibility criteria for this study have been carefully considered to ensure the safety of the study subjects. If there is a question about the inclusion/exclusion criteria listed below, the principal investigator should contact the medical monitor or designee before enrolling the subjects.

Subjects must meet *all* of the following criteria:

1. Signed Informed Consent Form
2. Age ≥ 18 years
3. Subject meets the following corresponding requirements for the part of the study they will enroll into:

   During Part A, subjects must have a histologically or cytologically documented, incurable or metastatic solid tumor that has progressed on (or they have been intolerant to) standard systemic therapy options for their tumor type in the metastatic setting or must have a tumor type for which no such standard systemic option exists.

   During Part B, subjects must have a histologically or cytologically documented diagnosis of gastric cancer, esophageal cancer, cholangiocarcinoma, NETs (excluding lung derived NET), NPC, HCC, sarcomas, both chondrosarcoma and soft tissue sarcoma (excluding leiomyosarcoma and including angiosarcoma, undifferentiated pleomorphic sarcoma and alveolar soft part sarcoma), or with agreement of the Sponsor, other tumors that have been treated with at least one line of standard systemic therapy for their respective tumor type in the metastatic setting with progressive locally advanced or metastatic disease that is not amenable to definitive local therapy with curative intent. Patients with MSI-H/dMMR tumors are eligible to enroll.

   a. Subjects with nasopharyngeal cancer must have received (or been intolerant) to a platinum-based combination as part of their prior therapy for advanced/metastatic disease.
   b. Subjects with soft tissue sarcoma and chondrosarcoma must have radiographic evidence of progression within the previous 6 months and must have received at least 1 line of systemic therapy.
   c. Subjects with esophageal cancer must have received (or been intolerant to) a platinum-based combination as part of their prior therapy for advanced/metastatic disease.
   d. Subjects with gastric cancer must have received (or been intolerant to) a fluoropyrimidine-platinum combination as part of their prior therapy for advanced/metastatic disease.
   e. Subjects with HCC must have received (or been intolerant to) sorafenib as part of their prior therapy for advanced/metastatic disease.
4. Measurable disease per RECIST v1.1 and irRECIST
5. Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1

6. Adequate organ and marrow function, as defined below:

    a. Hemoglobin ≥ 8.0 g/dL within first 2 weeks prior to first dose of toripalimab

    b. Absolute neutrophil count (ANC) ≥ 1.2 × 109/L (1,200/mm3)

    c. Platelet count ≥ 75 × 109/L (75,000/mm3)

    d. Total bilirubin ≤ 1.5 × upper limit of normal (ULN) except subjects with documented Gilbert's syndrome who must have a baseline total bilirubin ≤ 3.0 mg/dL

    e. Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ≤ 2.5 × ULN; for subjects with hepatic metastases, ALT and AST ≤ 5 × ULN

    f. Serum creatinine ≤ 1.5 × ULN OR calculated creatinine clearance (CrCl) or 24-hour urine CrCl ≥ 40 mL/minute

    g. Cockcroft-Gault formula will be used to calculate CrCl.(Section 9.4); 24-hour urine CrCl will be derived using the measured creatinine clearance formula (9.5)

    h. International normalized ratio (INR) and activated partial thromboplastin time (aPTT) ≤ 1.5 ×ULN; applies only to subjects who do not receive therapeutic anticoagulation; subjects receiving therapeutic anticoagulation (such as low-molecular weight heparin or warfarin) should be on a stable dose.

7. Willingness to provide consent for biopsy samples (In Part A, fresh pre-treatment biopsies will be requested from subjects with safely accessible lesions. For subjects who cannot provide a fresh pre-treatment biopsy, an archival specimen will be required. In Part B, fresh pre-treatment biopsies will be required from subjects with safely accessible lesions. Archival specimens will be requested).

8. Females of childbearing potential who are sexually active with a nonsterilized male partner must use effective contraception from time of screening, and must agree to continue using such precautions for 90 days after the final dose of toripalimab; cessation of birth control after this point should be discussed with a responsible physician. Periodic abstinence, the rhythm method, and the withdrawal method are not acceptable methods of birth control.

    Females of childbearing potential are defined as those who are not surgically sterile (i.e., bilateral tubal ligation, bilateral oophorectomy, or complete hysterectomy) or postmenopausal (defined as at least 12 months with no menses confirmed by follicle-stimulating hormone [FSH] levels. FSH testing will be conducted at the Screening visit to confirm post-menopausal status).

    Subjects must use effective contraception as described in Table 4.1.2-1.

9. Nonsterilized males who are sexually active with a female partner of childbearing potential must use effective contraception (see Table 4.1.2-1) from Day 1 and for 90 days after receipt of the final dose of toripalimab.

Table 4.1.2-1 Highly Effective Methods of Contraception

Barrier Methods	Hormonal Methods
• Male condom plus spermicide • Copper T intrauterine device • Levonorgestrel-releasing intrauterine system (e.g., Mirena®) [a]	• Implants • Hormone shot or injection • Combined pill • Minipill • Patch

[a] This is also considered a hormonal method.

4.1.3 Exclusion Criteria

Any of the following would exclude the subject from participation in the study:

1. Concurrent enrollment in another clinical study, unless it is an observational (non-interventional) clinical study or the follow-up period of an interventional study.
2. Any concurrent chemotherapy, radiotherapy, immunotherapy, or biologic therapy for cancer treatment. Concurrent use of hormones for non-cancer-related conditions (e.g., insulin for diabetes and hormone replacement therapy) is acceptable. NOTE: Local treatment of isolated lesions for palliative intent is acceptable (e.g., by local surgery or radiotherapy).
3. Receipt of any investigational anticancer therapy within 4 weeks prior to the first dose of toripalimab.
4. Current or prior use of immunosuppressive medication within 2 weeks prior to the first dose of toripalimab, with the exception of intranasal and inhaled corticosteroids or systemic corticosteroids not to exceed 10 mg/day of prednisone or equivalent.
5. In Part A: Prior exposure to immunotherapy such as but not limited to other anti-CTLA-4, anti-PD-1, or anti-PD-L1 antibodies excluding vaccines. In Part B: Exclusion of prior immunotherapy exposure will be limited to anti-PD-1, anti-PD-L1, or anti-PD-L2.
6. Prior allogeneic bone marrow transplantation or prior solid organ transplantation.
7. Major surgery (as defined by the investigator) within 4 weeks prior to first dose of toripalimab or still recovering from prior surgery.
8. Unresolved toxicities from prior anticancer therapy, defined as having not resolved to baseline or to NCI-CTCAE v4.03 Grade 0 or 1, or to levels dictated in the inclusion / exclusion criteria with the exception of alopecia. Subjects with irreversible toxicity that is

not reasonably expected to be exacerbated by toripalimab may be included (e.g., hearing loss) after consultation with the medical monitor.

9. Active or prior documented autoimmune disease within the past 2 years. NOTE: Subjects with vitiligo, Grave's disease not requiring systemic treatment other than thyroid hormone replacement (within the past 2 years), or psoriasis not requiring systemic treatment are not excluded. Subjects with a history of autoimmune hypothyroidism requiring only thyroid hormone replacement therapy will not be excluded.
10. Known history of tuberculosis.
11. Subjects who are known to be human immunodeficiency virus (HIV) positive.
12. Subjects with evidence of hepatitis B or C virus infection, unless their hepatitis is considered to have been cured. (Note that subjects with prior hepatitis B virus (HBV) infection must have HBV viral load (VL) <100 IU/mL before study enrollment, and must be treated according to local standards; hepatitis C virus (HCV) infection must have, before study enrollment, no detectable viral load and must be treated according to local standards).
13. Active or prior documented inflammatory bowel disease (e.g., Crohn's disease, ulcerative colitis).
14. History of primary immunodeficiency.
15. Uncontrolled intercurrent illness including, but not limited to, ongoing or active infection, symptomatic congestive heart failure according to New York Heart Association (NYHA) Functional Classification≥3, uncontrolled hypertension, unstable angina pectoris, cardiac arrhythmia, active peptic ulcer disease or gastritis, or psychiatric illness/social situations that would limit compliance with study requirements, substantially increase risk of incurring AEs from toripalimab, or compromise the ability of the subject to give written informed consent.
16. Symptomatic or untreated central nervous system metastases requiring concurrent treatment, inclusive of but not limited to surgery, radiation, and/or corticosteroids. Subjects with previously treated brain metastases may participate provided they are clinically stable for at least 4 weeks prior to study entry, have no evidence of new or enlarging metastases, and are off steroids.
17. Receipt of live attenuated vaccination within 4 weeks prior to study entry or within 4 weeks of receiving toripalimab.
18. Any condition that, in the opinion of the investigator or sponsor, would interfere with evaluation of toripalimab or interpretation of subject safety or study results.
19. Pregnant or breastfeeding women.

4.1.4 Subject Enrollment

Study participation begins (i.e., a subject is "enrolled") once a subject receives the first dose of study drug. Once informed consent is obtained, a screening number will be assigned by the site and the screening evaluations may begin to assess study eligibility (inclusion / exclusion) criteria. Once a subject is enrolled, a subject identification number (SID) will be assigned by [redacted].

A master log of all consented subjects will be maintained at the site and will document all screen failures (i.e., subjects who are consented but do not meet study eligibility criteria), including the reason(s) for screen failure.

Once subjects are screened and determined by the PI to be eligible, the investigational site will complete an enrollment form and forward the completed document to [redacted] to request enrollment into the study. [redacted] will designate the part of the study the subject will enroll into (Part A [dose-escalation] or Part B [expansion]) and the cohort number. The medical monitor may request to review the subject's medical chart to ensure they meet the inclusion/exclusion criteria.

Subjects who fail to meet the inclusion/exclusion criteria (i.e., screen failures) may be rescreened and will maintain their same screening number. Subjects can be rescreened 3 times.

TAB001-01 is a competitive enrollment study. Up to 30 sites will be participating in TAB001-01 in the United States and up to 15 sites will be participating in TAB001-01 in Europe. The anticipated accrual per site is approximately 6 subjects; however, given the tumor types of interest, the actual enrollment rate per site will vary.

4.1.5 Withdrawal Criteria

Permanent discontinuation of toripalimab: In Part A and Part B, an individual subject will not receive any further toripalimab if any of the following occur in the subject in question:

- Withdrawal of consent from the study
- Withdrawal of consent from further treatment with toripalimab
- Lost to follow-up
- An AE that, in the opinion of the investigator or the sponsor, contraindicates further dosing
- Any AE that meets criteria for discontinuation as defined in Section 3.1.7
- Dose-limiting toxicity (see Section 3.1.6.2 for definition of a DLT)

- Subject is determined to have met one or more of the exclusion criteria for study participation at study entry and continuing toripalimab might constitute a safety risk
- Pregnancy or intent to become pregnant
- Subject noncompliance that, in the opinion of the investigator or sponsor, warrants withdrawal (e.g., refusal to adhere to scheduled visits)
- Initiation of alternative anticancer therapy including another investigational agent

Subjects who are permanently discontinued from further receipt of toripalimab, regardless of the reason (withdrawal of consent, due to an AE, other), will be identified as having permanently discontinued treatment. Subjects who permanently discontinue treatment may either be considered to have completed the study or not to have completed the study (see Section 6.3).

Subjects who are permanently discontinued from receiving toripalimab will continue on study to complete their End of Treatment and 90-day Post Treatment visits and will be followed for safety per Section 5.4.1 and Section 5.5, including the collection of any protocol-specified blood specimens, unless consent is withdrawn or the subject is lost to follow-up or enrolled in another clinical study. If feasible, all subjects will be followed for progression free survival.

A subject who receives another experimental or anticancer therapy will not continue on the study. All visits will cease. Only related AEs/SAEs will be collected through 90 days after the last dose of toripalimab, as noted in Section 5.4.1.

Withdrawal of consent: If consent is withdrawn, the subject will not receive any further toripalimab or further study observation. Note that the subject may be offered additional tests to withdraw safely.

Lost to follow-up: Subjects will be considered lost to follow-up only if no contact has been established by the time the study is completed (as defined in Section 6.3), such that there is insufficient information to determine the subject's status at that time.

Note: Subjects who refuse continuing participation in the study, including phone contact, should be documented as "withdrawal of consent" rather than "lost to follow-up." Subjects would be considered lost to follow-up after 3 documented unsuccessful attempts in 3 months. Investigators should document attempts to re-establish contact with missing subjects. If contact with a missing subject is re-established, the subject should not be considered lost to follow-up. If the interruption was < 4 weeks, the subject may resume therapy in the next cycle and any evaluations should resume according to the protocol. If the interruption is ≥ 4

weeks, the end of treatment visit should be conducted followed by the 90-day post treatment visit if applicable.

4.1.6 Replacement of Subjects

Subjects are considered evaluable if they complete the first imaging evaluation or they discontinue toripalimab due to a DLT. Nonevaluable subjects may be replaced in the same dose cohort.

4.1.7 Withdrawal of Informed Consent for Data and Biological Samples

4.1.7.1 Biological Samples Obtained for the Main Study

Study data are protected by the use of an SID number, which is a number specific to the subject. The investigator is in control of the information that is needed to connect a study sample to a subject. A subject's consent to the use of data does not have a specific expiration date, but the subject may withdraw consent at any time by notifying the investigator. If consent is withdrawn, any samples collected prior to that time may still be given to and used by the sponsor but no new data or samples will be collected unless specifically required to monitor the safety of the subject.

4.1.7.2 [redacted]

[redacted]

4.2 Schedule of Study Procedures

4.2.1 Enrollment/Screening Period

Table 4.2.1-1 shows all procedures to be conducted at the screening visit.

Table 4.2.1-1 PART A and Part B Schedule of Evaluations: Screening

Procedure/Study Day	Day -28 to Day -1
Physical / Clinical	
Written informed consent	X
Confirm inclusion / exclusion criteria	X
Demographics, medical history, cancer history, cancer diagnosis and classification[a]	X
Vital signs (T, BP, HR, RR)[b]	X
Physical examination, height, body weight	X
ECOG performance status	X
12-lead ECG[c]	X
Record concomitant medications[d]	X
Disease assessments[e]	X
Local Laboratory Assessments	
CBC/automated differential/platelets	X
Serum chemistry	X
Thyroid panel (TSH, free T4)	X
Coagulation panel (aPTT, PT, INR)	X
Viral testing (Hep B SA, Hep B cAb, Hep C Ab [reflex HepC RNA], HIV)	X
Viral load (VL)[f]	
Serum pregnancy test[g]	X
FSH[h]	X
Urinalysis	X
Central Laboratory Assessments	
Archival tumor tissue[i]	X
Tumor biopsy[j]	X

Footnotes for Table 4.2.1-1 can be found on the following page.

Footnotes for Table 4.2.1-1 Schedule of Evaluations: Screening	
[a]	Includes history of treatment for the primary diagnosis, including prior systemic, radiation treatment and surgical treatment. Date of last prior cancer treatment must be documented. Radiographic studies performed prior to study entry may be collected for review by the investigator.
[b]	Vital signs are to be obtained in the seated or supine position after the subject has been resting for at least 5 minutes.
[c]	All ECGs will be obtained in triplicate (all 3 within a 5-minute time period at least 1 minute apart) after 10 minutes of supine rest. Record HR, PR interval, QRS interval, QT interval, QTcF interval and results.
[d]	Document complete medication history taken within 30 days prior to the Screening Visit.
[e]	Disease assessments include: computerized tomography (CT) or magnetic resonance imaging (MRI) scan of the chest, abdomen, and pelvis. The preferred method of disease assessment is CT with contrast. If CT with contrast is contraindicated, CT without contrast is preferred over MRI. The same method is preferred for all subsequent tumor assessments.
[f]	Viral load to only be obtained from subjects with history of hepatitis B virus (HBV) or hepatitis C virus (HCV).
[g]	Serum pregnancy testing obtained from females of childbearing potential only.
[h]	FSH should be obtained from females who are postmenopausal for < 12 months to confirm postmenopausal status.
[i]	Collection of archival tumor tissue for purpose of biomarker analysis. In Part A, archival tumor tissue will be required from subjects in which a fresh pre-treatment biopsy is not safely accessible. In Part B, archival tumor tissue will be requested. See Laboratory Manual for tissue collection, processing, and shipment.
[j]	In Part A, fresh pre-treatment biopsies will be requested from subjects with safely accessible lesions. In Part B, fresh pre-treatment biopsies will be required from subjects with safely accessible lesions. See Laboratory Manual for tissue collection, processing, and shipment.

4.2.2 Treatment Period

In Part A, procedures to be conducted during Cycle 1 are presented in Table 4.2.2-1, for Cycles 2, 4, 5, 6 and 7 in Table 4.2.2-2. Procedures to be conducted in Cycle 3 are presented in Table 4.2.2-3, for Cycles 8 and beyond in Table 4.2.2-4.

In Part B, procedures to be conducted during Cycle 1 are presented in Table 4.2.2-5, for Cycles 2, 4, 5, 6 and 7 in Table 4.2.2-6. Procedures to be conducted in Cycle 3 are presented in Table 4.2.2-7, for Cycles 8 and beyond in Table 4.2.2-8.

In Part A and Part B, procedures to be conducted during an unscheduled Visit or during the Follow-up Visit are presented in Table 4.2.3-1.

Whenever vital signs, 12-lead ECGs (in triplicate), and blood draws are scheduled for the same nominal time, the assessments should occur in the following order: 12-lead ECG, vital signs, and then blood draws. The timing of the first two assessments should be such that it allows the blood draw (e.g., PK blood sample) to occur at the exact nominal time.

Refer to the Laboratory Manual for complete details on central laboratory collections.

If toripalimab is infused peripherally, PK blood draws must be taken from the contra-lateral arm or from a central line. If toripalimab is infused via a central line, PK blood draws must be obtained peripherally.

Table 4.2.2-1 Part A Schedule of Evaluations: Cycle 1

Study Period	**Treatment Period**														
Procedure / Study Day (A Cycle is 28 days [4 weeks])	Day 1 Pre	Day 1 EOI (±5min)	Day 1 0.5hr (±5min)	Day 1 2hr (±15min)	Day 1 4hr (±15min)	Day 1 6hr (±15min)	Day 2 24hr (±2hr)	Day 3 48hr (±2hr)	Day 4 72hr (±2hr)	Day 8 168hr (±2hr)	Day 15 Pre (±2d)	Day 15 EOI (±5min)	Day 15 0.5hr (±5min)	Day 15 4hr (±15min)	Day 22 (±1 day)
Physical / Clinical															
Vital signs (T, BP, HR, RR)[a]	X	X	X		X		X		X	X	X	X	X	X	X
Abbreviated symptom-driven physical exam[b]	X									X	X				X
Weight	X										X				
ECOG performance status	X														
12-lead ECG[c]	X	X								X	X	X			X
Record adverse events[d]		X	X	X	X	X	X	X	X	X	X	X	X	X	X
Record concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Investigational Product Dosing															
Infuse toripalimab	X										X				
Local Laboratory Assessments[h]															
CBC/automated differential/platelets[e]	X						X			X	X				X
Serum chemistry[e]	X						X			X	X				X
Thyroid panel (TSH, free T4)											X				X
Coagulation panel (aPTT, PT, INR)											X				X
Autoantibody sample (ANA)	X														
Urine or serum pregnancy test[f,h]	X										X				
Urinalysis	X														
Central Laboratory Assessments[h]															
Pharmacokinetic samples	X	X	X	X	X	X	X	X	X	X	X	X			
Immunogenicity samples	X														
Pharmacodynamic samples[g]	X						X			X	X				

Footnotes for Table 4.2.2-1 can be found on the following page.

Footnotes for Table 4.2.2-1 PART A Schedule of Evaluations: Cycle 1

[a] On dosing days, vital signs (temperature, blood pressure, heart rate, & respiratory rate) will be measured within 30 min (-30 min) prior to start of toripalimab infusion, every 15 min (±5 min) during infusion, at end of infusion (EOI) (±5 min), 30 minutes (±15 min) and 4 hours (±15 min) post EOI.

[b] Abbreviated symptom driven physical examination obtained at the investigator's discretion. Exam to be completed if subject is experiencing AEs. Exam to be directed to the symptoms causing the AE.

[c] All ECGs will be obtained in triplicate (all 3 within a 5-min time period at least 1 min apart) after 10 minutes of supine rest. Record HR, PR interval, QRS interval, QT interval, QTcF interval and results. Obtained on dosing days (Days 1 & 15), obtain ECGs within 60 minutes prior to start of infusion and within ±15 min post EOI.

[d] AE collection begins at the start of the first infusion of toripalimab. AEs will be graded per NCI-CTCAE version 4.03. If an AE does not have a CTCAE grade, refer to protocol Appendix 1 (Section 9.1) for grading criteria.

[e] Laboratory results must be reviewed prior to infusion. May be obtained 48 hrs prior to infusion.

[f] Urine or serum pregnancy testing obtained from females of childbearing potential only.

[g] Refer to the Laboratory Manual for more detail about collection and processing of pharmacodynamic samples to include PD-1 RO & T cell subsets.

[h] See section 4.3.3.1 for whole blood/serum samples to be obtained if a subject experiences symptoms associated with irAEs and at the onset of any SAE, irAEs, during any suspected infusion related reaction, and at time of progression when a subject is taken off study, so long as the investigator believes the readouts would be informative, and that the collection would not pose an undue risk to the subject. These samples may include chemistry, CBC, thyroid panel, PK, ADA, ANA, serum and blood collection for pharmacodynamic analysis.

Table 4.2.2-2: Part A Schedule of Evaluations: Cycles 2, 4, 5, 6 and 7 *(Cycle 3 is in Table 4.2.2-3)*

Study Period	**Cycles 2, 4, 5, and 6**				**Cycle 7**			
	Treatment Period				**Treatment Period**			
Procedure / Study Day (A Cycle is 28 days [4 weeks])	Day 1 Pre (±2 days)	Day 1 EOI (±5min)	Day 15 Pre (±2 days)	Day 15 EOI (±5min)	Day 1 Pre (±2 days)	Day 1 EOI (±5min)	Day 15 Pre (±2 days)	Day 15 EOI (±5min)
Physical / Clinical								
Vital signs (T, BP, HR, RR)[a]	X	X	X	X	X	X	X	X
Abbreviated symptom-driven physical exam[b]	X				X			
Weight	X		X		X		X	
ECOG performance status	X				X			
12-lead ECG[c]	X	X	X	X				
Record adverse events[d]	X	X	X	X	X	X	X	X
Record concomitant medications	X	X	X	X	X	X	X	X
Investigational Product Dosing								
Infuse toripalimab	X		X		X		X	
Disease Evaluation								
Disease Assessments[e]	Every 8 weeks (±10 days) post C1D1				Every 8 weeks (±10 days) post C1D1			
Local Laboratory Assessments[j]								
CBC/automated differential/platelets[f]	X		X		X		X	
Serum chemistry[f]	X		X		X		X	
Thyroid panel (TSH, free T4)	At time of disease assessment				At time of disease assessment			
Coagulation panel (aPTT, PT, INR)	Every even cycle (Cycles 2, 4, & 6)							
Autoantibody sample (ANA)								
Urine or serum pregnancy test[g]	X		X					
Urinalysis	X							
Central Laboratory Assessments[j]								
Pharmacokinetic samples	X	X	X	X				
Immunogenicity samples	Every even cycle (2, 4, 6)							
Pharmacodynamic samples[h]	X							
Tumor biopsy[i]	PI discretion at the occurrence of progressive disease, pseudoprogression or partial response							

*Footnotes for **Table 4.2.2-2** can be found on the following page.*

Footnotes for Table 4.2.2-2 PART A Schedule of Evaluations: Cycles 2, 4, 5, 6 and 7

[a] On dosing days in Cycles 2 & 4, vital signs (T, BP, HR, RR) will be measured within 30 min (-30 min) prior to start of toripalimab infusion, every 30 min (±5 min) during infusion, and at EOI (±5 min). On dosing days in Cycles 5, 6 & 7, vital signs will be measured within 30 min (-30 min) prior to start of toripalimab infusion, and at EOI (±5 min). Vital signs are to be obtained in the seated or supine position after the subject has been resting for at least 5 minutes.

[b] Abbreviated symptom driven physical examination obtained at the investigator's discretion. Exam to be completed if subjects is experiencing AEs. Exam to be directed to the symptoms causing the AE.

[e] All ECGs will be obtained in triplicate (all 3 within a 5-min time period at least 1 min apart after 10 minutes of supine rest. Record HR, PR interval, QRS interval, QT interval, QTcF interval and results. Obtained on dosing days (Days 1 & 15), obtain ECGs within 60 minutes prior to start of infusion and within ±15 min post EOI.

[d] AEs will be graded per NCI-CTCAE version 4.03. If an AE does not have a NCI-CTCAE grade, refer to protocol Appendix 1 (Section 9.1)for grading criteria.

[e] Disease assessments include: CT or MRI scan of the chest, abdomen, and pelvis. The preferred method of disease assessment is CT with contrast. If CT with contrast is contraindicated, CT without contrast is preferred over MRI. The same method is preferred for all subsequent tumor assessments.

[f] Laboratory results must be reviewed prior to infusion. Samples may be obtained 48 hrs prior to infusion.

[g] Urine or serum pregnancy testing obtained from females of childbearing potential only.

[h] Pharmacodynamic sample collected pre-dose on Day 1 of Cycles 2, 4, 5 and 6. Refer to the Laboratory Manual for more detail about collection, processing, and shipment of pharmacodynamic samples to include PD-1 RO & T cell subsets.

[i] Post-treatment tumor biopsy at the PIs discretion at the occurrence of progressive disease, pseudoprogression or partial response. Biopsy to be taken from same baseline lesion. See Laboratory Manual for tissue collection, processing, and shipment.

[j] See section 4.3.3.1 for whole blood/serum samples to be obtained if a subject experiences symptoms associated with irAEs and at the onset of any SAE, irAEs, during any suspected infusion related reaction, and at time of progression when a subject is taken off study, so long as the investigator believes the readouts would be informative, and that the collection would not pose an undue risk to the subject. These samples may include chemistry, CBC, thyroid panel, PK, ADA, ANA, serum and blood collection for pharmacodynamic analysis.

Table 4.2.2-3 PART A Schedule of Evaluations: Cycle 3

Study Period	Cycle 3											
	Treatment Period											
Procedure / Study Day (A Cycle is 28 days [4 weeks])	Day 1 Pre (±2 days)	Day 1 EOI (±5min)	Day 15 Pre (±2 days)	Day 15 EOI (±5min)	Day 15 0.5hr (±5min)	Day 15 2hr (±15min)	Day 15 4hr (±15min)	Day 15 6hr (±15min)	Day 16 24hr (±2hr)	Day 17 48hr (±2hr)	Day 18 72hr (±2hr)	Day 22 (±1 day)
Physical / Clinical												
Vital signs (T, BP, HR, RR)[a]	X	X	X	X								
Abbreviated symptom-driven physical exam[b]	X		X									
Weight	X		X									
ECOG performance status	X											
12-lead ECG[c]	X	X	X	X								
Record adverse events[d]	X	X	X	X	X	X	X	X	X	X	X	X
Record concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X
Investigational Product Dosing												
Infuse toripalimab	X		X									
Disease Evaluation												
Disease Assessments[e]	X (±10 days)											
Local Laboratory Assessments[j]												
CBC/automated differential/platelets[f]	X		X									
Serum chemistry[f]	X		X									
Thyroid panel (TSH, free T4)	At time of disease assessment											
Coagulation panel (aPTT, PT, INR)												
Autoantibody sample (ANA)												
Urine or serum pregnancy test[g]	X		X									
Urinalysis	X											
Central Laboratory Assessments[j]												
Pharmacokinetic samples	X	X	X	X	X	X	X	X	X	X	X	X
Immunogenicity samples	X											
Pharmacodynamic samples[h]	X											
Tumor biopsy[i]	PI discretion at the occurrence of progressive disease, pseudoprogression or partial response											

Footnotes for Table 4.2.2-3 can be found on the following page.

Footnotes for Table 4.2.2-3 PART A Schedule of Evaluations: Cycle 3

[a] On dosing days, vital signs (T, BP, HR, RR) will be measured within 30 min (-30 min) prior to start of toripalimab infusion, every 30 min (±5 min) during infusion, and at EOI (±5 min). Vital signs are to be obtained in the seated or supine position after the subject has been resting for at least 5 minutes.

[b] Abbreviated symptom driven physical examination obtained at the investigator's discretion. Exam to be completed if subjects is experiencing AEs. Exam to be directed to the symptoms causing the AE.

[c] All ECGs will be obtained in triplicate (all 3 within a 5-min time period at least 1 min apart after 10 minutes of supine rest. Record HR, PR interval, QRS interval, QT interval, QTcF interval and results. Obtained on dosing days (Days 1 & 15), obtain ECGs within 60 minutes prior to start of infusion and within ±15 min post EOI.

[d] AEs will be graded per NCI-CTCAE version 4.03. If an AE does not have a NCI-CTCAE grade, refer to protocol Appendix 1 (Section 9.1)for grading criteria.

[e] Disease assessments include: CT or MRI scan of the chest, abdomen, and pelvis. The preferred method of disease assessment is CT with contrast. If CT with contrast is contraindicated, CT without contrast is preferred over MRI. The same method is preferred for all subsequent tumor assessments.

[f] Laboratory results must be reviewed prior to infusion. May be obtained 48 hrs prior to infusion.

[g] Urine or serum pregnancy testing obtained from females of childbearing potential only.

[h] Pharmacodynamic sample collected pre-dose on Day 1 of Cycle 3, Refer to the Laboratory Manual for more detail about collection, processing, & shipment of pharmacodynamic samples to include PD-1 RO & T cell subsets.

[i] Post-treatment tumor biopsy at the PIs discretion at the occurrence of progressive disease, pseudoprogression or partial response. Biopsy to be taken from same baseline lesion. See Laboratory Manual for tissue collection, processing, and shipment.

[j] See section 4.3.3.1 for whole blood/serum samples to be obtained if a subject experiences symptoms associated with irAEs and at the onset of any SAE, irAEs, during any suspected infusion related reaction, and at time of progression when a subject is taken off study, so long as the investigator believes the readouts would be informative, and that the collection would not pose an undue risk to the subject. These samples may include chemistry, CBC, thyroid panel, PK, ADA, ANA, serum and blood collection for pharmacodynamic analysis.

Table 4.2.2-4 PART A Schedule of Evaluations: Cycle 8 and Beyond

Study Period	**Study Procedures**			
Procedure / Study Day (A Cycle is 28 days [4 weeks])	Day 1 Pre (±2 days)	Day 1 EOI (±5min)	Day 15 Pre (±2 days)	Day 15 EOI (±5min)
Physical / Clinical				
Vital signs (T, BP, HR, RR)[a]	X	X	X	X
Abbreviated symptom-driven physical exam[b]	X			
Weight	X		X	
ECOG performance status	X			
12-lead ECG				
Record adverse events[c]	X	X	X	X
Record concomitant medications	X	X	X	X
Investigational Product Dosing				
Infuse toripalimab	X		X	
Disease Evaluation				
Disease Assessments[d]	Q8W (±10 days) post C1D1 through 12 months, then Q12W unless PI prefers the Q8W schedule			
Local Laboratory Assessments[h]				
CBC/automated differential/platelets[e]	X		X	
Serum chemistry[e]	X		X	
Thyroid panel (TSH, free T4)	At time of disease assessment			
Coagulation panel (aPTT, PT, INR)				
Autoantibody sample (ANA)				
Urine or serum pregnancy test				
Urinalysis				
Central Laboratory Assessments[h]				
Pharmacokinetic samples	Every 4 cycles (8, 12, 16, etc.)	Every 4 cycles (8, 12, 16, etc.)		
Immunogenicity samples	Every 4 cycles (8, 12, 16, etc.)			
Pharmacodynamic samples[f]				
Tumor biopsy[g]	PI discretion at the occurrence of progressive disease, pseudoprogression or partial response			

Footnotes for Table 4.2.2-4 can be found on the following page.

Footnotes for Table 4.2.2-4 PART A Schedule of Evaluations: Cycle 8 and Beyond

[a] Vital signs (temperature, blood pressure, heart rate, & respiratory rate) will be measured within 30 min (-30 min) prior to start of toripalimab infusion and at end of infusion (EOI) (±5 min). Vital signs are to be obtained in the seated or supine position after the subject has been resting for at least 5 minutes.

[b] Abbreviated symptom driven physical examination obtained at the investigator's discretion. Exam to be completed if subjects is experiencing AEs. Exam to be directed to the symptoms causing the AE.

[c] AE collection begins at the start of infusion of toripalimab. AEs will be graded per NCI-CTCAE version 4.03. If an AE does not have a NCI-CTCAE grade, refer to protocol Appendix 1 (Section 9.1) for grading criteria.

[d] Disease assessments include: CT or MRI scan of the chest, abdomen, and pelvis. The preferred method of disease assessment is CT with contrast. If CT with contrast is contraindicated, CT without contrast is preferred over MRI. The same method is preferred for all subsequent tumor assessments.

[e] Laboratory results must be reviewed prior to infusion. May be obtained 48 hrs prior to infusion.

[f] Refer to the Laboratory Manual for more detail about collection, processing, & shipment of pharmacodynamic samples to include PD-1 RO & T cell subsets.

[g] Post-treatment tumor biopsy at the PIs discretion at the occurrence of progressive disease, pseudoprogression or partial response. Biopsy to be taken from same baseline lesion. See Laboratory Manual for tissue collection, processing, and shipment.

[h] See section 4.3.3.1 for whole blood/serum samples to be obtained if a subject experiences symptoms associated with irAEs and at the onset of any SAE, irAEs, during any suspected infusion related reaction, and at time of progression when a subject is taken off study, so long as the investigator believes the readouts would be informative, and that the collection would not pose an undue risk to the subject. These samples may include chemistry, CBC, thyroid panel, PK, ADA, ANA, serum and blood collection for pharmacodynamic analysis.

Table 4.2.2-5 PART B Schedule of Evaluations Cycle 1

Study Period	**Treatment Period**												
Procedure / Study Day (A Cycle is 42 days [6 weeks])	Day 1 Pre	Day 1 EOI (±5min)	Day 1 0.5hr (±5min)	Day 1 2hr (±15min)	Day 1 4hr (±15min)	Day 1 6hr (±15min)	Day 2 24hr (±2hr)	Day 3[j] 48hr (±2hr)	Day 4[j] 72hr (±2hr)	Day 8 168hr (±2hr)	Day 15 (±2days)	Day 22 Pre (±2days)	Day 22 EOI (±5min)
Physical / Clinical													
Vital signs (T, BP, HR, RR)[a]	X	X	X		X		X		X	X		X	X
Abbreviated symptom-driven physical exam[b]	X									X	X	X	
Weight	X											X	
ECOG performance status	X												
12-lead ECG[c]	X	X								X	X	X	X
Record adverse events[d]		X	X	X	X	X	X	X	X	X	X	X	X
Record concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X
Investigational Product Dosing													
Infuse toripalimab	X											X	
Local Laboratory Assessments[k]													
CBC/automated differential/platelets[e]	X[l]						X			X	X	X	
Serum chemistry[e]	X[l]						X			X	X	X	
Thyroid panel (TSH, free T4)											X	X	
Coagulation panel (aPTT, PT, INR)											X	X	
Autoantibody sample (ANA)	X[l]												
Urine or serum pregnancy test[f]	X[l]											X	
Urinalysis	X[l]											X	
Central Laboratory Assessments[k]													
Pharmacokinetic samples – A[g]	X	X	X	X	X	X	X	X	X	X	X	X	X
Pharmacokinetic samples – B[h]	X	X											
Immunogenicity samples	X												
Pharmacodynamic samples[i]	X												

Footnotes for Table 4.2.2-5 can be found on the following page.

Footnotes for Table 4.2.2-5 PART B Schedule of Evaluations Cycle 1

[a] On dosing days (Days 1 & 22), vital signs (temperature, blood pressure, heart rate, & respiratory rate) will be measured within 30 min (-30 min) prior to start of toripalimab infusion, every 15 min (±5 min) during infusion, at end of infusion (EOI) (±5 min), 30 minutes (±15 min) and 4 hours (±15 min) post EOI. Vital signs are to be obtained in the seated or supine position after the subject has been resting for at least 5 minutes.

[b] Abbreviated symptom driven physical examination obtained at the investigator's discretion. Exam to be completed if subject is experiencing AEs. Exam to be directed to the symptoms causing the AE.

[c] All ECGs will be obtained in triplicate (all 3 within a 5-min time period at least 1 min apart) after 10 minutes of supine rest. Record HR, PR interval, QRS interval, QT interval, QTcF interval and results. On Days 1 & 22, obtain ECGs within 60 minutes prior to start of infusion and within ±15 min post EOI.

[d] AE collection begins at the start of the first infusion of toripalimab. AEs will be graded per NCI-CTCAE version 4.03. If an AE does not have a CTCAE grade, refer to protocol Appendix 1 (Section 9.1) for grading criteria.

[e] Laboratory results must be reviewed prior to infusion. May be obtained 48 hrs prior to infusion.

[f] Urine or serum pregnancy testing obtained from females of childbearing potential only.

[g] Full PK collection to be obtained on the first 20 subjects enrolled. Once the number of subjects for full PK collection is met, sites will be notified that the remaining subjects will only have trough and EOI PK as noted in the Schedule of Evaluations. Day 3 and 4 visits are only for the first 20 subjects enrolled in Part B.

[h] Following enrollment of the 20th subject in Part B, only trough and EOI PK samples are to be obtained as noted in the Schedule of Evaluations. Day 3 & 4 visit are not required for subjects beyond the first 20 enrolled.

[i] Refer to the Laboratory Manual for more detail about collection and processing of pharmacodynamic samples to include [redacted]

[j] Day 3 and 4 visits are only for the first 20 subjects enrolled in Part B.

[k] See section 4.3.3.1 for whole blood/serum samples to be obtained if a subject experiences symptoms associated with irAEs and at the onset of any SAE, irAEs, during any suspected infusion related reaction, and at time of progression when a subject is taken off study, so long as the investigator believes the readouts would be informative, and that the collection would not pose an undue risk to the subject. These samples may include chemistry, CBC, thyroid panel, PK, ADA, ANA, serum and blood collection for pharmacodynamic analysis.

[l] Screening labs obtained within 48 hours prior to Cycle 1 Day 1 will suffice as Cycle 1 Day 1 pre-dose labs.

Table 4.2.2-6 PART B Schedule of Evaluations: Cycles 2, 4, 5, 6 and 7 *(Cycle 3 is in Table 4.2.2-7)*

Study Period	**Cycles 2, 4, 5, and 6**				**Cycle 7**			
	Treatment Period				**Treatment Period**			
Procedure / Study Day (A Cycle is 42 days [6 weeks])	Day 1 Pre (±2 days)	Day 1 EOI (±5min)	Day 22 Pre (±2 days)	Day 22 EOI (±5min)	Day 1 Pre (±2 days)	Day 1 EOI (±5min)	Day 22 Pre (±2 days)	Day 22 EOI (±5min)
Physical / Clinical								
Vital signs (T, BP, HR, RR)[a]	X	X	X	X	X	X	X	X
Abbreviated symptom-driven physical exam[b]	X		X		X		X	
Weight	X		X		X		X	
ECOG performance status	X				X			
12-lead ECG[c]	X	X	X	X				
Record adverse events[d]	X	X	X	X	X	X	X	X
Record concomitant medications	X	X	X	X	X	X	X	X
Investigational Product Dosing								
Infuse toripalimab	X		X		X		X	
Disease Evaluation								
Disease Assessments[e]	Every 9 weeks (±10 days) post C1D1				Every 9 weeks (±10 days) post C1D1			
Local Laboratory Assessments[l]								
CBC/automated differential/platelets[f]	X		X		X		X	
Serum chemistry[f]	X		X		X		X	
Thyroid panel (TSH, free T4)	At time of disease assessment				At time of disease assessment			
Coagulation panel (aPTT, PT, INR)	Every even cycle (Cycles 2, 4, & 6)							
Urine or serum pregnancy test[g]	X		X		X		X	
Urinalysis	X		X		X		X	
Central Laboratory Assessments[l]								
Pharmacokinetic samples - A[h]	X	X	X	X				
Pharmacokinetic samples – B[i]	Every even cycle (2, 4, 6)	Every even cycle (2, 4, 6)						
Immunogenicity samples[j]	Every even cycle (2, 4, 6)							
Pharmacodynamic samples[j]	Every even cycle (2, 4, 6)							
Tumor biopsy[k]	PI discretion at the occurrence of progressive disease, pseudoprogression or partial response							

Footnotes for Table 4.2.2-6 can be found on the following page.

Footnotes for Table 4.2.2-6 PART B Schedule of Evaluations: Cycles 2, 4, 5, 6 and 7 (Cycle 3 is in Table 4.2.2-7)

[a] On dosing day in Cycles 2 & 4, vital signs (T, BP, HR, RR) will be measured within 30 min (-30 min) prior to start of toripalimab infusion, every 30 min (±5 min) during infusion, and at EOI (±5 min). On dosing days in Cycles 5, 6 & 7, vital signs will be measured within 30 min (-30 min) prior to start of toripalimab infusion, and at EOI (±5 min). Vital signs are to be obtained in the seated or supine position after the subject has been resting for at least 5 minutes.

[b] Abbreviated symptom driven physical examination obtained at the investigator's discretion. Exam to be completed if subjects is experiencing AEs. Exam to be directed to the symptoms causing the AE.

[c] All ECGs will be obtained in triplicate (all 3 within a 5-min time period at least 1 min apart after 10 minutes of supine rest. Record HR, PR interval, QRS interval, QT interval, QTcF interval and results. On Days 1 & 22 of Cycles 2, 4, 5 & 6, obtain ECGs within 60 minutes prior to start of infusion and within ±15 min post EOI.

[d] AEs will be graded per NCI-CTCAE version 4.03. If an AE does not have a NCI-CTCAE grade, refer to protocol Appendix 1 (Section 9.1) for grading criteria.

[e] Disease assessments include: CT or MRI scan of the chest, abdomen, and pelvis. The preferred method of disease assessment is CT with contrast. If CT with contrast is contraindicated, CT without contrast is preferred over MRI. The same method is preferred for all subsequent tumor assessments.

[f] Laboratory results must be reviewed prior to infusion. Samples may be obtained 48 hrs prior to infusion.

[g] Urine or serum pregnancy testing obtained from females of childbearing potential only.

[h] Peak and trough PK to be collected on Days 1 and 22 from the first 20 subjects enrolled in Part B as outlined in the Schedule of Evaluations.

[i] Peak and trough PK to be collected on Day 1 only for subjects enrolled beyond the first 20 in Part B.

[j] Immunogenicity and pharmacodynamic sample collected pre-dose on Day 1 of even Cycles (i.e.; Cycles 2, 4, 6, 8 and every 4 cycles thereafter: Cycles 12, 16, 20, etc.). Refer to the Laboratory Manual for more detail about collection, processing, and shipment of pharmacodynamic samples to include [redacted].

[k] Post-treatment tumor biopsy at the PIs discretion at the occurrence of progressive disease, pseudoprogression or partial response. Biopsy to be taken from same baseline lesion. See Laboratory Manual for tissue collection, processing, and shipment.

[l] See section 4.3.3.1 for whole blood/serum samples to be obtained if a subject experiences symptoms associated with irAEs and at the onset of any SAE, irAEs, during any suspected infusion related reaction, and at time of progression when a subject is taken off study, so long as the investigator believes the readouts would be informative, and that the collection would not pose an undue risk to the subject. These samples may include chemistry, CBC, thyroid panel, PK, ADA, ANA, serum and blood collection for pharmacodynamic analysis.

Table 4.2.2-7 PART B Schedule of Evaluations: Cycle 3

Study Period	**Treatment Period**												
Procedure / Study Day (A Cycle is 42 days [6 weeks])	Day 1 Pre (±2days)	Day 1 EOI (±5min)	Day 22 Pre (±2days)	Day 22 EOI (±5min)	Day 22 0.5hr (±5min)	Day 22 2hr (±15min)	Day 22 4hr (±15min)	Day 22 6hr (±15min)	Day 23[k] 24hr (±2hr)	Day 24[k] 48hr (±2hr)	Day 25[k] 72hr (±2hrs	Day 29[k] 168hr (±2hrs)	Day 36[k] 336hr (±2hr)
Physical / Clinical													
Vital signs (T, BP, HR, RR)[a]	X	X	X	X									
Abbreviated symptom-driven physical exam[b]	X		X										
Weight	X		X										
ECOG performance status	X												
12-lead ECG[c]	X	X	X	X									
Record adverse events[d]	X	X	X	X	X	X	X	X	X	X	X	X	X
Record concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X
Investigational Product Dosing													
Infuse toripalimab	X		X										
Disease Evaluations													
Disease Assessments[e]	Every 9 weeks (+/- 10 days) post C1D1												
Local Laboratory Assessments[l]													
CBC/automated differential/platelets[f]	X		X										
Serum chemistry[f]	X		X										
Thyroid panel (TSH, free T4)	At time of disease assessment												
Coagulation panel (aPTT, PT, INR)													
Urine or serum pregnancy test[g]	X		X										
Urinalysis	X		X										
Central Laboratory Assessments[l]													
Pharmacokinetic samples – A[h]	X	X	X	X	X	X	X	X	X	X	X	X	X
Pharmacokinetic samples – B[i]													
Immunogenicity samples			X										
Pharmacodynamic samples													
Tumor biopsy[j]	PI discretion at the occurrence of progressive disease, pseudoprogression or partial response.												

Footnotes for Table 4.2.2-7 can be found on the following page.

Footnotes for Table 4.2.2-7 PART B Schedule of Evaluations: Cycle 3

[a] On dosing days (Days 1 & 22), vital signs (T, BP, HR, RR) will be measured within 30 min (-30 min) prior to start of toripalimab infusion, every 30 min (±5 min) during infusion, and at EOI (±5 min). Vital signs are to be obtained in the seated or supine position after the subject has been resting for at least 5 minutes.

[b] Abbreviated symptom driven physical examination obtained at the investigator's discretion. Exam to be completed if subjects is experiencing AEs. Exam to be directed to the symptoms causing the AE.

[c] All ECGs will be obtained in triplicate (all 3 within a 5-min time period at least 1 min apart after 10 minutes of supine rest. Record HR, PR interval, QRS interval, QT interval, QTcF interval and results. Obtained on dosing days (Days 1 & 22), obtain ECGs within 60 minutes prior to start of infusion and within ±15 min post EOI.

[d] AEs will be graded per NCI-CTCAE version 4.03. If an AE does not have a NCI-CTCAE grade, refer to protocol Appendix 1 (Section 9.1) for grading criteria.

[e] Disease assessments include: CT or MRI scan of the chest, abdomen, and pelvis. The preferred method of disease assessment is CT with contrast. If CT with contrast is contraindicated, CT without contrast is preferred over MRI. The same method is preferred for all subsequent tumor assessments.

[f] Laboratory results must be reviewed prior to infusion. May be obtained 48 hrs prior to infusion.

[g] Urine or serum pregnancy testing obtained from females of childbearing potential only.

[h] Full PK collection to be obtained on the first 20 subjects enrolled.

[i] Once the first 20 subjects for full PK collection are enrolled, sites will be notified that the remaining subjects will only have trough and EOI PK as noted in the Schedule of Evaluations. Subsequently enrolled subjects (after the first 20) will not be required to attend Days 23, 24, 25, 29 and 36.

[j] Post-treatment tumor biopsy at the PIs discretion at the occurrence of progressive disease, pseudoprogression or partial response. Biopsy to be taken from same baseline lesion. See Laboratory Manual for tissue collection, processing, and shipment.

[k] Once the first 20 subjects are enrolled for full PK collection, the remaining subjects will not be required to attend Days 23, 24, 25, 29 and 36.

[l] See section 4.3.3.1 for whole blood/serum samples to be obtained if a subject experiences symptoms associated with irAEs and at the onset of any SAE, irAEs, during any suspected infusion related reaction, and at time of progression when a subject is taken off study, so long as the investigator believes the readouts would be informative, and that the collection would not pose an undue risk to the subject. These samples may include chemistry, CBC, thyroid panel, PK, ADA, ANA, serum and blood collection for pharmacodynamic analysis.

Table 4.2.2-8 PART B Schedule of Evaluations: Cycle 8 and Beyond

Study Period	**Study Procedures**			
Procedure / Study Day (A Cycle is 42 days [6 weeks])	Day 1 Pre (±2 days)	Day 1 EOI (±5min)	Day 22 Pre (±2 days)	Day 22 EOI (±5min)
Physical / Clinical				
Vital signs (T, BP, HR, RR)[a]	X	X	X	X
Abbreviated symptom-driven physical exam[b]	X		X	
Weight	X		X	
ECOG performance status	X			
12-lead ECG				
Record adverse events[c]	X	X	X	X
Record concomitant medications	X	X	X	X
Investigational Product Dosing				
Infuse toripalimab	X		X	
Disease Evaluation				
Disease Assessments[d]	Q9W (±10 days) post C1D1 through 12 months, then Q18W unless PI prefers the Q9W schedule			
Local Laboratory Assessments[h]				
CBC/automated differential/platelets[e]	X		X	
Serum chemistry[e]	X		X	
Thyroid panel (TSH, free T4)	At time of disease assessment			
Coagulation panel (aPTT, PT, INR)				
Urine or serum pregnancy test				
Urinalysis				
Central Laboratory Assessments[h]				
Pharmacokinetic samples	Every 4 cycles (8, 12, 16, etc.)	Every 4 cycles (8, 12, 16, etc.)		
Immunogenicity samples	Every 4 cycles (8, 12, 16, etc.)			
Pharmacodynamic samples[f]	Every 4 cycles (8, 12, 16, etc.)			
Tumor biopsy[g]	PI discretion at the occurrence of progressive disease, pseudoprogression or partial response			

Footnotes for Table 4.2.2-8 can be found on the following page.

Footnotes for Table 4.2.2-8 PART A Schedule of Evaluations: Cycle 8 and Beyond

[a] Vital signs (temperature, blood pressure, heart rate, & respiratory rate) will be measured within 30 min (-30 min) prior to start of toripalimab infusion and at end of infusion (EOI) (±5 min). Vital signs are to be obtained in the seated or supine position after the subject has been resting for at least 5 minutes.

[b] Abbreviated symptom driven physical examination obtained at the investigator's discretion. Exam to be completed if subjects is experiencing AEs. Exam to be directed to the symptoms causing the AE.

[c] AE collection begins at the start of infusion of toripalimab. AEs will be graded per NCI-CTCAE version 4.03. If an AE does not have a NCI-CTCAE grade, refer to protocol Appendix 1 (Section 9.1) for grading criteria.

[d] Disease assessments include: CT or MRI scan of the chest, abdomen, and pelvis. The preferred method of disease assessment is CT with contrast. If CT with contrast is contraindicated, CT without contrast is preferred over MRI. The same method is preferred for all subsequent tumor assessments.

[e] Laboratory results must be reviewed prior to infusion. May be obtained 48 hrs prior to infusion.

[f] Refer to the Laboratory Manual for more detail about collection, processing, & shipment of pharmacodynamic samples to include [redacted].

[g] Post-treatment tumor biopsy at the PIs discretion at the occurrence of progressive disease, pseudoprogression or partial response. Biopsy to be taken from same baseline lesion. See Laboratory Manual for tissue collection, processing, and shipment.

[h] See section 4.3.3.1 for whole blood/serum samples to be obtained if a subject experiences symptoms associated with irAEs and at the onset of any SAE, irAEs, during any suspected infusion related reaction, and at time of progression when a subject is taken off study, so long as the investigator believes the readouts would be informative, and that the collection would not pose an undue risk to the subject. These samples may include chemistry, CBC, thyroid panel, PK, ADA, ANA, serum and blood collection for pharmacodynamic analysis.

4.2.3 Part A and Part B Unscheduled and Follow-up Periods

Table 4.2.3-1 shows all procedures to be conducted during unscheduled delays and follow-up periods.

Whenever vital signs, 12-lead ECGs (in triplicate), and blood draws are scheduled for the same nominal time, the assessments should occur in the following order: 12-lead ECG, vital signs, and then blood draws. The timing of the first two assessments should be such that it allows the blood draw (e.g., PK blood sample) to occur at the exact nominal time.

Refer to the Laboratory Manual for complete details on central laboratory collections.

Table 4.2.3-1 Part A and PART B Schedule of Evaluations: Unscheduled and Follow-up Procedures

Study Period	**Unscheduled / Follow-up**		
Procedure / Study Day	**Unscheduled**	**End of Treatment**	**90 Days Post Treatment**
Timing	UNSCH	28 days (± 3 days) after last dose	90 days (± 7 days) after last dose
Subjects	Delay in dosing (e.g., following resolution of toxicity)	For all subjects	For all subjects
Physical / Clinical			
Vital signs (T, BP, HR, RR)[a]	X	X	X
Physical examination	X	X	
Abbreviated symptom driven physical exam[b]			X
ECOG performance status	X	X	X
12-lead ECG[c]	PI discretion		
Record adverse events[d]	X	X	X
Record concomitant medications	X	X	X
Disease Evaluation			
Disease Assessments[e]	PI discretion[f]	X	
Local Laboratory Assessments[i]			
CBC/automated differential/platelets	X		X
Serum chemistry	X	X	X
Thyroid panel (TSH, free T4)	PI discretion		
Autoantibody sample (ANA)	PI discretion		
Urine pregnancy test[g]			X
Urinalysis	PI discretion		
Central Laboratory Assessments[i]			
Tumor biopsy[h]		PI discretion at the occurrence of progressive disease, pseudoprogression or partial response	
Pharmacokinetic samples – Part A	PI discretion	X	X
Pharmacokinetic samples – Part B	X		X
Immunogenicity samples – Part A	PI discretion	X	X
Immunogenicity samples – Part B	X		X
Pharmacodynamic samples – Part B only	X		X

Footnotes for Table 4.2.3-1can be found on the following page.

Footnotes for Table 4.2.3-1 PART A and PART B Schedule of Evaluations: Unscheduled and Follow-up Procedures

[a] Vital signs are to be obtained in the seated or supine position after the subject has been resting for at least 5 minutes.
[b] Abbreviated symptom driven physical examination obtained at the investigator's discretion. Exam to be completed if subjects is experiencing AEs. Exam to be directed to the symptoms causing the AE.
[c] All ECGs will be obtained in triplicate (all 3 within a 5-minute time period at least 1 minute apart). Record HR, PR interval, QRS interval, QT interval, QTcF interval and results.
[d] AE collection begins at the start of infusion of toripalimab. AEs will be graded per NCI-CTCAE version 4.03. If an AE does not have a NCI-CTCAE grade, refer to protocol Appendix 1 (Section 9.4) for grading criteria.
[e] Disease assessments include: CT or MRI scan of the chest, abdomen, and pelvis. The preferred method of disease assessment is CT with contrast. If CT with contrast is contraindicated, CT without contrast is preferred over MRI. The same method is preferred for all subsequent tumor assessments. CT/MRI to be performed at PI discretion at the onset of dyspnea, cough, chest pain or discomfort, and other respiratory symptoms.
[g] Urine pregnancy testing obtained from females of childbearing potential only.
[h] End of treatment tumor biopsy at the PIs discretion at the occurrence of progressive disease, pseudoprogression or partial response. Biopsy to be taken from same baseline lesion if possible. See Laboratory Manual for tissue collection, processing, and shipment.
[i] See section 4.3.3.1 for whole blood/serum samples to be obtained if a subject experiences symptoms associated with irAEs and at the onset of any SAE, irAEs, during any suspected infusion related reaction, and at time of progression when a subject is taken off study, so long as the investigator believes the readouts would be informative, and that the collection would not pose an undue risk to the subject. These samples may include chemistry, CBC, thyroid panel, PK, ADA, ANA, serum and blood collection for pharmacodynamic analysis.

4.3 Description of Study Procedures

4.3.1 Efficacy

4.3.1.1 Disease Assessment

Tumor assessments will be based on RECIST v1.1 and irRECIST guidelines, and will be performed during screening and treatment according to the schedule presented in Section 4.2. As far as possible, for consistency, the same medically qualified staff person who has been trained in RECIST and irRECIST should evaluate and measure lesions at each disease assessment. For those subjects who discontinue toripalimab as a result of confirmed PD, disease evaluation will be performed at the end of treatment visit if clinically appropriate (i.e., in the absence of rapidly deteriorating clinical status). Additional disease assessments may be performed as clinically indicated. In addition, when available, scans performed after disease progression in subjects who permanently discontinue toripalimab will be obtained, when possible, to determine if there was any delayed activity, unless consent is withdrawn, or the subject is lost to follow-up or starts receiving another experimental or anticancer therapy.

Sites will be required to store electronic copies of all scans and the sponsor may arrange for possible centralized storage of all imaging data. The centralized storage of imaging data would allow for possible independent centralized review of disease assessments.

The initial post treatment tumor assessment performed approximately 8 weeks (± 10 days) (Part A) or approximately every 9 weeks (± 10 days) (Part B) after Cycle 1, Day 1 will not be used to make decisions regarding continued subject participation in the study unless observed disease progression is accompanied by rapidly deteriorating clinical status. Subjects may continue to receive toripalimab Q2W (± 2 days) (Part A) or Q3W (Part B) in the setting of progressive disease (PD) when all the following criteria described in Section 3.1.5 are met:

- Absence of clinical symptoms or signs indicating clinically significant disease progression
- No decline in Eastern Cooperative Oncology Group (ECOG) performance status from baseline
- Absence of rapid disease progression or threat to vital organs or critical anatomical sites (e.g., CNS metastasis, respiratory failure due to tumor compression, spinal cord compression) requiring urgent alternative medical intervention; no significant, unacceptable or irreversible toxicities related to study treatment.

[redacted]

CT Scan with Contrast of Chest, Abdomen, and Pelvis

CT scans should be performed with contiguous cuts in slice thickness of 5 mm or less. Spiral CT should be performed using a 5-mm contiguous reconstruction algorithm.

MRI Scans

MRI of the abdomen and pelvis is acceptable for measurement of lesions provided that the same anatomical plane is used for serial assessments. If possible, the same imaging device should be used for serial evaluations. In case of MRI, measurements will be preferably performed in the axial (transverse) plane on contrast-enhanced T1 and T2 -weighted imaging along with gadolinium enhanced imaging should be performed. The field of view matrix, number of excitations, phase encode steps, use of fat suppression and fast sequences should be optimized for the specific body part being imaged as well as the scanner utilized. However, there are no specific sequence recommendations.

All positive MRI scans at screening should be repeated during restaging.

Baseline: Measurable Lesion Definitions and Target Lesion Selection

At baseline, tumor lesions/lymph nodes will be categorized measurable or non-measurable as follows:

- **Measurable Lesions** - Must be accurately measured in at least one dimension (longest diameter in the plane of measurement is to be recorded) with a minimum size of:
  - 10 mm by CT or MRI scan (or no less than double the slice thickness) for non-nodal lesions and ≥15 mm in short axis for nodal lesions.
  - 10 mm caliper measurement by clinical exam (when superficial).

- 20 mm by chest X-ray.
- 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 in follow-up, only the short axis will be measured and followed.
- Lytic or mixed lytic-blastic lesions with a measurable soft tissue component ≥10 mm can be selected as target lesions.

- **Nonmeasurable Lesion Definitions – Non-target lesions will include:**
  - Measurable lesions not selected as target lesions.
  - All sites of non-measurable disease, such as neoplastic masses that are too small to measure because their longest uninterrupted diameter is <10 mm (or < two times the axial slice thickness). i.e., the longest perpendicular diameter is ≥10 and <15 mm.
  - Other types of lesions that are confidently felt to represent neoplastic tissue, but are difficult to measure in a reproducible manner. These include bone metastases, leptomeningeal metastases, malignant ascites, pleural or pericardial effusions, ascites, inflammatory breast disease, lymphangitis cutis/pulmonis, cystic lesions, ill-defined abdominal masses, skin lesions, etc.
  - Pathological nodes (those with a 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.

Special considerations regarding lesion measurability – Bone lesions, cystic lesions, and lesions previously treated with local therapy require particular comment:

Bone lesions:

- Bone scan, (positive emission tomography (PET) scan or plain films are not considered adequate imaging techniques to measure bone lesions. However, these techniques can be used to confirm the presence or disappearance of bone lesions.
- Lytic bone lesions or mixed lytic-blastic lesions, with *identifiable soft tissue components,* that can be evaluated by cross sectional imaging techniques such as CT or MRI can be considered as measurable lesions if the *soft tissue component* meets the definition of measurability described above.
- Regardless of the imaging modality, blastic bone lesions are non-measurable and therefore will not be selected as target lesions.

Cystic lesions:

- 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.

Lesions with prior local treatment:

- Tumor lesions situated in a previously irradiated area, or in an area subjected to other loco-regional therapy, are usually not considered measurable unless there has been demonstrated progression in the lesion.

Assessment of overall tumor burden and measurable disease per RECIST v1.1

- To assess objective response or future progression, it is necessary to estimate the overall tumor burden at baseline and use this as a comparator for subsequent measurement. Measurable disease is defined by the presence of at least one measurable lesion.

Baseline documentation of 'target' and 'non-target' lesions

- When more than one measurable lesion is present at baseline, all lesions up to a maximum of five lesions total (and a maximum of two lesions per organ) representative of all involved organs should be identified as target lesions and will be recorded and measured at baseline (this means in instances where patients have only one or two organ sites involved, a maximum of two and four lesions respectively will be recorded).

- Target lesions should be selected on the basis of 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.

- A sum of 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.

- All other lesions (or sites of disease) including pathological lymph nodes should be identified as non-target lesions and should also be recorded at baseline. Measurements are not required and these lesions should be followed as 'present', 'absent', or in rare

cases 'unequivocal progression'. It is possible to record multiple non-target lesions involving the same organ as a single item on the case record form (e.g. 'multiple enlarged pelvic lymph nodes' or 'multiple liver metastases').

- **Assessment of overall tumor burden and measurable disease per irRECIST Target Lesions -** 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. Occasionally, the largest lesion may not lend itself to reproducible measurement in which case the next largest lesion which can be measured reproducibly should be selected.
- **Non-target Lesions -** All lesions or sites of disease not recorded as target lesions should be recorded as non-target lesions at baseline. There is no limit to the number of non-target lesions that can be recorded at baseline.

Follow-up: Recording of Target and New Measurable Lesion Measurements

- The longest diameters of non-nodal target and new non-nodal measurable lesions, and short axis of nodal target and new nodal measurable lesions will be recorded. Together they determine the TMTB at follow-up.

Follow-up: Definition of Measurable New Lesions

- In order to be selected as new measurable lesions (≤2 lesions per organ, ≤5 lesions total, per timepoint), new lesions must meet criteria as defined for baseline target lesion selection and meet the same minimum size requirements of 10 mm in the long diameter and minimum 15 mm in the short axis for new measurable lymph nodes. New measurable lesions shall be prioritized according to size, and the largest lesions shall be selected as new measured lesions.

Follow-up: Non-Target Lesion Assessment

The RECIST 1.1 definitions for the assessment of non-target lesions apply.

The response of non-target lesions primarily contributes to the overall response assessments of irCR and irNon-CR/Non-PD (irNon). Non-target lesions do not affect irPR and irSD assessments. Only a massive and unequivocal worsening of non-target lesions alone, even without progression in the TMTB is indicative of irPD.

Response Criteria

Evaluation of tumors based upon RECIST v1.1 (Eisenhauer et al, 2009)

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 diameters of target lesion, taking as reference the baseline sum diameters.
Progressive Disease (PD):	At least a 20% increase in the sum of 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 progression).
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.

Special notes on the assessment of target lesions

Lymph nodes: Lymph nodes identified as target lesions should always have the actual short axis measurement recorded (measured in the same anatomical plane as the baseline examination), even if the nodes regress to below 10 mm on study. This means that when lymph nodes are included as target lesions, the 'sum' of lesions may not be zero even if complete response criteria are met, since a normal lymph node is defined as having a short axis of <10 mm.

Target lesions that become '*too small to measure*': While on study, all lesions (nodal and non-nodal) recorded at baseline should have their actual measurements recorded at each subsequent evaluation, even when very small (e.g. 2 mm). However, sometimes lesions or lymph nodes which are recorded as target lesions at baseline become so faint on CT scan that the radiologist may not feel comfortable assigning an exact measure and may report them as being 'too small to measure'. When this occurs, it is important that a value be recorded on the CRF. If it is the opinion of the radiologist that the lesion has likely disappeared, the measurement should be recorded at 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. This default value is derived from the 5 mm CT slice thickness. The measurement of these lesions is potentially non-reproducible, therefore providing this default value will prevent false responses or progressions based upon

measurement error. However, if the radiologist is able to provide an actual measure, that should be recorded, even if it is below 5 mm.

Lesions that split or coalesce on treatment: When non-nodal lesions 'fragment', the longest diameters of the fragmented portions should be added together to calculate the target lesion sum. Similarly, as lesions coalesce, a plane between them may be maintained that would aid in obtaining maximal diameter measurements of each individual lesion. If the lesions have truly coalesced such that they are no longer separable, the vector of the longest diameter in this instance should be the maximal longest diameter for the 'coalesced lesion'.

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).
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):	*Unequivocal* progression of existing non-target lesions. (*Note:* the appearance of one or more new lesions is also considered progression).

Special notes on the assessment of target lesions

When the patient also has measurable disease: In this setting, to achieve 'unequivocal progression' on the basis of the non-target disease, there must be an overall level of substantial worsening in non-target disease such that, even in presence of SD or PR in target disease, the overall tumor burden has increased sufficiently to merit discontinuation of therapy. A modest 'increase' in size of one or more non-target lesions is usually not sufficient to qualify for unequivocal progression status. The designation of overall progression *solely* on the basis of change in non-target disease in the face of SD or PR of target disease will therefore be extremely rare.

New lesions

The appearance of new malignant lesions denotes disease progression. The finding of a new lesion should be unequivocal: i.e. not attributable to differences in scanning technique, change in imaging modality or findings thought to represent something other than tumor.

A lesion identified on a follow-up study in an anatomical location that was not scanned at baseline is considered a new lesion and will indicate disease progression.

Evaluation of Best Overall Response

The best overall response is the best response recorded from the start of the study treatment until the end of treatment taking into account any requirement for confirmation.

At each time point of tumor evaluation, an overall response will depend on the findings of both target and non-target disease and will also take into consideration the appearance of new lesions (Table 4.3.1-1). The overall response will be assessed by the investigator based on target lesions, non-target lesions and new lesions assessed. The confirmation of CR and PR is required; and a response of CR or PR at one time point must be confirmed by subsequent tumor assessment no less than 4 weeks after first response criteria are met.

Table 4.3.1-1 Time point overall response: patients with target (+/- non-target) lesions

Target lesions	Non-Target lesions	New lesions	Overall response
CR	CR	No	CR
CR	Non-CR/non-PD	No	PR
CR	Not evaluated	No	PR
PR	Non-PD or not all evaluated	No	PR
SD	Non-PD or not all evaluated	No	SD
Not all evaluated	Non-PD	No	Inevaluable (NE)
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

The best overall response (BOR) will be derived from overall responses at different time points, and defined as Table 4.3.1-2 (RECIST 1.1, Eisenhauer EA, et al, 2009).

Table 4.3.1-2 Best Overall Response when CR and PR confirmation is required per RECIST v 1.1

Overall Response First Time Point	Overall response Subsequent Time Point	Best Overall response
CR	CR	CR
CR	PR	PR
CR	SD	SD provided minimum criteria for SD duration met, otherwise, PD
CR	PD	SD provided minimum criteria for SD duration met, otherwise, PD
CR	NE	SD provided minimum criteria for SD duration met, otherwise NE
PR	CR	PR
PR	PR	PR
PR	SD	SD
PR	PD	SD provided minimum criteria for SD duration met, otherwise, PD
PR	NE	SD provided minimum criteria for SD duration met, otherwise NE
SD	SD	SD provided minimum criteria for SD duration met, otherwise NE
SD	PD	SD provided minimum criteria for SD duration met, otherwise PD
SD	NE/Not done	SD provided minimum criteria for SD duration met, otherwise NE
PD	Not Applicable	PD
NE	NE	NE

CR = complete response, PR = partial response, SD = stable disease, PD = progressive disease, and NE = not evaluable.
Note: For this study, minimum criteria for SD duration is 4 weeks.

- 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 objective progression even after discontinuation of treatment. Symptomatic deterioration is not a descriptor of an objective response: it is a reason for stopping study therapy.
- In some circumstances, it may be difficult to distinguish residual disease from normal tissue. When the evaluation of complete response depends upon this determination, it is recommended that the residual lesion be investigated (fine needle aspirate/biopsy) to confirm the complete response status.

Confirmatory Measurement/Duration of Response per RECIST v1.1

Confirmation

- The main goal of confirmation of objective response (CR/PR) is to avoid overestimating the response rate observed. In cases where confirmation of response is not feasible, it should be made clear when reporting the outcome of such studies that the responses are not confirmed.
- To be assigned a status of PR or CR, changes in tumor measurements must be confirmed by repeat assessments that should be performed no less than 4 weeks after the criteria for response are first met. Longer intervals as determined by the study protocol may also be appropriate.
- In the case of SD, measurements must have met the SD criteria at least once after study entry at a minimum interval (in general not less than 6-8 weeks) that is defined in the study protocol.

Duration of overall response

- The duration of overall response is measured from the time measurement criteria are first met from CR/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 on study).
- The duration of overall complete response is measured from the time measurement criteria are first met for CR until the first date that recurrent 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 sum on study* (if the baseline sum is the smallest, this is the reference for calculation of PD).

Evaluation of tumors based upon the irRECIST (http://www.irrecist.com/**).**

Overall Tumor Assessments

- **Immune-related Complete Response** (irCR**) –** Complete disappearance of all measurable and non-measurable lesions. Lymph nodes must decrease to < 10 mm in short axis. Confirmation of response is not necessary.

  Immune-related Partial Response (irPR) **-** Decrease of ≥ 30% TMTB relative to baseline, non-target lesions are irNN, and no unequivocal progression of new non-measurable lesions.

- **Immune-related Stable Disease** (irSD) **-** Failure to meet criteria for irCR or irPR in the absence of irPD.
- **Immune**-related NN (irNN) – No target disease was identified at baseline and at follow-up the patient fails to meet criteria for irCR or irPD.
- **Immune-relate Progressive Disease (irPD) –** Minimum 20% increase and minimum 5 mm absolute increase in TMTB compared to nadir, or irPD for non-target or new non-measurable lesions. Confirmation of progression is recommended minimum 4 weeks after the first irPD assessment.
- **Immune-related NE (irNE) – used in exception cases where insufficient data exists.**

Additional Guidance per irRECIST:

Total Measured Tumor Burden (TMTB)

Baseline-selected target lesions and new measurable lesions should NOT be assessed separately. Measurements of those lesions should be combined into the TMTB to provide combined assessment.

New Measurable Lesions

Criteria for unidimensional lesion measurement apply to both target and new measurable lesions:

A minimum of 10 mm in the longest diameter for non-nodal lesions, and a minimum 15 mm in the short axis for lymph nodes. But smaller lesions of the non-target or new non-measurable tumor burden do not get measured.

irPR if not Target Lesions

If new measurable lesions appear in patients with no target lesions at baseline, irPD will be assessed. That irPD timepoint will be considered a new baseline, and all subsequent timepoints will be compared to it for response assessment. irPR is possible if the TMTB of new measurable lesions decreased by ≥30% compared to the first irPD documentation.

Non-Target Lesions

Baseline selected non-target lesions can never convert to measurable lesions, not even if they increase in size at subsequent timepoints and become measurable. Only true new lesions can be measured and contribute to the TMTB.

irPD Based on Non-Target Lesions

A substantial and unequivocal increase of non-target lesions is indicative of progression.

irPD Based on New Non-Measurable Lesions

The reviewer may assign irPD for the patient with multiple new lesions of 9 mm if they are considered to be a sign of unequivocal, massive worsening.

irPD Confirmation

Progression confirmation no less than 4 weeks after the initial irPD assessment is recommended especially in the case of marginal disease growth and if the first irPD assessment is within the compound-specific tumor flare window.

Best Overall Response (irBOR)

The immune-related overall responses at each time point of tumor assessment will be evaluated based on measurable and non-measurable lesions by investigator using criteria in Table 4.3.1-3 (Wolchock et al., 2009). The confirmation of irCR and irPR is not required. However, per irRECIST, the confirmation of irPD is recommended by using the subsequent tumor evaluation at least 4 weeks after the first irPD.

Table 4.3.1-3 Table Derivation of irRC Overall Responses

Measurable response	Nonmeasurable response		Overall response
Index and new, measurable lesions (tumor burden),* %	Non-index lesions	New, nonmeasurable lesions	Using irRC
↓100	Absent	Absent	irCR†
↓100	Stable	Any	irPR†
↓100	Unequivocal progression	Any	irPR†
↓≥50	Absent/Stable	Any	irPR†
↓≥50	Unequivocal progression	Any	irPR†
↓<50 to <25↑	Absent/Stable	Any	irSD
↓<50 to <25↑	Unequivocal progression	Any	irSD
≥25?	Any	Any	irPD†

*Decreases assessed relative to baseline, including measurable lesions only (>5 × 5 mm).
†Assuming response (irCR) and progression (irPD) are confirmed by a second, consecutive assessment at least 4 wk apart.

Best overall response (irBOR) will be derived from overall responses at different time points for a subject. The order of irBOR is irCR, irPR, irSD and irPD.

4.3.2 Medical History and Physical Examination, Electrocardiogram, and Vital Signs

A complete physical examination and an abbreviated symptom-driven physical examination will be conducted according to the schedule presented in Section 4.2. Note that “physical examination” implies that a licensed independent healthcare provider (i.e., physician, physician’s assistant, or licensed nurse practitioner) will perform the exam, and this is the requirement for this study; “physical assessment” or “health assessment” should not be used.

Vital signs (oral temperature, blood pressure, heart rate, and respiratory rate) will be assessed according to the schedule presented in Section 4.2. At any time, if an infusion reaction occurs, obtain vital signs every 15 minutes until symptoms resolve. Vital signs are to be obtained in the seated or supine position after the subject has been resting for at least 5 minutes.

Twelve (12)-lead ECGs will be obtained after 10 minutes of supine rest and recorded for all subjects according to the schedule presented in Section 4.2. All ECGs recorded during the study will be obtained in triplicate (all 3 within a 5-minute time period at least 1 minute apart). The same method of assessment should be used for each subject throughout the study. Date and time settings should be checked at the start of each study day and aligned with an official timekeeper for all machines used in the study. Skin preparation should be thorough and electrode positions should be according to standard 12-lead ECG placement. The following variables will be reported: heart rate, RR, PR, QRS, QT and QTcF intervals. Additional 12-lead ECGs may be added by the investigator if clinically indicated, e.g., in the event of a cardiac AE.

4.3.3 Clinical Laboratory Tests

A Laboratory Manual will be provided to the sites that specifies the procedures for collection, processing, storage, and shipment of samples, as well as laboratory contact information, specific to this clinical research study.

Clinical laboratory safety tests will be performed in a licensed clinical laboratory. Urine pregnancy tests may be performed at the site using a licensed test (dipstick). Clinically significant abnormal laboratory results should be repeated as soon as possible (preferably within 24 to 48 hours).

Where performing serum safety laboratory tests is not locally available or obtaining them would present a hardship for the subject, plasma tests may be used.

The following clinical laboratory tests will be performed (see Section 4.2 for the schedule of tests):

Serum Chemistry (Local Laboratory)

- Glucose
- Sodium
- Potassium
- Chloride
- Blood urea nitrogen (BUN)
- Creatinine
- Calcium
- Magnesium
- Lactate dehydrogenase (LDH)
- Total protein
- Albumin
- Alkaline phosphatase (ALP)
- Total bilirubin
- Direct bilirubin (obtain anytime total bilirubin is 2 × ULN)
- Alanine transaminase (ALT)
- Aspartate transaminase (AST)

- Phosphorous
- Amylase
- Lipase

Note for serum chemistries: Tests for AST, ALT, ALP, and total bilirubin must be conducted concurrently and assessed concurrently.

Where performing serum safety laboratory tests is not locally available or obtaining them would present a hardship for the subjects, plasma tests may be used.

Thyroid Panel (Local Laboratory)

- Thyroid-stimulating hormone (TSH)
- Free thyroxine (Free T4)

Coagulation Panel (Local Laboratory)

- Prothrombin time (PT)
- International normalized ratio (INR)
- Activated partial thromboplastin time (aPTT)

Virology (Local Laboratory)

- Hepatitis B surface antigen (HepB SA)
- Reflex Hepatitis C RNA (HepC RNA)
- Hepatitis B core antibody (HepB cAb)
- Human immunodeficiency virus (HIV)
- Hepatitis C antibody (HepC Ab)
- Viral Load (VL)

Hematology (Local Laboratory)

- Red blood cell (RBC) count
- White blood cell (WBC) count
- Hemoglobin (Hgb)
- Automated white blood cell differential
- Hematocrit (Hct)
- Neutrophils (absolute)
- MCV
- Lymphocytes (absolute)
- MCH
- Eosinophils (absolute)
- MCHC
- Monocytes (absolute)
- RDW
- Platelet count

Urinalysis (Local Laboratory)

- pH
- Ketone
- Specific gravity
- WBC
- Color
- Blood
- Clarity
- Protein
- Nitrate
- Glucose

Testing for pregnancy or ability to become pregnant (Local Laboratory)

- Urine human chorionic gonadotropin (hCG)
- Follicle Stimulating Hormone (FSH)
- Serum beta-hCG (at screening only)

Autoantibody Testing (Local Laboratory)

- Anti-nuclear antibody (ANA)

Complement Studies (Central Laboratory)[a]

- CH50
- C3
- C4

Immune Complex Assays (Central Laboratory)[a]

- C1q binding assay
- Raji cell assay

[a] **Refer to Section 4.3.3.1 for guidance on safety tests related to Serum Sickness**

4.3.3.1 Other Safety Tests

Safety will be determined by reporting of AEs; by findings on physical exams; and by vital signs, ECG, and laboratory tests to include CBC, chemistry, thyroid panel and urinalysis. The severity of AEs, laboratory abnormalities, or other abnormal clinical assessments will be graded based on the NCI-CTCAE v4.03.

Special attention will be given to monitor any instance of irAEs such as dermatitis, colitis, pneumonitis or pulmonary toxicities.

Whole blood and serum samples should be obtained in the event subjects experience symptoms associated with irAEs and at the onset of any SAE, irAEs, during any suspected infusion related reaction, and at time of progression when a subject is taken off study, so long as the investigator believes the readouts would be informative, and that the collection would not pose an undue risk to the subject. These samples may include chemistry, CBC, thyroid panel, PK, ADA, ANA, serum and blood collection for pharmacodynamic analysis.

In the event of a serum sickness like reaction (see NCI-CTCAE), with symptoms such as fever, rash, and arthritis, the following laboratory tests should be obtained at the time of evaluation: CBC with differential, serum chemistry including BUN, creatinine and liver function tests, complement studies including CH50, C3, C4, C1q binding assay, Raji cell assay (if the complement and C1q binding assays are not definitive but serum sickness is still suspected), and urinalysis to detect urine protein and blood and rule out possible infection.

4.3.4 Pharmacokinetic Evaluation and Methods

Measurement of toripalimab in serum will be performed using a validated capture ELISA method.

Blood samples for measurement of toripalimab concentrations in serum will be collected according to the schedule presented in Section 4.2.

Extensive time points will be collected during Cycles 1 (Part A and Part B [first 20 subjects]) and Cycle 3 (Part A and Part B [first 20 subjects]), after which peak (end of infusion [EOI]) and trough levels will be collected with each dose through Cycle 6 and every 4th cycle on Day 1 beginning in Cycle 8 (Part A and first 20 subjects in Part B). In Part B, after the first 20 subjects are enrolled, PK for the subsequently enrolled subjects will be obtained at peak (EOI) and trough on Day 1 of Cycles 1 and 2, on Day 1 of every even cycle through Cycle 6, and every 4th cycle on Day 1 beginning in Cycle 8. Additional PK samples may be collected at the discretion of the principal investigator and the onset of any SAE or irAE, and when the subject is taken off study. Details for collection, aliquoting, storage, and shipment of serum samples for PK evaluations are presented in a separate Laboratory Manual.

If toripalimab is infused peripherally, PK blood draws must be taken from the contralateral arm or from a central line. If toripalimab is infused via a central line, PK blood draws must be obtained peripherally. If the infusion was interrupted, the reason for interruption must be documented on the eCRF.

4.3.5 Immunogenicity Evaluation and Methods

Presence of ADA will be assessed in samples obtained according to the schedule presented in Section 4.2. Samples will be measured for the presence of ADA using a validated immunoassay.

4.4 Biomarker Evaluation and Methods

Blood and tumor samples for pharmacodynamic analyses will be obtained according to the schedule presented in Section 4.2. Details for collection, storage, and shipment of biologic samples are presented in a separate Laboratory Manual.

4.4.1 Pharmacodynamic Measurements

Pharmacodynamic measurements using [whole blood, serum and/or plasma] samples include PD-1 RO assays to measure target engagement and lymphocyte subset analysis. TopAlliance Biosciences will also conduct additional pharmacology studies, to further characterize the activity of toripalimab.

Pharmacokinetic results will be correlated with pharmacodynamic outcomes where possible.

Pharmacodynamic measurements using paired, pre and post treatment biopsies may also be performed. Samples will be processed to enable immunohistochemistry (IHC) and/or gene expression analysis to evaluate the immunologic status of the tumor microenvironment and assess the impact of toripalimab treatment within the tumor microenvironment.

4.4.2 Predictive Biomarkers

Candidate biomarkers for subject selection will be assessed to determine whether these biomarkers predict which subjects are most likely to respond to treatment with toripalimab.

Pembrolizumab is an approved agent for the treatment of unresectable or metastatic MSI-H or dMMR solid tumors that have progressed following prior treatment and who have no satisfactory alternative treatment options or colorectal cancer that has progressed following treatment with a fluoropyrimidine, oxaliplatin, and irinotecan. MSI and/or MMR status information of all patients enrolled will be collected when available.

[redacted]

4.5 Archival Tumor Samples and Tumor Biopsies

4.5.1 Archival Tumor Samples

Archival tumor samples are required for all subjects not providing fresh pre-treatment biopsies, and adequate tissue for biomarker analysis must be deemed available during the screening period. For subjects who have provided fresh pre-treatment biopsies, archival specimens will also be requested. Formalin fixed paraffin embedded (FFPE) tumor samples will be collected for IHC and additional correlative markers (e.g., tumor mutation analysis, RNA analysis, and immunodiversity). If a tumor block cannot be provided for this study, then only freshly prepared unstained sections should be provided as described in the Laboratory Manual.

4.5.2 Tumor Biopsies

Fresh pre-treatment tumor biopsies that are safely accessible will be requested from all subjects in Part A and required from all subjects in Part B. Image-guided core needle tumor biopsy will be performed according to institutional practice during screening.

Following initiation of toripalimab, post-treatment tumor biopsies will be at the PIs discretion at the occurrence of progressive disease, pseudoprogression or partial response. Tumor lesions used for biopsy should not be lesions used as RECIST/irRECIST target lesions, unless there are no other lesions suitable for biopsy. If a RECIST/irRECIST target lesion is used for biopsy the lesion must be ≥ 2 cm in longest diameter. Additional tumor biopsies are permitted as clinically indicated (e.g., for mixed responses or upon PD), and as long as the additional biopsy does not pose unacceptable medical risk to a subject as determined by the investigator.

For all fresh biopsies, if clinically practical, at each time point, subjects will provide 4 core biopsies, but a minimum of at least 3 core biopsies are required. The first and third core biopsies will be placed in formalin and processed for FFPE at the central laboratory, while the second and fourth core biopsies (fourth biopsy, if available) will be immediately stored in RNA Later.

Tumor biopsies will be stored at an appropriate vendor selected by TopAlliance Biosciences. Core and punch biopsies may be used for correlative studies such as IHC, tumor mutation analysis, RNA analysis, proteomic analysis, and immunodiversity. Additional details for sample collection, processing, storage, and shipment will be provided in the Laboratory Manual.

4.6 Estimate of Volume of Blood to Be Collected

Dose-escalation and Dose-Expansion Phases

Blood draw volumes at screening and during each cycle are provided in Table 4.5.2-1 (Part A) and Table 4.5.2-2 (Part B). The total volume to be collected will depend on the number of doses administered and the length of follow-up.

Table 4.5.2-1 Blood Draw Volumes – Part A

Timepoint	Blood Draw Volume	Volume Equivalent
Screening	27mL	Approximately 1 ounce
Cycle 1	132mL	Approximately 5 ounces
Cycles 2, 4, & 6	60mL	Approximately 2 ounces
Cycle 3	89mL	Approximately 3 ounces
Cycle 5	48mL	Approximately 1.5 ounces
Cycle 7 & 10	24mL	Approximately 1 ounce
Cycle 8	35mL	Approximately 1 ounce
Cycles 9, 11, 13, 14, 15, 17, 18, & 19	20mL	Approximately 4 teaspoons
Cycle 12, 16, & 20	31mL	Approximately 1 ounce
End of Treatment & 90 Days Post Treatment	16mL	Approximately 1 tablespoon
Unscheduled Visit	20mL	Approximately 4 teaspoons

Table 4.5.2-2 Blood Draw Volumes – Part B

Timepoint	Blood Draw Volume	Volume Equivalent
Screening	37mL	Approximately 7 teaspoons
Cycle 1	125mL	Approximately 4 ounces
Cycles 2, 4, & 6	53mL	Approximately 2 ounces
Cycle 3	65mL	Approximately 2 ounces
Cycle 5	36mL	Approximately 7 teaspoons
Cycle 7	24mL	Approximately 1 ounce
Cycles 8, 12, 16, & 20	41mL	Approximately 8 teaspoons
Cycles 9, 10, 11, 13, 14, 15, 17, 18, & 19	24mL	Approximately 4 teaspoons
End of Treatment & 90 Days Post Treatment	15mL	Approximately 1 tablespoon
Unscheduled Visit	19mL	Approximately 4 teaspoons

4.7 Study Suspension or Termination

The sponsor reserves the right to temporarily suspend or terminate this study at any time. The reasons for temporarily suspending or terminating the study may include but are not limited to the following:

- The incidence or severity of AEs in this or other studies indicates a potential health hazard to subjects
- Subject enrollment is unsatisfactory
- Non-compliance that might significantly jeopardize the validity or integrity of the study
- Sponsor decision to terminate development
- Sponsor decision to terminate the study based on a planned futility analysis

If TopAlliance Biosciences determines that temporary suspension or termination of the study is required, TopAlliance Biosciences will discuss the reasons for taking such action with all participating investigators (or head of the medical institution, where applicable). When feasible, TopAlliance Biosciences will provide advance notice to all participating investigators (or head of the medical institution, where applicable) of the impending action.

If the study is suspended or terminated for safety reasons, TopAlliance Biosciences will promptly inform all investigators, heads of the medical institutions (where applicable), and/or institutions conducting the study. TopAlliance Biosciences will also promptly inform the relevant regulatory authorities of the suspension/termination along with the reasons for such action. Where required by applicable regulations, the investigator or head of the medical institution must inform the IRB/IEC promptly and provide the reason(s) for the suspension/termination. If the study is suspended for safety reasons and it is deemed appropriate by the sponsor to resume the study, approval from the relevant regulatory authorities (and IRBs/IECs when applicable) will be obtained prior to resuming the study.

4.8 Investigational Products

4.8.1 Identity of Investigational Product(s)

TopAlliance Biosciences will provide the investigator(s) with investigational product, toripalimab (Table 4.8.1-1) using a designated distribution center.

Table 4.8.1-1 Identification of Investigational Products

Investigational Product	Manufacturer	Concentration and Formulation as Supplied
Toripalimab	TopAlliance Biosciences	Supplied as a sterile liquid containing 240 mg toripalimab. [redacted]

w/v = weight per volume.

Toripalimab will be supplied to sites in cartons each containing 1 single dose vial. White labels describing the contents will be applied to vials containing toripalimab. Label text describing the contents will be printed directly on the carton. No other coding will be included.

4.8.1.1 Investigational Product Dose Preparation

All dose preparations are to be prepared using proper aseptic technique. Each vial of toripalimab should be examined for signs of damage (e.g., defective crimp, cracks or other damage to the vial). If the vial is damaged, it MUST NOT be used and should be returned to TopAlliance Biosciences for investigation.

Toripalimab

Do not shake the vial. Do not foam the vial contents.

Once the container closure integrity of the vial has been breached, toripalimab must be fully infused within 4 hours.

Toripalimab Preparation

The toripalimab dose to be administered to the subject will be diluted in 0.9% NaCl. The toripalimab volume, 0.9% NaCl volume, and total deliverable volume for each dose level is captured in Table 4.8.1-2.

Table 4.8.1-2 Toripalimab, 0.9% NaCl and Total Deliverable Volume

Dose Level (mg)	Toripalimab Volume (mL)	0.9% NaCl Volume (mL)	Total Deliverable Volume (mL)
80	2	98	100
240	6	94	100
480	12	88	100

Note that empty IV bags should be used and filled with the appropriate volume of 0.9% NaCl and toripalimab (e.g.; for the 80mg dose level, add to the empty IV bag, 98mLs of 0.9% NaCl followed by 2mLs of toripalimab).

Dose Preparation Steps

No incompatibilities between toripalimab in diluent and plastics passing compatibility tests (i.e., polyolefin and polyvinylchloride IV bags; polycarbonate syringe) have been observed.

Toripalimab does not contain preservatives and any unused portion must be discarded. Preparation of toripalimab is to be performed aseptically. Total in-use storage time from removal of toripalimab from the refrigerator and diluent to completion of administration should not exceed 4 hours at room temperature. If storage time exceeds these limits, a new dose must be prepared from new vials.

Dose should be prepared in an IV bag for IV infusion. An empty IV bag must be used (i.e., empty bag provided from manufacturer). To prepare the IV bag, first determine the volume of toripalimab and 0.9% NaCl required based upon the assigned Dose Level (Table 4.8.1-2). Second, add the required volume of 0.9% NaCl to the IV bag as appropriate for the intended dose. Third, add the required dose volume of toripalimab to the IV bag. Gently mix the solution in the bag or syringe by inverting up and down. Avoid shaking the IV bag to prevent foaming.

Following preparation of the dose, the entire contents of the IV bag should be administered as an IV infusion at a constant rate. See Section 4.8.1.2 for treatment administration.

Investigational Product Inspection

Each vial selected for dose preparation should be carefully inspected. Toripalimab is supplied as a sterile liquid dosage form filled in a glass vial configuration. The products must be stored refrigerated at 2°C to 8°C until ready to use.

Toripalimab drug product container closure system is a particle-free, pyrogen-free, sterile 6 mL glass vial, with 20 mm stoppers (butyl rubber) and 20 mm aluminum crimp. The label is white.

If there are any defects noted with toripalimab, the Investigator and Site Monitor should be notified immediately. Refer to the Section 4.8.1.4 for further instructions.

4.8.1.2 Treatment Administration

The first day of dosing is considered Day 1. In Part A, toripalimab will be administered by IV infusion on Day 1 and Day 15 of a 28-day treatment cycle. In Part B, toripalimab will be administered by IV infusion on Day 1 and Day 22 of a 42-day treatment cycle. Cycles may be repeated every 28 days (± 2d) (Part A) or every 42 days (± 2d) (Part B) in the absence of confirmed PD, clinical deterioration, and if investigators consider that subjects continue to receive benefit from treatment.

The final solution containing toripalimab will be infused IV via a volumetric syringe pump or infusion pump at a constant rate. A 0.22 or 0.2-μm in-line filter should be used for IV infusion. toripalimab will be administered IV over a minimum of 60 minutes in Cycle 1. After Cycle 1, the infusion duration may be decreased to infuse over a minimum of 30 minutes depending upon subject tolerance and occurrence of AEs. Slowly infusing the study drug will allow sufficient time to interrupt the infusion in the case of infusion reactions. The infusion time may be extended at any time to reduce infusion reactions. Flush the IV line with a volume of normal saline equal to the priming volume of the infusion set used after the contents of the IV bag are fully administered.

4.8.1.3 Monitoring of Dose Administration

Vital signs to include temperature, blood pressure, heart rate, and respiratory rate will be monitored during and after infusions as follows:

Part A: Cycle 1, Days 1 & 15:

> Within 30 minutes (± 30 minutes) prior to start of toripalimab infusion, every 15 minutes (± 5 minutes) during infusion, at the end of infusion (± 5 minutes), and 30 minutes (± 5 minutes) and 4 hours (± 15 minutes) post end of infusion of toripalimab, followed by a 2-hour (± 15 minute) period of observation (Cycle 1 only).

All cycles beyond Cycle 1, Days 1 & 15:

Within 30 minutes (± 30 minutes) prior to start of toripalimab infusion, every 30 minutes (± 5 minutes) during infusion, and at the end of infusion (± 5 minutes) of toripalimab.

Part B: Cycle 1 Day 1:

Within 30 minutes (± 30 minutes) prior to start of toripalimab infusion, every 15 minutes (± 5 minutes) during infusion, at the end of infusion (± 5 minutes), and 30 minutes (± 5 minutes) and 4 hours (± 15 minutes) post end of infusion of toripalimab, followed by a 2-hour (± 15 minute) period of observation.

Cycles 2, 3 and 4:

Within 30 minutes (± 30 minutes) prior to start of toripalimab infusion, every 30 minutes (± 5 minutes) during infusion and at end of infusion (± 5 minutes).

Cycles 5 and beyond:

Within 30 minutes (± 30 minutes) prior to start of toripalimab infusion and at end of infusion (± 5 minutes).

Refer to Section 4.2 and Section 4.3.2 for more information regarding assessment of vital signs. Refer to Section 3.1.7.3 for information on the management of toripalimab related toxicities.

As with any antibody, allergic reactions to dose administration are possible. Appropriate drugs and medical equipment to treat acute anaphylactic reactions must be immediately available, and study personnel must be trained to recognize and treat anaphylaxis. The study site must have immediate access to emergency resuscitation teams and equipment in addition to the ability to admit subjects to an intensive care unit if necessary.

4.8.1.4 Reporting Product Complaints

Any defects with toripalimab must be reported *immediately* to TopAlliance Biosciences by the site with further notification to the site monitor. During the investigation of the product complaint, all toripalimab must be stored at labeled conditions unless otherwise instructed.

TopAlliance Biosciences contact information for reporting product complaints:

Email: productcomplaints@topalliancebiosciences.com

Email subject line should include: “Toripalimab Product Complaint”

4.8.2 Additional Study Medications

No other study medications are specified for use in this clinical protocol.

4.8.3 Labeling

Labels for toripalimab will be prepared in accordance with Good Manufacturing Practice (GMP) and local regulatory guidelines. The label will fulfill GMP Annex 13 requirements for labeling. If applicable, label text will be translated into local languages, as required.

4.8.4 Storage

Store toripalimab between 2°C to 8°C.

4.8.5 Treatment Compliance

Toripalimab is administered by study site personnel, who will monitor compliance. The study monitor will evaluate treatment compliance during monitoring visits.

4.8.6 Accountability

The investigator's or site's designated toripalimab manager is required to maintain accurate toripalimab accountability records. Upon completion of the study, copies of toripalimab accountability records will be returned to TopAlliance Biosciences or their designee. All unused toripalimab will be returned to an TopAlliance Biosciences-authorized depot or disposed of upon authorization by TopAlliance Biosciences.

4.9 Treatment Assignment and Blinding

4.9.1 Methods for Assigning Treatment Groups

A designated form will be used for enrollment to a cohort and assignment of unblinded toripalimab. A subject is considered enrolled into the study when the investigator notifies the Clinical Research Organization (CRO) of the subject's eligibility and the CRO assigns the part (A or B) of the study the subject will be enrolled into. The CRO will also assign the cohort into which the subject will be enrolled.

All subjects will receive toripalimab.

If there is a delay in the administration of toripalimab such that it will not be administered within the timeframe specified on the Enrollment Form, the study monitor must be notified *immediately*.

4.9.2 Methods for Ensuring Blinding

This study is not blinded.

4.10 Restrictions During the Study and Concomitant Treatment(s)

The Investigator must be informed as soon as possible about any medication taken from the time of screening through 90 days post last dose of toripalimab. Subjects may continue their baseline medication(s) as long as the medications are not prohibited as outlined in Section 4.10.2. The daily dose of each medication should be maintained throughout the study, if possible. Any concomitant medication(s), including herbal preparations, taken during the study will be recorded in the eCRF. The eCRFs will capture the medication(s), dosage, route of administration, start and stop dates, and the indication for which it was given.

4.10.1 Permitted Concomitant Medications

Investigators may prescribe concomitant medications or treatments deemed necessary to provide adequate supportive care except for those medications identified as "excluded" as listed in Section 4.10.2. Specifically, subjects should receive full supportive care during the study, including transfusions of blood and blood products, and treatment with antibiotics, anti-emetics, anti-diarrheals, and analgesics, and other care as deemed appropriate, and in accordance with their institutional guidelines.

4.10.1.1 Prophylactic Pre-Medications

Primary prophylaxis against infusion-related reactions is not permitted during this study in order to avoid obscuring potential safety signals and enable a future assessment regarding whether premedications should be required for all subjects in future studies. However, at the discretion of the investigator, secondary prophylaxis (i.e., prevention of infusion-related reaction following initial episode) is appropriate and will be permitted with the following recommended regimen: acetaminophen (e.g., 650 to 1000 mg) and diphenhydramine (e.g., 12.5 to 25 mg) may be administered approximately 30 minutes prior to the start of the toripalimab infusion. Consideration can be given to premedicating with non-sedating anti-histamines (e.g., cetrizine) instead of diphenhydramine for subjects with recurrent infusion related reactions.

At the discretion of the investigator, administer intravenous doses of meperidine (e.g., 10 to 25 mg) and promethazine (e.g., 12.5 to 25 mg) or their equivalents just prior to the start of the toripalimab infusion.

NOTE: Pre-treatment medications may need to be repeated during the course of the infusion; therefore, this should be taken into consideration when deciding on the dosage of the pre-treatment medications.

4.10.1.2 Corticosteroids

The following corticosteroids are permitted while on study:

- Intranasal or inhaled corticosteroids or systemic corticosteroids at physiologic doses not to exceed 10 mg/day of prednisone or equivalent.
- Systemic corticosteroids required for the control of infusion reactions or irAEs must be tapered and be at non-immunosuppressive doses (≤ 10 mg/day of prednisone or equivalent) for at least 2 weeks before the next study drug administration. For irAEs that are Grade 2 (moderate), prednisone 0.5 mg/kg/day or equivalent should be initiated if symptoms persist beyond a week. For Grade 3 (severe) or Grade 4 (life threatening) irAEs, prednisone 1-2 mg/kg/day or equivalent should be given until symptoms have improved to Grade 1 (mild) or less, then tapered slowly over a month or more. Note that approximate equivalent doses for prednisone 5 mg are: methylprednisolone 4 mg; dexamethasone 0.75 mg; and hydrocortisone 20 mg. Note that for the irAE of diarrhea, if corticosteroids are not effective after about 3 days, treatment with the TNF inhibitor infliximab in a dose of 5 mg/kg should be considered, but should be avoided in patients with immune-mediated hepatitis.
- Corticosteroids as prophylactic treatment for subjects with contrast allergies to diagnostic imaging contrast dyes will be permitted.

4.10.1.3 Vaccination

The use of live, attenuated vaccines within 4 weeks prior to receiving a toripalimab dose is prohibited. After treatment with toripalimab, it is best to wait until at least 4 weeks have transpired or until recovery of immune responses (e.g., B lymphocytes) before giving live, attenuated vaccines. However, the use of killed vaccines for the prevention of influenza is permitted at the discretion of the investigator. The use of killed vaccines for the prevention of any infectious disease may be permitted on a case-by-case basis and must be discussed with the medical monitor prior to its use. All vaccinations administered during the study must be recorded in the eCRF.

4.10.1.4 Prophylactic Therapies

Palliative/therapeutic therapies such as radiotherapy for pain, thoracentesis or paracentesis for comfort may be administered after consultation with the medical monitor.

4.10.1.5 Treatment of Isolated Lesions

Treatment of isolated/symptomatic lesions by local surgery or radiation therapy is permitted for palliative or potentially curative management at any time during the study, provided that

the isolated lesion is not the only target lesion being assessed. All interventions should be discussed in advance with the medical monitor. Radiation therapy should be scheduled to minimize treatment delays.

4.10.2 Prohibited Concomitant Medications

Subjects must be instructed not to take any medications, including over-the-counter products, without first consulting with the investigator.

The following medications are considered exclusionary during the study. The sponsor must be notified if a subject receives any of these during the study.

- Any investigational anticancer therapy.
- Any concurrent chemotherapy, immunotherapy, biologic, or hormonal therapy for cancer treatment. Concurrent use of hormones for noncancer-related conditions (e.g., insulin for diabetes and hormone replacement therapy) is acceptable.
- Live attenuated vaccines
- Immunosuppressive medications including, but not limited to systemic corticosteroids at doses beyond 10 mg/day of prednisone or equivalent, methotrexate, azathioprine, and tumor necrosis factor alpha (TNF-α) blockers. Use of immunosuppressive medications for the management of toripalimab related AEs in subjects with contrast allergies is acceptable. In addition, use of inhaled and intranasal corticosteroids or systemic corticosteroids are permitted at physiologic doses not to exceed 10 mg/day of prednisone or equivalent.

  NOTE: Local treatment of isolated lesions for palliative intent is acceptable (e.g., by local surgery or radiotherapy).

4.11 Statistical Evaluation

4.11.1 General Considerations

There will be no formal hypothesis testing. All statistical analyses will be performed using SAS Version 9.3 or higher, unless otherwise noted. In general, analysis of categorical variables will include counts and percentage of subjects in each category observed. For continuous variables, the sample size (n), mean, standard deviation (SD), mean, median, minimum, and maximum will be presented. Missing data will not be imputed unless otherwise stated. Subject demographics, baseline characteristics, and disposition will be characterized using descriptive statistics.

No formal interim analysis is planned for this study. However, a review of safety data and available PK data will be performed after completion of each dose escalation cohort. A statistical analysis plan (SAP) will fully describe the planned analyses for this study.

4.11.2 Sample Size

The sample size will include up to 18 subjects in escalation phase plus approximately 280 subjects in expansion phase for a total of up to approximately 298 subjects. Assuming a 10% drop out rate, a total of up to approximately 327 subjects are expected to be enrolled. Expansion cohorts may include 5 disease-specific cohorts, and at the discretion of the Sponsor, another tumor cohort, to a maximum of 80 subjects in a sarcoma cohort (minimum of 40 subjects with either angiosarcoma, undifferentiated pleomorphic sarcoma or alveolar soft part sarcoma) and 40 subjects for the other 5 cohorts. The indications initially pursued in the expansion phase will be decided based on responses in the escalation phase, and other considerations.

4.11.3 Safety Analysis

4.11.3.1 MTD Evaluation

Maximum tolerated dose evaluation will be based on the DLT evaluable subjects. DLT events will be summarized descriptively.

4.11.3.2 Analysis of Safety Endpoints

The results from AEs, CMs, vital signs, ECGs, safety lab results, and physical examinations will be provided in listings. AEs and medical history will be coded using the MedDRA version 19.1 or higher. CMs will be coded using WHODrug version September 2016 or higher. Safety summaries will include the Safety Population, i.e. subjects receiving any amount of toripalimab. Summaries of AEs and other parameters will be provided in summary tables to assess frequency of incidence. Shift tables for AEs, ECGs, and other Safety parameters will be generated to assess changes from baseline. A list of preferred terms designated as AESIs will be provided in the SAP.

4.11.4 Efficacy Analyses

Efficacy analyses will include all subjects who received study drug. ORR and DCR will be presented for each dose cohort in Part A and expansion cohort in Part B. For the expansion phase, PFS will be presented for each expansion cohort. For PFS and OS, subjects not achieving the endpoint will be censored at the time of last endpoint assessment. If a subject receives alternate therapy prior to PD (or irPD, respectively) or death without PD, this subject will be censored at the date of their last radiological assessment prior to start of

alternate therapy. Median response times and associated 95% confidence intervals will be presented for descriptive summaries.

4.11.5 Analysis of Immunogenicity

Analyses of immunogenicity will be performed for the Safety Population. The immunogenic potential of toripalimab will be assessed by summarizing the number and percentage of subjects who develop detectable ADA. The impact of ADA on PK, pharmacodynamics, safety, and efficacy may be assessed if data allow.

4.11.6 Analysis of Pharmacokinetics

The PK-Evaluable Population will include those patients who had sufficient PK data to be included in the PK analyses, as assessed by the Pharmacokineticist. Individual toripalimab concentrations will be tabulated by dose cohort in Part A and by each cohort in Part B along with descriptive statistics. Noncompartmental PK data analysis will be performed if data allow. Descriptive statistics of noncompartmental PK parameters for toripalimab will be provided and may include AUC, C_{max}, CL, V_d, and $t_{1/2z}$. Population PK analysis may also be performed. The relationship between PK, pharmacodynamics, safety and efficacy will be assessed if data allow.

4.11.7 Analysis of Pharmacodynamics

The PD-Evaluable Population will include those subjects who had sufficient PD data to be to be included in the PD analyses, as assessed by the Translational Scientist. Sufficiency will be determined based on the number and placement of time points with valid assay results, and the ability to fully characterize the PD profile. Within this population, inclusion of subjects in each summary will be reviewed separately for each biomarker of interest. [redacted] s. At a minimum, all relevant PD data of all data will be reported in data listings. PK results will be correlated with pharmacodynamic outcomes where possible.

4.11.8 [redacted]

[redacted]

4.11.9 Interim Analysis

No formal interim analysis will be performed.

5 ASSESSMENT OF SAFETY

5.1 Definition of Adverse Events

The International Conference on Harmonisation (ICH) Guideline for Good Clinical Practice (GCP) E6(R1) defines an AE as:

Any untoward medical occurrence in a patient or 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 a medicinal product, whether or not considered related to the medicinal product.

An AE includes but is not limited to any clinically significant worsening of a subject's pre-existing condition. An abnormal laboratory finding (including ECG finding) that requires an action or intervention by the investigator, or a finding judged by the investigator to represent a change beyond the range of normal physiologic fluctuation, should be reported as an AE.

Adverse events may be treatment emergent (i.e., occurring after initial receipt of toripalimab) or nontreatment emergent. A nontreatment-emergent AE is any new sign or symptom, disease, or other untoward medical event that begins after written informed consent has been obtained but before the subject has received toripalimab.

Elective treatment or surgery or preplanned treatment or surgery (that was scheduled prior to the subject being enrolled into the study) for a documented pre-existing condition that did not worsen from baseline is not considered an AE (serious or nonserious). An untoward medical event occurring during the prescheduled elective procedure or routinely scheduled treatment should be recorded as an AE or SAE unless the investigator deems the event to be related to the use of the study drug.

Progression of disease is considered an efficacy outcome parameter, and for AE/SAE reporting purposes, is excluded from the definition of an AE and SAE. Similarly, death from progressive disease will not be considered an AE or SAE.

5.2 Definition of Serious Adverse Events

An SAE is any AE that:

- Results in death

- Is immediately life-threatening
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect in offspring of the subject
- Is an important medical event that may jeopardize the subject or may require medical intervention to prevent one of the outcomes listed above
    - Medical or scientific judgment should be exercised in deciding whether expedited reporting is appropriate in this situation. Examples of medically important events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias, or convulsions that do not result in hospitalizations; or development of drug dependency or drug abuse.

5.3 Definition of Adverse Events of Special Interest

An adverse event of special interest (AESI) is one of scientific and medical interest specific to understanding of toripalimab and may require close monitoring and rapid communication by the investigator to the sponsor. An AESI may be serious or nonserious. The rapid reporting of AESIs allows ongoing surveillance of these events in order to characterize and understand them in association with the use of this toripalimab.

5.3.1 Adverse event(s) of special interest

Adverse events that are considered AESIs and require immediate reporting are listed below:

- Hepatic function abnormality meeting the definition of Hy's law. See Section 5.7.3 for the definition and reporting of AESIs of hepatic function abnormality.
- ≥ Grade 3 endocrinopathy (e.g., hypophysitis, thyroiditis, adrenal insufficiency)
- ≥ Grade 3 dermatologic AE
- ≥ Grade 3 pneumonitis
- ≥ Grade 3 enterocolitis
- ≥ Grade 3 serum sickness (see Section 4.3.3.1)

AESIs ≥ Grade 3 are required to be reported ***within 24 hours of knowledge of the event*** to TopAlliance Biosciences Patient Safety representative ([redacted]) using the SAE/AESI

Report Form, even if the event is considered to be nonserious (see Section 5.6 for contact information).

5.4 Recording of Adverse Events

Adverse events will be recorded on the eCRF using a recognized medical term or diagnosis that accurately reflects the event. Adverse events will be assessed by the investigator for severity, relationship to toripalimab, possible etiologies, and whether the event meets criteria of an SAE and therefore requires immediate notification to TopAlliance Biosciences Patient Safety representative ([redacted]). See Section 5.2 for the definition of SAEs and 9.1 for guidelines for assessment of severity and relationship. If an AE evolves into a condition that meets the regulatory definition of "serious," it will be reported on the SAE Report Form.

Infusion of biological products is commonly associated with infusion related reactions. Anaphylaxis and infusion related reactions have some common manifestations and may be difficult to distinguish from each other. Infusion related reactions are commonly observed during or shortly after the first time exposure to therapeutic monoclonal antibodies delivered through intravenous infusion. These reactions are less common following subsequent exposures. Unlike infusion related reactions, anaphylaxis is a rare event, usually occurring after subsequent exposure to an antigen, and it is most commonly accompanied by severe systemic skin and or mucosal reactions. The Investigator is advised to carefully examine symptoms of adverse reactions observed during or shortly after exposure to toripalimab, and consider the above mentioned facts prior to making a final diagnosis. Reactions occurring at the time of or shortly after subsequent infusions of toripalimab are to be judged by the investigator at his/her own discretion. For the Investigator's convenience and in order to facilitate consistency in judgments, a copy of the National Institute of Allergy and Infectious Diseases (NIAID) and Food Allergy and Anaphylaxis Network (FAAN) guidance for anaphylaxis diagnosis is provided in Section 9.2.

5.4.1 Time Period for Collection of Adverse Events

AEs and SAEs will be collected from the start of the first dose, throughout the treatment period, and through the 90 days post last dose of toripalimab.

All AEs or other clinically significant AEs occurring up to 90 days after administration of the last dose of study drug will be collected for subjects continuing in the study. For subjects who discontinue from the study within 90 days after the administration of the last dose of study drug:

- Study drug-related AE information will be collected and should be followed to resolution / stabilization.
- AEs that lead to the discontinuation should be followed to resolution / stabilization.
- A telephone contact for the safety update would be acceptable if the subject cannot manage an office visit.

Only study drug-related serious or other clinically significant (e.g., late emerging irAEs that are not serious) AEs will be collected for all subjects > 90 days after the administration of the last dose of study drug.

A nonserious AE is an AE that does not have a classification of serious. The collection of nonserious AE information should begin at initiation of study drug and should conclude 90 days after last dose of study drug. Nonserious AEs should be followed to resolution or stabilization, or reported as SAEs if they become serious (see Section 5.2). Follow-up is also required for nonserious AEs that cause interruption or discontinuation of study drug, or those that are present at the end of study treatment as appropriate. All identified nonserious AEs must be recorded and described on the nonserious AE page of the eCRF.

5.5 Follow-up of Unresolved Adverse Events

Any AEs that are unresolved by End of study visit are followed up by the investigator for as long as medically indicated, but without further recording in the eCRF. TopAlliance Biosciences retains the right to request additional information for any subject with ongoing AE(s)/SAE(s) at the end of the study, if judged necessary.

5.6 Reporting of Serious Adverse Events

Within 24 hours of identifying an SAE, regardless of the presumed relationship to toripalimab, the investigator or qualified designee must complete the SAE/AESI Report Form and fax or email it to TopAlliance Biosciences Patient Safety representative (PAREXEL International Medical Services).

Patient Safety representative contact information:

Name: [redacted]
Email: [redacted]
Fax: [redacted]

The sponsor is responsible for reporting certain SAEs as expedited safety reports to applicable regulatory authorities, ethics committees, and participating investigators, in accordance with ICH Guidelines and/or local regulatory requirements. The sponsor may be required to report certain SAEs to regulatory authorities within 7 calendar days of being notified about the event; therefore, it is important that investigators submit additional information requested by the sponsor as soon as it becomes available.

Investigators should provide all available information at the time of SAE/AESI Report Form completion. Investigators should not wait to collect additional information to fully document the event before notifying TopAlliance Biosciences Patient Safety representative of an SAE. When additional information becomes available, investigators should submit a follow-up SAE Report Form. Any follow-up information to an SAE also needs to be provided to TopAlliance Biosciences Patient Safety representative within 24 hours of learning of the new information.

5.7 Other Events Requiring Immediate Reporting

5.7.1 Dose-limiting Toxicity

Dose-limiting toxicities are defined in Section 3.1.6.2. Any subject who the principal investigator believes has experienced a toxicity that meets the DLT criteria should be reported within 24 hours of knowledge of the event to [redacted] Medical Monitor so that the sponsor can confirm the occurrence of a DLT and notify all of the other investigators.

5.7.2 Overdose

An overdose is defined as a subject receiving a dose of toripalimab in excess of that specified in the IB, unless otherwise specified in this protocol.

Any overdose of a study subject with the toripalimab, with or without associated AEs/SAEs, is required to be reported within 24 hours of knowledge of the event to [redacted] Medical Monitor. If the overdose results in an AE, the AE must also be recorded on the AE eCRF (see Section 5.4). Overdose does not automatically make an AE serious, but if the consequences of the overdose are serious, for example death or hospitalization, the event is serious and must be reported as an SAE (Section 5.6). TopAlliance Biosciences does not recommend specific treatment for an overdose. The investigator will use clinical judgment to treat any overdose.

5.7.3 Hepatic Function Abnormality

Adverse events of hepatic function abnormality of special interest to the sponsor are defined as any increase in ALT or AST to greater than 3 × ULN **and concurrent** increase in bilirubin to greater than 2 × ULN and no reason exists other than exposure to the study drug (i.e., Hy's law cases). Concurrent findings are those that derive from a single blood draw or from separate blood draws taken within 8 days of each other. In the event of hepatic function abnormality where the etiology is unknown, timely follow-up investigations and inquiries should be initiated by the investigational site, based on medical judgment, to make an informed decision regarding the etiology of the event.

If the underlying diagnosis for the hepatic function abnormality is known (including progression of pre-existing disease such as primary or metastatic malignancy), the diagnosis should be recorded as an AE/SAE.

If the underlying diagnosis for the hepatic function abnormality remains unknown, the term "hepatic function abnormal" should be used to report the AE/SAE.

Hepatic function abnormality of unknown etiology, or which is considered attributable to toripalimab, is required to be reported as "hepatic function abnormal" ***within 24 hours of knowledge of the event*** to TopAlliance Biosciences Patient Safety representative using the SAE/AESI Report Form, even if the event is considered to be non-serious (see Section 5.6 for contact information). The investigator will review the data with the medical monitor. The investigator should then use clinical judgment to establish the cause based on local standard of care and follow the subject by conducting testing as clinically indicated.

If, after appropriate workup, in the opinion of the investigator, the underlying diagnosis for the abnormality remains unexplained, or is considered attributable to toripalimab, permanent discontinuation of dosing for the study subject should be considered.

Each reported event of hepatic function abnormality will be followed by the investigator and evaluated by the sponsor.

5.7.4 Pregnancy

Pregnancy in a female subject who has received toripalimab is required to be reported ***within 24 hours of knowledge of the event*** to TopAlliance Biosciences Patient Safety representative using the Pregnancy Notification Form (see Section 5.6 for contact information).

Subjects who become pregnant during the treatment period and prior to their first follow up visit must not receive additional doses of toripalimab but will not be withdrawn from the study. The reporting period for the occurrence of a pregnancy is through 90 days after the last dose of toripalimab. The pregnancy will be followed for outcome of the mother and

child (including any premature terminations) and should be reported to TopAlliance Biosciences Patient Safety representative after outcome.

Pregnancy in a female clinical trial subject is not an SAE per se. Complications of such pregnancies, for example, spontaneous abortion, may qualify as an SAE and should be reported as an SAE even if they occur greater than 90 days past the last dose of toripalimab.

Should the investigator become aware of a pregnancy in the partner of a male study subject who has received toripalimab, this should be reported ***within 24 hours of knowledge of the event*** to TopAlliance Biosciences Patient Safety representative using the Pregnancy Notification Form (see Section 5.6 for contact information). The sponsor will endeavor to collect follow-up information on such pregnancies provided the partner of the study subject provides consent.

6 STUDY AND DATA MANAGEMENT

6.1 Training of Study Site Personnel

Before the first subject is entered into the study, a TopAlliance Biosciences representative will review and discuss the requirements of the Clinical Study Protocol and related documents with the investigational staff and also train them in any study-specific procedures and system(s) utilized.

The principal investigator will ensure that appropriate training relevant to the study is given to all of these staff, and that any new information relevant to the performance of this study is forwarded to the staff involved.

The principal investigator will maintain a record of all individuals involved in the study (medical, nursing and other staff).

6.2 Monitoring of the Study

During the study, a TopAlliance Biosciences representative will have regular contacts with the study site, including visits to:

- Provide information and support to the investigator(s).
- Confirm that facilities remain acceptable.
- Confirm that the investigational team are adhering to the protocol, that data are being accurately and timely recorded in the eCRFs, that biological samples are handled in accordance with the Laboratory Manual and that study drug accountability checks are being performed.

- Perform source data verification (a comparison of the data in the eCRFs with the subject's medical records at the hospital or practice, and other records relevant to the study) including verification of informed consent of participating subjects. This will require direct access to all original records for each subject (e.g., clinic charts).
- Ensure withdrawal of informed consent to the use of the subject's biological samples is reported and biological samples are identified and disposed of/destroyed accordingly, and the action is documented, and reported to the subject.

The TopAlliance Biosciences representative will be available between visits if the investigator(s) or other staff at the center needs information and advice about the study conduct.

6.2.1 Source Data

All source documents should be completed in a neat, legible manner to ensure accurate interpretation of data. Data reported in the eCRF derived from source documents should be consistent with the source documents.

The primary source document for this study will be the subject's medical record. If the investigator(s) maintain separate research records, both the medical record and the research records will be considered the source documents for the purposes of auditing the study.

The anonymity of subjects must be maintained. Subjects will be identified by their initials and an assigned subject number on eCRFs and other documents submitted to the sponsor. Documents that identify the subject beyond initials and subject number will not be submitted to the sponsor (e.g., the signed informed consent document) and must be maintained in strict confidence by the investigator, except to the extent necessary to allow auditing by the regulatory authorities, study monitor, or sponsor representatives.

Data recorded on source documents will be entered into eCRFs. The investigator must promptly review the completed eCRFs for each subject. A study monitor representing the sponsor will review the source documents against the eCRF on a regular basis through the study period.

The principal investigator at each/the center should comply with all the terms, conditions, and obligations of the Clinical Study Agreement, or equivalent, for this study. In the event of any inconsistency between this clinical study protocol and the Clinical Study Agreement, the terms of Clinical Study Protocol shall prevail with respect to the conduct of the study and the treatment of subjects and in all other respects, not relating to study conduct or treatment of subjects, the terms of the Clinical Study Agreement shall prevail.

Agreements between TopAlliance Biosciences and the principal investigator must be in place before any study-related procedures can take place, or subjects are enrolled.

6.2.2 Archiving of Study Documents

The investigator follows the principles outlined in the Clinical Study Agreement.

6.3 Study Timetable and End of Study

An individual subject will be considered to have completed the study if the subject was followed through the last protocol-specified visit/assessment (including telephone contact), regardless of the number of doses of toripalimab that was received.

Subjects will be considered not to have completed the study if consent was withdrawn or the subject was lost to follow-up (see Section 4.1.5).

The end of the study ("study completion") is defined as the date of the last protocol-specified visit/assessment (including telephone contact) for the last subject in the study.

6.4 Data Management

Data management will be performed by a CRO according to the study specific Data Management Plan.

A Web Based Data Capture (WBDC) system will be used for data collection and query handling. The investigator will ensure that data are recorded on the eCRFs as specified in the study protocol and in accordance with the instructions provided.

The investigator ensures the accuracy, completeness, and timeliness of the data recorded and of the provision of answers to data queries according to the Clinical Study Agreement. The investigator will sign the completed eCRFs. A copy of the completed eCRFs will be archived at the study site.

7 ETHICAL AND REGULATORY REQUIREMENTS

7.1 Ethical Conduct of the Study

The study will be performed in accordance with ethical principles that have their origin in the Declaration of Helsinki and are consistent with ICH/GCP, and applicable regulatory requirements.

7.2 Subject Data Protection

The informed consent form (ICF) will incorporate (or, in some cases, be accompanied by a separate document incorporating) wording that complies with relevant data protection and privacy legislation.

The anonymity of subjects must be maintained. Subjects will be identified by their initials and an assigned subject number on eCRFs and other documents submitted to the sponsor. Documents that identify the subject beyond initials and subject number will not be submitted to the sponsor (e.g., the signed ICF) and must be maintained in strict confidence by the investigator, except to the extent necessary to allow auditing by the regulatory authorities, study monitor, or sponsor representatives.

TopAlliance Biosciences will not provide individual genotype results to subjects, any insurance company, any employer, their family members, general physician or any other third party, unless required to do so by law**.**

Extra precautions are taken to preserve confidentiality and prevent genetic data being linked to the identity of the subject. In exceptional circumstances, however, certain individuals might see both the genetic data and the personal identifiers of a subject. For example, in the case of a medical emergency, a TopAlliance Biosciences medical monitor or an investigator might know a subject's identity and also have access to his or her genetic data. Also, Regulatory authorities may require access to the relevant files, though the subject's medical information and the genetic files would remain physically separate.

7.3 Ethics and Regulatory Review

An IRB/IEC should approve the final study protocol, including the final version of the ICF and any other written information and/or materials to be provided to the subjects. The investigator will ensure the distribution of these documents to the applicable IRB/IEC, and to the study site staff.

The opinion of the IRB/IEC should be given in writing. The investigator should submit the written approval to TopAlliance Biosciences or designee before enrollment of any subject into the study.

The IRB/IEC should approve all advertising used to recruit subjects for the study.

TopAlliance Biosciences or designee should approve any modifications to the ICF that are needed to meet local requirements.

If required by local regulations, the protocol should be re-approved by the IRB/IEC annually.

Before enrollment of any subject into the study, the final study protocol, including the final version of the ICF, is approved by the national regulatory authority or a notification to the national regulatory authority is done, according to local regulations.

TopAlliance Biosciences will handle the distribution of any of these documents to the national regulatory authorities.

TopAlliance Biosciences will provide Regulatory Authorities, IRB/IEC and principal investigators with safety updates/reports according to local requirements, including suspected unexpected serious adverse reactions (SUSARs), where relevant.

Each principal investigator must inform the IRB/IEC of:

- Changes in informed consent
- Revisions of other documents originally submitted for review
- Serious and/or unexpected adverse events occurring during the study
- New information that may adversely affect the safety of subjects or the conduct of the study
- Annual update and/or request for re-approval
- Study completion

7.4 Informed Consent

A copy of the proposed informed consent document must be submitted to the sponsor for review and comment prior to submission to the reviewing IRB/IEC. The consent form must be approved by the IRB/IEC and contain all elements required by national, state, local and institutional regulations or requirements.

The principal investigator(s) at each center will:

- Ensure each subject is given full and adequate oral and written information about the nature, purpose, possible risk and benefit of the study
- Ensure each subject is notified that they are free to discontinue from the study at any time
- Ensure that each subject is given the opportunity to ask questions and allowed time to consider the information provided
- Ensure each subject voluntarily provides signed and dated informed consent before conducting any procedure specifically for the study

- Ensure the original, signed ICF(s) is/are stored in the Investigator's Study File
- Ensure a copy of the signed ICF is given to the subject
- Ensure that any incentives for subjects who participate in the study as well as any provisions for subjects harmed as a consequence of study participation are described in the ICF that is approved by an IRB/IEC

7.5 Changes to the Protocol and Informed Consent Form

Protocol revisions will be prepared and approved by TopAlliance Biosciences and the medical monitor. Minor revisions will be submitted as administrative changes. If there are any substantial changes to the study protocol, then these changes will be documented in a study protocol amendment and where required in a new version of the study protocol.

All protocol amendments will be signed by the principal investigator and approved by the relevant IRB/IEC and if applicable, also the national regulatory authority approval, before implementation. Local requirements are to be followed for revised protocols. Documentation of IRB/IEC approval must be forwarded to the sponsor

TopAlliance Biosciences or their designee will distribute any subsequent amendments and new versions of the protocol to each principal investigator(s). For distribution to IRB/IEC see Section 7.3.

If a protocol amendment alters the study design, increases potential risk to the subject or otherwise affects statements in the ICF, the ICF must be revised accordingly and submitted to TopAlliance Biosciences and the IRB/IEC for review and approval before the revised ICF is used. The approved consent form must be used to obtain informed consent from new subjects prior to enrollment and must be used to obtain ICF subjects already enrolled if they are affected by the amendment.

If local regulations require, any administrative change will be communicated to or approved by each IRB/IEC.

7.6 Audits and Inspections

Authorized representatives of TopAlliance Biosciences, a regulatory authority, or an IRB/IEC may perform audits or inspections at the clinical sites, including source data verification. The purpose of an audit or inspection is to systematically and independently examine all study-related activities and documents, to determine whether these activities

were conducted, and data were recorded, analyzed, and accurately reported according to the protocol, GCP, guidelines of the ICH, and any applicable regulatory requirements. The investigator will contact TopAlliance Biosciences immediately if contacted by a regulatory agency about an inspection at the site.

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9 APPENDIX

9.1 Appendix 1: Additional Safety Guidance

Assessment of Severity

Assessment of severity is one of the responsibilities of the investigator in the evaluation of AEs and SAEs. Severity will be graded according to the NCI-CTCAE v4.03 as provided below. The determination of severity for all other events not listed in the NCI-CTCAE should be made by the investigator based upon medical judgment and the severity categories of Grade 1 to 5 as defined below.

- Grade 1 (mild): An event that is usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living.
- Grade 2 (moderate): An event that is usually alleviated with additional specific therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the subject.
- Grade 3 (severe): An event that requires intensive therapeutic intervention. The event interrupts usual activities of daily living, or significantly affects the clinical status of the subject.
- Grade 4 (life threatening): An event, and/or its immediate sequelae, that is associated with an imminent risk of death or with physical or mental disabilities that affect or limit the ability of the subject to perform activities of daily living (eating, ambulation, toileting, etc.).
- Grade 5 (fatal): Death (loss of life) as a result of an event.

It is important to distinguish between serious criteria and severity of an AE. Severity is a measure of intensity whereas seriousness is defined by the criteria in Section 5.2. A Grade 3 AE need not necessarily be considered an SAE. For example, a Grade 3 headache that persists for several hours may not meet the regulatory definition of an SAE and would be considered a nonserious event, whereas a Grade 2 seizure resulting in a hospital admission would be considered an SAE.

The NCI-CTCAE v4.03 will be provided in the Study Procedure Manual, and can be downloaded from the Cancer Treatment Evaluation Program (CTEP; http://www.eortc.be/services/doc/ctc/CTCAE_4.03_2010-06-14_QuickReference_5x7.pdf).

Assessment of Relationship

Relationship to toripalimab

The investigator is required to provide an assessment of relationship of AEs and SAEs to the toripalimab.

An event will be considered "not related" to use of the toripalimab if any of the following are met:

- An unreasonable temporal relationship between administration of the toripalimab and the onset of the event (e.g., the event occurred either before, or too long after, administration of toripalimab for it to be considered product-related).
- A causal relationship between the toripalimab and the event is biologically implausible (e.g., death as a passenger in an automobile accident).
- A clearly more likely alternative explanation for the event is present (e.g., typical adverse reaction to a concomitant drug and/or typical disease-related event).

Individual AE/SAE reports will be considered "related" to use of toripalimab if the "not related" criteria are not met.

"Related" implies that the event is considered to be "associated with the use of the drug" meaning that there is "a reasonable possibility" that the event may have been caused by the product under investigation (i.e., there are facts, evidence, or arguments to suggest possible causation).

9.2 Appendix 2: National Institute of Allergy and Infectious Diseases and Food Allergy and Anaphylaxis Network Guidance for Anaphylaxis Diagnosis

The National Institute of Allergy and Infectious Diseases (NIAID) and Food Allergy and Anaphylaxis Network (FAAN) Network Guidance for Anaphylaxis define anaphylaxis as a serious allergic reaction that is rapid in onset and may cause death (Sampson et al, 2006). They recognize 3 categories of anaphylaxis, with criteria designated to capture from 80% of cases (category 1) to > 95% of all cases of anaphylaxis (for all 3 categories).

1. Acute onset of an illness (minutes to several hours) with involvement of the skin, mucosal tissue, or both (e.g., generalized hives, pruritus or flushing, swollen lips-tongue-uvula) AND AT LEAST ONE OF THE FOLLOWING:
   a. Respiratory compromise (e.g., dyspnea, wheeze-bronchospasm, stridor, reduced peak expiratory flow [PEF], hypoxemia).
   b. Reduced blood pressure (BP) or associated symptoms of end-organ dysfunction (e.g., hypotonia [collapse], syncope, incontinence).
2. Two or more of the following that occur rapidly after exposure to a likely allergen for that patient (minutes to several hours):
   a. Involvement of the skin-mucosal tissue (e.g., generalized hives, itch-flush, swollen lips-tongue-uvula).
   b. Respiratory compromise (e.g., dyspnea, wheeze-bronchospasm, stridor, reduced peak expiratory flow [PEF], hypoxemia).
   c. Reduced BP or associated symptoms (e.g., hypotonia [collapse], syncope, incontinence).
   d. Persistent gastrointestinal symptoms (e.g., crampy abdominal pain, vomiting).
3. Reduced BP after exposure to known allergen for that patient (minutes to several hours):
   a. Infants and children: low systolic BP (age specific) or greater than 30% decrease in systolic BP.
   b. Adults: systolic BP of less than 90 mm Hg or greater than 30% decrease from that person’s baseline.

9.3 Appendix 3: Eastern Cooperative Oncology Group Performance Status

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

(Oken et al, 1982)

9.4 Appendix 4: Cockcroft-Gault Formula

Estimated creatinine clearance, or glomerular filtration rate =

[(140-Age) × Mass (in kg)] \ [72 × Serum creatinine (in mg/dL)]

If the patient is female, multiply the above by 0.85

If the subject is obese (> 30% over ideal body weight), use ideal body weight in calculation of estimated creatinine clearance.

Calculation of Ideal Body Weight

Ideal Body Weight (IBW) in kg

Males = 50 + [2.3 × each inch over 5 ft]

or 50 + [2.3 kg × (each cm over 152.4/2.54)]

Females = 45.5 + [2.3 × each inch over 5 ft]

or 45.5 + [2.3 kg × (each cm over 152.4/2.54)]

Calculation for Obesity

[(actual weight - IBW)/IBW] × 100%. If this value is > 30% then the person is obese.

Example:

Subject weight = 160. Subject ideal weight = 120

160-120 = 40

40 / 120 = 0.33

0.33 × 100% = 33%

9.5 Appendix 5: Measured Creatinine Clearance Formula (Adjusted for Body Surface Area)

Creatinine Clearance = CrCl (measured) × 1.73/body surface area (BSA)

where CrCl (measured) = $U_{cr} \times U_{vol}) / (S_{cr} \times T_{min})$

And BSA (m^2) = $([Height(cm) \times Weight(kg)] / 3600)^{½}$ (Mosteller, 1987)

U_{cr}: Urine creatinine (mg/dL)

U_{vol}: Urine volume collected (mL)

S_{cr}: Serum creatine (mg/dL)

T_{min}: Total collection time (minutes)

9.6 New York Heart Association (NYHA) Functional Classification

NYHA CLASS	Symptoms
I	Cardiac disease, but no symptoms and no limitation in ordinary physical activity, e.g. no shortness of breath when walking, climbing stairs etc.
II	Mild symptoms (mild shortness of breath and/or angina) and slight limitation during ordinary activity
III	Marked limitation in activity due to symptoms, even during less-than-ordinary activity, e.g. walking short distances (20-100m). Comfortable at rest.
IV	Severe limitations. Experiences symptoms even while at *rest.* Mostly bedbound patients.

(Little, Brown & Co., 1994)