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TopAlliance Biosciences
Antibody For Better Treatment

TopAlliance Biosciences
Protocol #: TAB001-01

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

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Statistical Analysis Plan

Version 2.0
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[redacted] **Approvals**

[redacted] Date
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TopAlliance Biosciences, Inc.

[redacted] Date
[redacted]

MODIFICATION HISTORY

Unique Identifier for this Version	Date of the Document Version	Author	Significant Changes from Previous Version
1.0	26May2020	[redacted]	Not Applicable – First Version
2.0	21Jul2022	[redacted]	• Increased sample size according to protocol amendments. • Part B will be summarized by tumor type, instead of cohort number.

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List of Abbreviations

Abbreviation or Specialist Term	Definition
ADA	Anti-drug antibody
AE	Adverse event
AESI	Adverse event of special interest
ANA	Anti-nuclear antibody
ATC	Anatomical/Therapeutic/Chemical
AUC	Area under the concentration-time curve
BMI	Body mass index
BOR	Best Overall Response
BPM	Beats per minutes
C1D1	Cycle 1 day 1
Cl	Clearance
CM	Concomitant medication
C_{max}	Maximum observed drug concentration
CR	Complete response
CS	Clinically significant
CT	Computerized tomography
CTCAE	Common Terminology Criteria for Adverse Events
DCR	Disease Control Rate
DLT	Dose limiting toxicity
dMMR	Mismatch repair deficient
DoR	Duration of Response
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
EDC	Electronic data capture
HCC	Hepatocellular carcinoma
IgG4κ	Immunoglobulin gamma 4, kappa
irAE	Immune-related Adverse Event
irBOR	Immune-related Best Overall Response
irCR	Immune-related Complete Response
irNE	Immune-related Not Evaluable
irNN	Immune related irNon-CR/Non-PD
irOR	Immune-related Objective Response
irPD	Immune-related Progressive Disease
irPR	Immune-related Partial Response
irRECIST	Immune-related Response Evaluation Criteria in Solid Tumors
irSD	Immune-related Stable Disease
ITT	Intent-to-Treat
IV	Intravenous
mAb	Monoclonal antibody
MedDRA	Medical Dictionary for Regulatory Activities
MFD	Maximum feasible dose
mg	Milligram

MH	Medical history
MRI	Magnetic Resonance Imaging
MSI-H	Microsatellite instability-high
MTD	Maximum tolerated dose
NADIR	Smallest sum of target lesion measurements
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Events
NCS	Not clinically significant
NE	Not evaluable
NET	Neuroendocrine tumor
NPC	Nasopharyngeal cancer
ORR	Objective response rate
OS	Overall Survival
PD	Progressive disease
PD	Pharmacodynamic
PD-1	Programmed cell death protein 1
PD-L1	Programmed death-ligand 1
PFS	Progression-free survival, based on the first observation of disease progression by RECIST/irRECIST or death due to any cause.
PI	Principal Investigator
PK	Pharmacokinetic
PR	Partial response
PT	Preferred Term
Q2W	Every 2 weeks
Q3W	Every 3 weeks
Q8W	Every 8 weeks
Q9W	Every 9 weeks
Q12W	Every 12 weeks
Q18W	Every 18 weeks
RECIST	Response Evaluation Criteria in Solid Tumors
RP2D	Recommended phase 2 dose
S228P	Serine to proline substitution at amino acid 228
SAE	Serious adverse event
SAP	Statistical analysis plan
SD	Stable disease
SI	International System of Units
SOC	System Organ Class
$t_{½z}$	Terminal elimination half-life
TEAE	Treatment-emergent adverse event
TNM	Tumor Nodes Metastasis
V_d	Volume of distribution
WHO-DD	World Health Organization Drug Dictionary

I. Introduction

A. Background

Toripalimab, also known as TAB001 and JS001 is a humanized IgG4κ (immunoglobulin gamma 4, kappa) monoclonal antibody (mAb) specific for human programmed cell death-1 (PD-1), a co-inhibitory receptor expressed on T cells. Toripalimab is being evaluated for the treatment of cancers as immune therapy.

Similar to other anti-PD-1 antibodies, toripalimab has a high affinity and blocks interaction between PD-1 and its ligand, programmed death ligand 1 (PD-L1). However, toripalimab contains a substitution at amino acid 228 from serine to proline (S228P) to minimize Fab arm exchange (Labrijn AF et al, 2009). Thus toripalimab possesses the special characteristics of more prolonged binding to human PD-1 compared to other such antibodies, as measured by the dissociation coefficient. This provides the possibility of prolonged action of the drug toripalimab in the tissues. Based on the results of nonclinical pharmacology studies, toripalimab binds to human PD-1 and blocks the interaction between PD-1 and its ligands. Toripalimab inhibits the inhibitory signaling cascade triggered by interactions between PD-1 and its ligands. In primary cell-based assays, using cells obtained from healthy donors and cancer subjects, toripalimab increases T cell proliferation, effector cytokine production, and survival following stimulation with a variety of antigens.

As of 16 December 2019, toripalimab has been administered to approximately 1241 subjects participating in a total of 26 Phase I-III clinical trials in China. As of 16 December 2019, toripalimab has been administered to 109 subjects in 1 Phase I clinical trial in the United States.

This study (TAB001-01) is being conducted to evaluate the safety, tolerability, and pharmacokinetic (PK) of toripalimab in subjects with advanced malignancies or hard-to-treat cancers, with a starting dose of 80 mg. The protocol TAB001-001 describes the general approach to analysis of the trial data. This statistical analysis plan (SAP) describes additional details needed to complete such an analysis.

B. Protocol and Amendment History

This SAP is based on version 6.0 of Protocol TAB001-01 dated 8Oct2019. The protocol amendment history is shown in the table below.

Version	Approval Date	Salient Change, if any*
Original Protocol Version 1.0	16 February 2017	

Amendment 1 Version 2.0	5 December 2017	
Amendment 2 Version 3.0	2 January 2018	
Amendment 3 Version 3.1	5 January 2018	
Amendment 3 Version 4.0	14 August 2018	
Amendment 5 Version 5.0	14 February 2019	
Amendment 6 Version 5.1	8 March 2019	
Amendment 7 Version 6.0	8 October 2019	
Amendment 8 Version 7.0	25 June 2020	Change in expansion cohort disease indications; increased sample size

*Changes expected to require accommodation in analysis plan.

This SAP will govern the analysis of data from this study. The plan may be modified until the study clinical database is locked. Any deviations from the analysis plan will be documented as such in the study report.

II. Protocol Objectives

A. 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).

B. Secondary Objectives

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

C. [redacted]

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- [redacted]

- [redacted]
- [redacted]

III. Study Endpoints

A. Primary Endpoints

- 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.

B. 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 rate (ORR) and disease control rate (DCR), duration of response (DoR), and progression-free survival (PFS) 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) and OS in Part B.
- The endpoints for assessment of immunogenicity of toripalimab include the number and percentage of subjects who develop detectable anti-drug antibodies (ADA).

C. [redacted]

- [redacted]

IV. Study Design

A. Design Overview

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 that are refractory to standard therapy or for which no standard therapy exists. In Part A, a cycle is 28 days (4 weeks) in which toripalimab is administered IV Q2W. In Part B, a cycle is 42 days (6 weeks) in which toripalimab is administered IV Q3W.

Part A- Dose Escalation

Part A will follow a standard 3+3 design and will enroll cohorts of 3-6 subjects sequentially at escalating doses of 80 mg, 240 mg and 480 mg. Dose escalation will continue up to a flat dose of 480 mg or until identification of a MTD or the MFD, resulting in up to a total of 18 immunotherapy-naïve subjects (no prior exposure to immunotherapy). 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 decision to discontinue study treatment to protect the best interests of a subject.

Table 1: Standard (3+3) Dose Escalation Procedure

Number of Subjects with DLT at a Given Dose Level	Escalation Decision Rule
0 out of 3	3 subjects are entered at the next dose level
1 out of 3	3 more subjects are entered at this dose level. If 0 out of these 3 subjects experience DLT, proceed to the next dose level. If 1 or more of this 2nd group of 3 subjects experiences a DLT, then dose escalation is stopped. Three more subjects will be entered either at the lower dose level or an intermediate dose level.
>=2	Dose escalation will be stopped. Three additional subjects will be entered at either the previous lower level or an intermediate dose level.
<2 out of 6, 7, or 8 at highest dose level	This dose will be considered tolerable. At least 6 subjects must be enrolled at the

	maximum tolerated dose and can be up to 10 subjects.

Note: Intrasubject dose escalation will not be allowed.

Dose-limiting Toxicity

The period for evaluating DLTs will be from the start of the first dose of toripalimab to the planned 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 Protocol 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.

DLT is defined as all Grade 3 or higher AEs that occur during the DLT evaluation period and are at least possibly related to toripalimab (See more details in the section 3.1.6.2 of protocol).

Delayed DLTs are AEs that meet the DLT criteria but occur outside of the DLT evaluation period. Delayed DLTs will be evaluated on a case-by-case basis upon consultation between the sponsor and the Principal Investigator (PI). If the delayed DLT constitutes a laboratory based toxicity not associated with clinical signs or symptoms, confirmation of the laboratory results will be obtained. The effect of delayed DLT on the dose escalation cohort will also be considered as described in protocol section 3.1.6.2. The same reporting rule will be applied to both DLT and delayed DLT.

Maximum Tolerated Dose (MTD)

The MTD is defined as the highest dose level at which no more than one out of 6 subjects experiences a DLT during the first cycle of study treatment.

Part B-Dose Expansion

- In Part B, up to 280 subjects will be enrolled. Enrollment will consist of solid tumors that may include but not limited to esophageal carcinoma, gastric carcinoma, cholangiocarcinoma, neuroendocrine tumors (NETs) (excluding lung derived NET), nasopharyngeal carcinoma (NPC), hepatocellular carcinoma (HCC), sarcomas, both chondrosarcoma soft tissue sarcoma (excluding leiomyosarcoma and including angiosarcoma, undifferentiated pleomorphic sarcoma and alverolar 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 microsatellite instability-high (MSI-H) / mismatch repair deficient (dMMR) tumors are eligible to enroll. The dose 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 toripalimab (JS001) in studies performed in China (see Protocol Section 1.4) as well as safety data from subjects treated in Part A of this study. Subjects will receive toripalimab 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.

B. Study Population

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. The inclusion and exclusion criteria for study enrollment are in protocol sections 4.1.2 and 4.1.3, respectively, of the protocol V7.0 dated 25 June 2020.

C. Sample Size

The sample size will include up to 18 subjects in the escalation phase plus approximately 280 subjects in the 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 cohort may include 5 disease specific expansion cohorts, and at the discretion of the Sponsor, another tumor cohort, to a maximal 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.

D. Treatment Randomization

Not applicable.

E. Assessment Schedule

All subjects undergo assessments during screening, treatment period, unscheduled visits, and follow-up periods as described in section 4 of the protocol.

- For both escalation phase (Part A) and expansion phase (Part B), screening evaluations occur within -28 to -1 days prior to administration of the first study drug. (See details on Table 4.2-1 and Table 4.2-6 of the protocol)
- For part A, evaluations in the treatment period vary for each 28-day cycle. Cycle 1 includes assessments on Days 1, 2, 3, 4, 8, 15 and 22. Cycle 3 includes assessments on Days 1, 15, 16, 17, 18, and 22. Cycles 2, 4 and beyond include

assessments on Days 1 and 15. (For Part A, see details on Table 4.2-2 to Table 4.2-5 of the protocol)

- For Part B, evaluations in the treatment period vary for each 42-day cycle. Cycle 1 includes assessments on Days 1, 2, 3, 4, 8, 15 and 22. Cycle 3 includes assessments on Days 1, 22, 23, 24, 25, 29 and 36. Cycle 2, 4 and beyond include assessments on Days 1 and 22. (For Part B, see details on Table 4.2-6 to Table 4.2-9 of the protocol)
- For Part A and B, end of treatment evaluation occurs 28 days (±3 days) after last dose, and Post-treatment evaluation occurs 90 days (±7 days) after the last dose of study drug. (See details on Table 4.2-10 of the protocol)
- For Part A and B, evaluations may be performed at unscheduled visits that subjects make to the clinic outside the visit window. (See details on Table 4.2-10 of the protocol)
- For Part A, disease assessments will occur during the screening visit, every 8 weeks (Q8W) (±10 days) post cycle 1 day 1 (C1D1) through 12 months, then every 12 weeks (Q12W) unless the PI prefers the Q8W schedule.
- For Part B, disease assessments will occur during the screening visit, every 9 weeks (Q9W) (±10 days) post C1D1 through 12 months, then every 18 weeks (Q18W) unless the PI prefers the Q9W schedule.
- If there is a disease progression, the subject would continue on to the next regulatory scheduled visit and thereafter as per the Schedule of Evaluations. However, 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.

V. Interventions

A. Clinical Trial Material

Study drug will be administered by the IV route Q2W in Part A or Q3W in Part B. Study drug will be administered for a minimum of 60 minutes at Cycle 1; upon completion of Cycle 1, the infusion time may be reduced to a minimum of 30 minutes depending on subject tolerance. Toripalimab may be administered in the setting of progressive disease (PD) as long as certain criteria are met as described in Protocol Section 3.1.5 .

B. Study Procedures

Details of study procedures are in Section 4.3 of the protocol.

VI. General Analytical Considerations

There will be no formal hypothesis testing. All statistical analyses will be performed using SAS Version 9.3 or higher for windows [SAS Institute Inc; Cary, NC, USA].

A. Data Sources

Electronic Data Capture (EDC) system will be used for data collection and query handling. The investigator will ensure that data are recorded on the electronic case report forms (eCRFs) as specified in the study protocol and in accordance with the instructions provided. Sections 6.2-6.4 of the protocol provides additional details regarding data recording and handling.

B. Definition of Baseline

Baseline is defined as the last available non-missing observation or assessment prior to the first administration of study drug on C1D1. This will be taken from the evaluation records on pre dose at C1D1, or last non-missing value during screening period.

C. Missing Data

In general, unless stated otherwise, missing data will not be imputed with other values. All data recorded in the eCRF will be included in data listings. If a baseline value is missing, no change from baseline will be calculated.

Exceptionally, some partial dates will be imputed with the following convention to calculate the relative study day or duration.

D. Imputation rule for missing and partial dates

Adverse Event Date

For the missing or partial date (missing day and/or month) of AE start, the following imputation rules will be applied:

- If year is missing, no imputation will be performed.
- If year is present and both month and day are missing, the day and month will be imputed with the day and month of the first study dose date if the year is equal to the year of first dose. Otherwise, the month and day will be imputed as the first day of the year (01 Jan).
- If only day is missing, and if the year and month are equal to the first dose date, the day will be resolved as day of the first dose date. Otherwise, the day will be imputed as "01".

For the missing or partial date of AE end:

- If year is missing, no imputation will be performed, and the AE will be assumed as ongoing. If year is present and both month and day are missing, the missing month and date will be imputed as the last day of the year, 31 December.

- If only day is missing, the missing date will be imputed as the last day of that month.

Date of Cancer Diagnosis

Date of cancer diagnosis will be imputed when partial dates are collected. In case of missing month and day and available year, the corresponding date will be replaced with "01JULYYYY". In case of missing day, the date will be replaced with the middle date of a month "15MMMYYYY". If, after imputation, the diagnosis date becomes greater than the date of informed consent, then diagnosis date is to be replaced with the date of informed consent.

Date of Death

For the missing or partial date (missing day and/or month) of date of death, the following imputation rules will be applied:

- If year is missing, the date of death will be imputed as date subject last known alive + 1.
- If year is present and both month and day are missing, the date of death will be imputed as date subject last known alive + 1 if the year is equal to the year of subject last known alive. Otherwise, the month and day will be imputed as the first day of the year (01 Jan).
- If only day is missing, and if the year and month are equal to the date subject last known alive, the date of death will be resolved as date subject last known alive + 1. Otherwise, the day will be imputed as "01".

E. Interim Analyses or Timing of Analyses

No formal interim analyses are planned for this study.

F. Test Sizes

Not applicable. No formal statistical hypothesis testing will be performed.

G. Analysis Populations

Enrolled Population
All enrolled subjects (consented and assigned an enrollment number) regardless of receipt of the investigational product will comprise the Enrolled population. This population will be used only for the summary of protocol deviation.

Safety Population
Safety Population will consist of all subjects who receive at least one partial or complete dose of toripalimab.

For this non-randomized study, the definition of the Intent-to-Treat (ITT) population is the same as the definition of the Safety population. Rather than defining and referencing two populations with the same underlying definition, all analyses that would normally be attributed to the ITT population (e.g. efficacy) will be attributed to the Safety Population.

PK-Evaluabel Population
The PK-Evaluable Population will include those subjects who had sufficient PK data to be included in the PK analyses, as assessed by the Pharmacokineticist.

Pharmacodynamic (PD)-Evaluable Population
The PD-Evaluable Population will include those subjects who had sufficient PD data to be included in the PD analyses, as assessed by the Sponsor. 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.

Screened Population
All subjects who signed the informed consent form will comprise the Screened population. This population will be used for the summary of disposition and the listing of screening and enrollment status.

H. Data Display Characteristics

Data displays produced for this study will include three types—summary tables, data listings, and figures. Unless stated otherwise, data listings will be produced for all recorded data. Summary tables and/or figures will be produced as specified in following sections.

Data listings will list the data recorded on the eCRF for each subject, and may include key derivations. They will typically be ordered by dose cohort in Part A and by tumor type in Part B, subject ID, and time of assessment. When expedient, additional levels of ordering hierarchy may be applied to reflect subsets of assessments within subject.

Summary tables will display descriptive statistics calculated for each of the dose cohorts in Part A and tumor types in Part B, unless described otherwise in the following sections VII to IX.

Continuous data will be summarized with the number of nonmissing values, mean, standard deviation, minimum, maximum and median. Categorical data will be summarized with the number of subjects with nonmissing values for each of the possible categories. Percentages of subjects with each of the possible values will be calculated from the number of subjects in the corresponding

populations, unless stated otherwise. Some continuous variables may also be grouped into categorical levels and evaluated in frequency tables. Time-to-event variables will be estimated by the Kaplan-Meier method.

VII. Subject Accountability

A. Subject Characteristics

Subject listings of demographics, baseline characteristics, medical history, cancer diagnosis and classification, prior systemic anti-cancer therapy, prior radio-therapy, prior anti-cancer surgery, prior and concomitant procedures, subsequent anti-cancer therapy will be provided for the safety population. For the cancer diagnosis listing, the time since initial diagnosis of malignancy and the time since diagnosis of metastatic disease (relative to informed consent) will be included.

In addition, the following summaries by dose cohort in Part A and by tumor type in Part B will be provided:

Demographic and Baseline Characteristics*:* Demographic variables include age, sex, ethnicity and race. Age will be calculated as the number of years elapsed between birth date and the date of informed consent. Baseline Characteristics include baseline Eastern Cooperative Oncology Group (ECOG) Performance Status, weight and body mass index (BMI). BMI will be calculated as weight (kg) / [height (m)]^2.

Medical History*:* Medical history (MH) will be coded using Medical Dictionary for Regulatory Activities (MedDRA) (version 25.0), and will be summarized for the Safety population as the numbers and percentage of subjects reporting each MH term, by System Organ Class (SOC) and preferred term.

Cancer Diagnosis History and Classification*:* Time since initial diagnosis, time since initial metastatic diagnosis, stage at initial diagnosis, primary tymor location, cancer histology, original histological grades, Tumor Nodes Metastasis (TNM) Staging (T, N and M categories) will be summarized.

Anti-Cancer Systemic Therapy History*:* A summary of number of prior anti-therapy regimens, time from the last systemic treatment to study drug start, type of medication, best overall response to prior anti-cancer therapy (partial response [PR], complete response [CR], progressive disease [PD], stable disease [SD], Unknown or Not Applicable), and reason for regimen discontinuation will be provided. The prior anti-cancer systemic therapy will be coded using WHODrug B2 Enhanced March 2017.

Radiotherapy History*:* A summary of number of subjects with prior radiotherapy, purpose of radiotherapy, and best response to radiotherapy (PR, CR, PD, SD, Not Evaluable) will be provided.

Post Anti-Cancer Therapy Medications: A listing will display the alternative anti-cancer therapy medications subjects received after discontinuation of the study treatment, and the dates the therapy started/ended or whether the therapy was ongoing.

B. Disposition

A tabulation of subject disposition will be presented by dose cohort in Part A and by tumor type in Part B, and will include the number of subjects in each population (Enrolled, Safety, PK, PD), as well as completion status and the primary reasons for withdrawal from treatment and the study for the Safety population.

A listing of subject disposition will also be prepared.

C. Protocol Deviations and Population Inclusions

Major protocol deviation that could potentially affect the efficacy or safety conclusion of the study will be identified prior to database lock, and will be summarized by deviation category and dose cohort in Part A and by tumor type in Part B.

A listing will identify subjects who were enrolled even though they did not meet one or more eligibility criteria.

VIII. Efficacy Analyses

Efficacy analyses will include all subjects in the safety population, and will be presented by dose cohort in Part A and by tumor type in Part B. Time-to-event analyses will be performed in Part B only, as dose cohorts in Part A have limit number of subjects/events.

A. Efficacy Outcomes and Analyses

Efficacy parameters will be defined as follows:

Overall Survival (OS)

OS is defined as the time from date the first dose of toripalimab until death due to any cause. OS time for subjects not achieving the endpoint will be censored at the last known alive date. OS analysis will be performed for Part B only.

If a subject has a death record, then OS in month will be calculated as [Date of Death -Study Treatment Start Date +1]/30.4375.

If death is not reported, subject will be censored at their last contact date, and the overall survival time in month will be [Last Known Alive Date - Study Treatment Start Date +1]/30.4375.

The number and percentage of subjects for those who died and for those who are censored for analysis (i.e., did not die) will be reported. Kaplan-Meier method will be used to estimate the survival curve, median survival time and the 95% confidence interval. Median follow-up time (months) and total follow-up time (person-years) will be reported.

Best Overall Response

Within each visit an overall response will be determined by the investigator based on target lesions, non-target lesions and new lesions assessed by computerized tomography (CT)-based/magnetic resonance imaging (MRI) radiography. The best overall response is defined as the best response recorded from the start of treatment until the occurrence of disease progression, considering any confirmation requirement.

Tumor response to treatment and best overall response will be evaluated using both RECIST v1.1 (Eisenhauer EA, et al, 2009) and irRECIST (immune-related RECIST, www. irrecist.com).

Best Overall Response using RECIST v1.1 (BOR)

According to RECIST v1.1, overall response includes CR, PR, SD, PD, and Not Evaluable (NE). The confirmation of CR and PR is required; 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. Overall response will be assigned at each tumor assessment by the investigator, in accordance with the criteria described in protocol section 4.3.1.1 (reference table 4.3.1-1 of protocol v7.0).

The best overall response (BOR) will be derived from overall responses at different time points, and defined as Table 2 (RECIST 1.1, Eisenhauer EA, et al, 2009). The number and proportion of subjects with CR, PR, SD, PD or NE as their BOR per RECIST v1.1 will be summarized by dose cohort in Part A and by tumor type in Part B.

Table 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.

Best Overall Response using irRECIST (irBOR)

According to irRECIST, immune-related overall response (irOR) includes Immune-related Complete Response (irCR), Immune-related Partial Response (irPR), Immune-related Stable Disease (irSD), Immune related irNon-CR/Non-PD (irNN), Immune-related Progressive Disease (irPD), and Immune-related Not Evaluable (irNE). Per protocol, the confirmation of irCR and irPR is not required. Per irRECIST, the confirmation of irPD is recommended by using the subsequent tumor evaluation at least 4 weeks after the first irPD. At each tumor assessment, irOR will be assigned by the investigator, in accordance with the criteria described in protocol section 4.3.1.1 (reference table 4.3.1-3 of protocol 7.0).

irBOR will be derived from overall responses at different time points for a subject; BOR order is irCR, irPR, irSD, irNN and irPD. The number and proportion of subjects with irCR, irPR, irSD, irNN or irPD as their best overall response per irRECIST will be summarized by dose cohort in Part A and tumor type in Part B.

Objective Response Rate (ORR)

ORR will be defined and analyzed separately for each response criteria, as follows:

- For RECIST v1.1 - number of subjects achieving BOR of CR or PR, divided by the number of treated subjects.
- For irRECIST - number of subjects achieving irBOR of irCR or irPR, divided by the number of treated subjects.

Subjects without at least one post-baseline radiological assessment will be treated as non-responders. ORR will be presented by dose cohort in Part A and tumor type in Part B, with 95% exact confidence intervals.

Disease Control Rate (DCR)

DCR will be defined and analyzed separately for each response criteria, as follows:

- For RECIST v1.1 - number of subjects achieving BOR of CR, PR or SD, divided by the number of treated subjects.
- For irRECIST - number of subjects achieving irBOR of irCR, irPR or irSD, divided by the number of treated subjects.

Subjects without at least one post-baseline radiological assessment will be treated as non-responders. DCR will be presented by dose cohort in Part A and tumor type in Part B, with exact 95% exact confidence intervals.

Progression-Free Survival (PFS)

PFS will be defined and analyzed separately for each response criteria, for Part B only, as follows:

- For RECIST v1.1 - time from the first dose of toripalimab to the first PD or death due to any cause, whichever occurs first.
- For irRECIST – time from the first dose of toripalimab to the first confirmed irPD or death due to any cause, whichever occurs first.

Subjects not achieving the PFS endpoint will be censored at the date of their last radiological 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. Subjects who experience a PFS event right after two or more consecutive missed assessments will be censored at the date of last assessment prior to the missed ones.

PFS will be analyzed by using Kaplan-Meier method and their summary statistics will be presented by tumor type with the median, estimates at 6, 12, 15, 18 months, with associated 95% confidence interval.

Duration of Response (DoR)

DoR will be defined and analyzed separately for each response criteria, as follows:

- For RECIST v1.1 - time from the date of first confirmed response (CR or PR) to the date of first PD or death due to any cause, whichever occurs first.
- For irRECIST – time from the date of first response (irCR or irPR) to the date of first confirmed irPD or death due to any cause, whichever occurs first.

DoR will be analyzed for subjects with a response only. The same censoring rules for PFS will be applied to DoR. Descriptive statistics for DoR will be presented by tumor type in Part B only. In addition, DoR will be analyzed using the method of Kaplan-Meier and be presented for each tumor type as a median with associated 95% confidence interval.

Sum of Target Tumor Measurements

The sum of tumor length of target lesions will be calculated as the sum of the longest diameters of non-nodal lesions and short axis for nodal lesions if lymph nodes is applicable as defined by RECIST v1.1 criteria.

The descriptive statistics will be presented for the sum of tumor measurement, its absolute and percent change from baseline at different time points, maximum post-baseline, minimum post-baseline, and last observation post-baseline. The daily change and daily percent change of sum of target lesions from nadir (the smallest sum of target lesion measurement among all time points including baseline) to progression or last post baseline observation will be summarized. The daily change is the difference between progression (or last post baseline observation) and nadir divided by days between two measurements. The daily percent change is calculated as 100*(the daily change from nadir to progression or last post baseline observation) / (sum of target tumor measurements at nadir). If the nadir is reached at more than one visit, then the latest visit will be used to calculate the daily change and daily % change from nadir to progression or last post baseline observation. The daily change and daily % change of sum of target lesions from baseline to nadir will be summarized. The daily change from baseline to nadir is the difference from baseline to nadir divided by days between the two time points. The daily % change from baseline to nadir is calculated as 100*(the daily change from baseline to nadir) / (sum of target tumor measurements at baseline). If the nadir is reached at more than one visit, then the earliest visit will be used to calculate the daily change and daily % change from baseline to nadir.

IX. Safety Analyses

Safety analyses will include all subjects in the Safety Population. Summaries of safety data will be presented by dose cohort in Part A and by tumor type in Part B.

A. Exposure

Exposure to toripalimab will be summarized with descriptive statistics for the following:

- total number of infusion
- duration of Toripalimab (weeks), defined as (date of last dose of study drug– date of first dose study drug +1)/7
- cumulative dose exposure (mg), defined as the sum of the doses administered
- dose intensity (mg/cycle, calculated as [total cumulative dose (mg) / duration of dosing (cycles)])
- Relative dose intensity, defined as (dose intensity) / (planned dose intensity) *100

The number of subjects with infusions interrupted, infusions delayed, infusions not given, and infusion permanently discontinued will also be summarized. Separate listings will be provided for toripalimab administration and exposure. A listing will be provided with the information from the study drug administration eCRF form and derived exposure measures as above.

B. Adverse Events

The production of data summaries and listings for AEs and SAEs will be based on the clinical data collected on the AE eCRF. A reconciliation of SAEs reported per the pharmacovigilance database and SAEs reported on the AE eCRF will be performed.

Treatment Emergent Adverse Events (TEAE) are defined as those AEs occurring during or after the first dose of toripalimab and within the follow up period of 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 (or >90 days after the last dose of study drug if AEs are drug-related or other clinically significant (e.g., late emerging immune-related adverse events (irAE) that are not serious), and those existing AEs that worsened during the study or in the follow up period. AEs will be coded to SOC and Preferred Terms (PT) using the MedDRA version 25.0 or higher, and graded by the investigator using NCI-CTCAE version 4.03 or higher. An listing of aggregated SOC and PT is provided by the sponsor. Aggregated SOC and PT will be used to table summaries. AE listings will display both SOC/PT by MedDRA version 25.0 and aggregated SOC/PT.

An AE of special interest (AESI) is one of scientific and medical interests specifical to understanding of toripalimab and may require close monitoring and rapid communication by the investigator to the sponsor. AESI will be designated by the investigator on the eCRF, and will include:

- Hepatic function abnormality meeting the definition of Hy's law.
- ≥ Grade 3 endocrinopathy (e.g., hypophysitis, thyroiditis, adrenal insufficiency)
- ≥ Grade 3 dermatologic AE
- ≥ Grade 3 pneumonitis
- ≥ Grade 3 enterocolitis
- ≥ Grade 3 serum sickness(see protocol section 4.3.3.1)

Refer to protocol section 5.3 for additional details.

Summary tables of AEs will display counts and percentages of subjects who reported at least one TEAE for each system organ class and/or preferred term represented in the AE data. A subject that has multiple occurrences of an adverse event will be counted once within each SOC and similarly once within each PT, using the strongest level of relationship and worst severity grade as applicable. If causality data is missing, 'Related' will be imputed.

The following AE summaries will be produced:

- An overall summary of adverse event which summarizes the number of subjects with at least one TEAE, TEAE related to toripalimab, SAE, serious TEAE, serious TEAE related to toripalimab, AESI, irAE. It will also summarizes the number of subjects with at least one grade 3+ event for each categories listed above. In addition, DLT, AE leading to toripalimab's discontinuation, dose interruption, dose reduction, DLT leading to discontinuation of toripalimab, AE leading to death and delayed DLT will be summarized respectively.
- Summary tables of TEAE by SOC and PT, and subset is as following:
  - All TEAEs
  - TEAEs related to toripalimab. It will include TEAE with a drug relationship of 'Definitely Related', 'Probably Related' or 'Possibly Related', or a missing relationship to toripalimab.
  - Serious TEAEs
  - Serious and related TEAEs. The table includes all TEAE that are serious and related to toripalimab
  - Serious TEAEs with CTCAE grade ≥ 3 and related to toripalimab
  - TEAEs with CTCAE grade ≥ 3
  - TEAEs with CTCAE grade ≥ 3 and related to toripalimab
  - Immue-related TEAEs with CTCAE grade ≥ 3
- All TEAEs by SOC, PT and CTCAE toxicity grade. Subject incidence of TEAE by SOC, PT, and maximum CTCAE toxicity grade. At each level of subject

summaries, a subject is classified according to the maximum CTCAE toxicity grade if a subject reported one or more events.

- Summary tables of TEAE by PT, and subset is as following:
  - All TEAEs
  - TEAEs of special interest
  - Immune-related TEAEs

The following AE listings will be produced. Unless specified, the listings include all AEs – both treatment-emergent and non-treatment-emergent.

- All AEs
- All serious AEs
- AEs related to study drug toripalimab
- AEs leading to toripalimab discontinuation
- AEs resulting in toripalimab dose interruption
- AEs resulting in toripalimab dose reduction
- AESIs
- Immune-related AEs DLTs
- Delayed DLTs
- AEs resulting in death
- TEAEs leading to toripalimab discontinuation
- TEAEs resulting in toripalimab dose interruption
- TEAEs resulting in toripalimab dose reduction
- TEAEs resulting in death
- Grade 3+ TEAEs of special interest

The listings will be presented with the SOC, aggregated SOC, PT, aggregated SOC, and verbatim term. Among subjects, it will be sorted by dose cohort in Part A and by tumor type in Part B, and subject number. Within subject, it will be sorted by start date, end date, SOC and PT.

C. Clinical Laboratory Results

Laboratory samples (including hematology, serum chemistry, coagulation, thyroid panel, urinalysis, and pregnancy test) will be processed by local labs. For each parameter, the lab results will be standardized to the International System of Units (SI) units to facilitate grading and data summarization. The analysis data will include both the original local lab results/units and the standardized lab results/units.

All relevant laboratory tests will be graded according to NCI-CTCAE version 5.0. CTCAE grading will be performed using the normalized values and the common

published reference ranges. For laboratory tests covered by CTCAE, a Grade 0 will be assigned for all non-missing values not graded as 1 or higher.

All listings and summaries of laboratory parameters will be presented separately for each laboratory panel (hematology, coagulation, serum chemistry, thyroid panel, and urinalysis).

For each parameter, descriptive statistics will be used to summarize values at baseline, maximum post-baseline, maximum change post-baseline, minimum post-baseline, minimum change post-baseline, last observation post-baseline, and change of last observation post-baseline.

For parameters with CTCAE grading, a shift table will present the number and percentage of subjects with laboratory shifts from baseline to the worst post-baseline toxicity grade, by dose cohort in Part A and by tumor type in Part B. For parameters with both low and high CTCAE grade definitions, shifts will be reported separately for each direction.

For parameters that do not have defined CTCAE grades, a shift table will present subjects whose values shift from low or normal at baseline to high at any post-baseline observation; from normal or high at baseline to low at any post-baseline observation; from low or normal at baseline to high at last observation post-baseline; from normal or high at baseline to low at last observation post-baseline. Shift tables will include all available assessments, including unscheduled assessments, and the denominator for percentages will be the number of subjects in the Safety population with non-missing baseline value.

Lab data will be presented in data listings, and will include standardized values and units, normal ranges, CTCAE grade, and clinically significance where applicable.

D. Vital Signs

For each vital signs measurement, including respiratory rate (breaths/min), blood pressure (systolic and diastolic, mmHg), pulse rate (beats per minutes [bpm]), and temperature (°C), descriptive statistics will be used to summarize values at baseline, maximum post-baseline, minimum post-baseline, and last observation post-baseline. Weight (kg) and height (cm) at baseline will be summarized as well.

A shift table will present by dose cohort in Part A and by tumor type in Part B the number and percentage of subjects with vital signs shifts from: high or normal at baseline to low at any post-baseline observation; high or normal at baseline to low at the last post-baseline observation; low or normal at baseline to high at any post-baseline observation; and low or normal at baseline to high at the last post-baseline observation. The shift table will include all available assessments, including unscheduled assessments, and the denominator for percentages will be the number of

subjects in the Safety population. The high/low flagging criteria for vital signs parameters are defined in Table 3 below:

Table 3: Vital Signs Parameter Flagging Criteria

Parameter	Low	High
Respiratory Rate	<12 breaths per minute	>18 breaths per minute
Systolic Blood Pressure	<90 mmHg	>120 mmHg
Diastolic Blood Pressure	<60mmHg	>80mmHg
Pulse Rate	<60 beats per minute	> 100 beats per minute
Temperature	<36.5°C	>37.3°C

All vital signs results will be presented in a listing as well.

E. Physical Examination

Physical Exam data will be presented in a listing.

F. ECGs

ECG measurements are recorded in triplicate, with 3 measurements obtained within a 5-minute time period at least 1 minute apart. For summaries of ECG parameters (Heart rate, PR interval, RR interval, QRS interval, and QT interval), the average of the 3 measurements will be used. If less than 3 measurements are obtained at a given visit and time point, the average of the available measurements will be used.

Descriptive statistics for actual values and changes from baseline for ECG parameters will be presented for baseline, maximum post-baseline, minimum post-baseline and last post-baseline observation.
For ECG overall interpretation results (Normal, Abnormal clinically significant [CS], or Abnormal not clinically significant [NCS]), a shift table will be presented to summarize shifts from baseline to worst post-baseline result and last observation post-baseline. These tables will include all available assessments, including unscheduled assessments, and the denominator for percentages will be the number of subjects in the Safety population with a non-missing response at both baseline and post-baseline visit.

A QTcF summary table will repsent descriptive statistics for the maximal QTcF value post-baseline. It will also the number and percentage of subjects with QTcF post-baseline maximal value in (470,500] and >500, and QTcF post-baseline maximal change ≥30 and ≥60.

ECG measurements with overall evaluation results and clinically significant ECG findings will be presented in listings.

G. ECOG Performance Status

For ECOG performance status, a summary table will present ECOG status by visit and a shift table will present shifts from baseline to maximum and minimum post-baseline. The shift table will include all available assessments, including unscheduled assessments, and the denominator for percentages will be the number of subjects in the Safety population with a non-missinng response at both baseline and post-baseline visit.

ECOG performance status will be presented in a listing as well.

H. Immunogenicity

A summary of anti-drug antibody (ADA) data will include the following:

- Number and percentage of subjects who develop detectable ADA at different time points (baseline, treatment, or follow up period)
- Number and percentage of subjects with persistent on-treatment ADA with 2 or more consecutive ADA positive
- Number and percentage of subjects with ADA positive at last assessment during treatment period
- Number and percentage of subjects who have ADA negative
- Time from first treatment to first ADA positive

All details of ADA assessments will be presented in a listing.

The ADA positive subgroup will include subjects who have ADA positive at baseline, treatment period or follow up period. The ADA negative subgroup will consist of subjects who have at least one ADA assessment at baseline, treatment period or follow up period, and all available assessments are negative. The impact of positive ADA on safety (TEAE and immune-related TEAE) and efficacy (best overall tumor response) will be assessed among subjects received MTD if data allow.

The following summaries will be presented separately for the ADA positive and ADA negative subgroups:

- Overall summary of AEs
- TEAEs that are immune-related by preferred term and maximum CTCAE toxicity grade
- Toripalimab related serious TEAEs by preferred term and maximum CTCAE toxicity grade
- Best Overall Response using RECIST v1.1 (BOR)

The impact of positive ADA results on PK and pharmacodynamics may be assessed if data allow.

I. Prior and Concomitant Medications

Prior and concomitant medications will be coded to Anatomical/Therapeutic/Chemical (ATC) class and PT using the World Health Organization Drug Dictionary (WHO-DD) version B2 Enhanced March 2017).

Prior medication is defined as any medication with a stop date prior to the date of first dose of study drug. Concomitant medication is defined as any medication with a start date prior to the date of the first dose of study treatment and continuing after the first dose of study drug or with a start date between the dates of the first and last dose of study drug, inclusive. Any medication with a start date after the date of the last dose of study drug will not be considered a concomitant medication.

The prior and concomitant medications will be summarized by ATC classification level 2 and PT; if a subject reports the occurrence of a particular medication more than once, the medication is only counted once.

All prior and concomitant medications reported in EDC will be presented in listings. If a medication cannot be determined as prior or concomitant medication due to imcomplete start date and/or end date, it will be labeled as "Undertermined".

J. Other Safety Assessments

Listings of tumor marker assessment, mutations status assessment, virology, suspected serum sickness, and complement studies and immune complex assays will be produced, if data is available. A listing of autoantibody (anti-nuclear antibody ANA), anti-smooth muscle antibody, and Type 1 anti-liver kidney microsomal antibody will be also presented, if data is available.

X. Pharmacokinetic and Pharmacodynamic Analyses

PK and PD analysis will be defined in a separate plan, and performed and reported by a separate vendor. PK and PD data are not within the scope of this SAP.

XI. References

Labrijn AF, Buijsse AO, van den Bremer ET, et al. "Therapeutic IgG4 antibodies engage in Fab-arm exchange with endogenous human IgG4 in vivo." Nat Biotechnol 2009; 27(8): 767-771.

Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, Dancey J, Arbuck S, Gwyther S, Mooney M, Rubinstein L, Shankar L, Dodd L, Kaplan R, Lacombe D, Verweij J. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Cancer 2009; 45(2):228-47.