STATISTICAL ANALYSIS PLAN

A Multicenter, Single-arm, Phase II Clinical Trial Evaluating the Efficacy and Safety of IBI308 Monotherapy in the treatment of relapsed or Refractory Extranodal NK/T-Cell Lymphoma, Nasal Type (ORIENT-4)

Protocol Number: CIBI308D201

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VERSION HISTORY

SAP Version	Approval date	Description of changes
1.0	*2019-06-24*	*Update according to protocol amendment 2.0 and reorganized to new SAP template*

ABBREVATION

ADA	Anti-drug antibody
AE	Adverse event
BDRM	Blinded data review meeting
BMI	Mody mass index
CI	Confidence interval
CR	Complete response
CSR	Clinical study report
CTCAE	Common Terminology Criteria for Adverse Events
DCR	Disease control rate
DMC	Data monitoring committee
DoR	Duration of response
ECG	Electrocardiography
ECOG PS	Eastern Cooperative Oncology Group Performance Status
eCRF	Electronic case report form
FAS	Full analysis set
GCP	Good clinical practice
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
irAE	Immune related adverse event
MedDRA	Medical Dictionary for Regulatory Activities
ORR	Objective response rate
PD	Disease progression
PFS	Progression free survival
PK	Pharmacokinetics
PP	Per protocol
PR	Partial response
SAE	Serious adverse event
SAP	Statistical analysis plan
SD	Stable disease
SS	Safety set
TEAE	Treatment emergent adverse event
TTR	Time to response

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1 Introduction

This statistical analysis plan (SAP) is based on CIBI308D201 "A Multicenter, Single-arm, Phase II Clinical Trial Evaluating the Efficacy and Safety of IBI308 Monotherapy in the treatment of relapsed or Refractory Extranodal NK/T-Cell Lymphoma, Nasal Type (ORIENT-4)" protocol, version 2.0 on July 05, 2017 and China regulator guidances. The objective of this SAP is to provide detailed definition of the endpoints and planned statistical analyses.

1.1 STUDY OBJECTIVES

- Primary Objectives

  To evaluate the objective response rate (ORR) of IBI308 monotherapy in the treatment of relapsed or refractory extranodal natural killer (NK)/T-Cell lymphoma, nasal type (ENKTL-NT).

- Secondary Objectives

  - To evaluate the rate of complete response (CR) and partial response (PR) of IBI308 monotherapy in the treatment of relapsed or refractory ENKTL-NT;
  - To evaluate the disease control rate (DCR) of IBI308 monotherapy in the treatment of relapsed or refractory ENKTL-NT;
  - To evaluate the time to response (TTR) of IBI308 monotherapy in the treatment of relapsed or refractory ENKTL-NT;
  - To evaluate the duration of response (DOR) of IBI308 monotherapy in the treatment of relapsed or refractory ENKTL-NT;
  - To evaluate the progression-free survival (PFS) and 6-month PFS rate of IBI308 monotherapy in the treatment of relapsed or refractory ENKTL-NT;
  - To evaluate the overall survival (OS) and 12-month OS rate of IBI308 monotherapy in the treatment of relapsed or refractory ENKTL-NT;
  - To evaluate the safety of IBI308 monotherapy in the treatment of relapsed or refractory ENKTL-NT;
  - To evaluate the quality of life of subjects with relapsed or refractory ENKTL-NT after IBI308 monotherapy, using EuroQoL 5 Dimensions 5 Levels (EQ-5D-5L) and European Organization for Research and Treatment of Cancer Quality-of-Life Questionnaire-Core 30 (EORTC QLQ-C30).

1.2 STUDY DESIGN

This is a multicenter, single-arm, phase II clinical trial evaluating the efficacy and safety of IBI308 monotherapy in the treatment of relapsed or refractory ENKTL-NT.

This study will enroll patients with relapsed or refractory ENKTL-NT to receive IBI308 200mg IV Q3W until progression disease (PD), death, intolerable toxicity, withdrawal of ICF, or other reasons stated in the protocol with a maximum treatment duration of 24 months. For subjects who experience PD for the first time and are clinically stable, the investigator can continue treatment until subsequent PD, death, intolerable toxicity, withdrawal of ICF, or other reasons stated in the protocol with a maximum treatment duration of 24 months.

The primary efficacy endpoint of this study is ORR defined as percentage of subjects with radiological CR or PR as best overall response. The primary endpoint is analyzed after last subjects completing up to 24 weeks followup. Lugano 2014 criteria will be used for ORR. After 24 weeks, IWG 2007 criteria will used to assess responses.

Subjects will continue safety followup upto 90 days after last dose of study treatment.

1.3 SAMPLE SIZE

The hypothesis of this study is to evaluate the effectiveness of ORR based on Lugano 2014:

H0: ORR≤30%

H1: ORR>30%

For the primary efficacy endpoint ORR, the point estimate and its (100-α)% confidence interval (α maybe different from 5 if interim analysis is added) will be provided using binomial distribution. If the lower limit of the confidence interval is greater than 30%, the effectiveness of IBI308 is established for r/r ENKTL. This is a single-arm trial, and 20-60 subjects are planned to be enrolled for the study. Under the assumption of an ORR=50%, with 43 subjects, there is 80% power to reject H0 under a two-sided type I error rate of 0.05.

After first 20 subjects enrolled, a safety evaluation will be conducted before continuing enrollment.

1.4 RANDOMIZATION AND MASKING

NA

1.5 CHANGE OF STATISTICAL ANALYSIS PLAN IN PROTOCOL

1.5.1 Change in Protocol Amendment

NA

1.5.2 Changes in Statistical Analysis Plan

See version history.

2 Endpoints

Assessment schedule for each endpoint collected is described in Appendix 1.

2.1 PRIMARY EFFICACY ENDPOINT

ORR as estimated by binomial distribution.

2.2 SECONDARY ENDPOINT

TTR、DOR、PFS、OS and 6 months PFS rate and OS rate.

2.3 SAFETY ENDPOINT

Incidence rates of all adverse events (AE), treatment emergent adverse event (TEAE), adverse event of special interest(AESI) and serious adverse event (SAE), relationship to study treatment and severity. Changes in vital signs, physical exam and clinical laboratory evaluation before and after study treatment.

2.4 IMMUNOGENICITY ENDPOINT

Anti drug antibody (ADA) and neutralizing antibody (NAb) will be tested.

2.5 PHARMACODYNAMIC ENDPOINT

NA

2.6 QUALITY OF LIFE ENDPOINT

Qualifty of life will be evaluated by EQ 5D-5L and EORTC QLQ-C30 changen over time.

2.7 BIOMARKER ANALYSIS:

Biomarker samples will be collected to analyze PD-L1 expression in tumor tissues and RNA sequence and TILs.

Blood samples will be analyzed for peripheral blood EBV-DNA changes over time, immune cell changes, immune-related cytokine changes and correlation with efficacy.

3 Analysis Population

3.1 ANALYSIS SET

Analysis sets include Safety set (SS), full analysis set (FAS), per protocol set (PPS):

1) SS: Subjects receiving at least one dose of study treatment

2) FAS: Subjects receiving at least one dose of study treatment and with measurable disease at baseline. Subjects may be excluded if not satisfying ENKTL criteria by central pathological review.

3) PPS: Subset of FAS and without major protocol deviation nor use of prohibited medication nor poor compliance.

3.2 MAJOR PROTOCOL DEVIATION

Major protocol deviation is defined as deviation will have important impact on efficacy. In this study, deviations listed below are considered as major and subjects with major deviation will not be included in PPS:

- Do not meet major inclusion/exclusion criteria;
- Use of prohibited medication;
- Poor compliance (<80% or >120%, less than 2 cycles of treatment);
- Actual received treatment is different from being assigned.

Major protocol deviations will be reviewed at Blind Data Review Meeting (BDRM) and listed before database lock.

Major protocol deviation will be listed with detailed descriptions.

4 Data Handling Convention

4.1 GENERAL RULES

- **Observation Period Definition**

Observation period is defined as:

Screening period: from inform consent to first dose of study treatment.

On-treatment period: from first dose to last dose.

Treatment residual period: last dose +1 to last dose + 90 days.

Treatment emergent period include both on-treatment period and treatment residual period.

Post-treatment period: from last dose+91 days to end of study.

4.2 SPECIAL HANDLING OF EFFICACY DATA

NA

4.3 MISSING VALUE AND EXTREM VALUES

Missing of date variables: if the date is partial or incomplete, the imputation will be done based on the following rules following appropriate logic:

- if year, month and date are all missing, then do not impute;

- if month and date are missing, it will be assumed as July 1st with no conflict with other date variables;
- if dates are missing, it will be assumed as 15th with no conflict with other date variables;

- Original date collected from CRF will be shown in the listings.

• Missing data handling of other variables

Efficacy variables: All missing in the primary efficacy endpoints due to early withdrawal or lost follow up will be treated as "unable to evaluate ". In the calculation of time to event variables (e.g. PFS, DOR), subjects who have tumor evaluation missing after treatment will be reviewed to determine the time of censoring during data review meeting prior to database lock.

There will be no missing value imputation for baseline and safety data.

The extreme value of laboratory data identified as being caused by improper handling of specimens and blood samples will be replaced by unplanned visit data in the visit window (if available) as defined by the protocol. If these values cannot be replaced, they will be set as missing and be excluded from the analyses.

• Definition of baseline

The last non-missing data before first study drug administration will be defined as the baseline.

• Data derivation rules

Age (year) = (Informed Consent Date of Signature – Birth Date +1)/365.25, round to 1 decimal digits;

Course of first diagnosis (Day) = Informed Consent Date of Signature – Birth Date +1;

For efficacy related data derivation, see the sections which define efficacy endpoints.

- **Missing Relationship of AE to Study Treatment**

If relationship is missing, no imputation is made but will be considered as related.

- **Missing CTCAE grade**

Missing grade will not be imputed but will be counted in summary as grade ≥3 and will be listed separately.

- **Handling of Outliners**

NA

4.4 TIME WINDOWS

First dose date of the study treatment is defined as Day 1. Visit day definition: measurement date – first dose date +1; if measurement date is before first dose date, then visit day is defined as measurement date-first dose date.

All data will be analyzed according to flowchart and nominal visit name on eCR. No visit window will be applied.

Unscheduled visit will be used for baseline calculation. There will be no analysis over time for clinical laboratory evaluation, vital sign, ECG. Therefore no time window will be applied. Summary by all post-baseline results and worst post-baseline results will be analyzed.

4.5 STUDY CENTER EFFECT

NA

5 Statistical Methods

5.1 GENERAL RULES

All the statistical analyses will be performed with SAS 9.2 (or higher).

Unless otherwise stated, all TFLs will follow the rules below:

- Baseline value: last available data before first dose.
- Significant level and multiplicity adjustment: 5% two-sided level, no adjustment will be made.
- Summary statistics for continuous variables: N, mean, standard deviation, median, Q1, Q3, min and max.
- Categorical variables: number of subjects and percentage.
- Denominator in percentage calculation: unless otherwise specified, subjects with missing values will not be included. Number of subjects with missing value will be provided.

5.2 SUBJECT DISPOSITION

Subject Disposition

Number and percentage of subjects enrolled, treated, treatment continued after PD, early discontinuation of treatment will be summarized. The above information will also be summarized by study centers.

Listing will be provided for subject discontinued early.

In percentage calculation described above (except for screen failure and enrollment rate), denominators will be number of subjects receiving study treatment. In by center summary, number of subjects in each major category (screened, treated, discontinued, end of study, treated beyond PD, analysi population) will be provided.

Protocol Deviations

Summary will be provided for number and percentage of subjects with major protocol deviation. Listing will be provided for subjects with major protocol deviation and inclusion/exclusion criteria deviation.

5.3 DEMOGRAPHICS AND DISEASE CHRACTERISTICS

5.3.1 Demographics and Disease Characteristics

Demographics and disease Characteristics will be summarized in SS, FAS and PPS for the following variables:

- Age, Sex, Ethnicity
- Smoking history: smoking status, daily smoking quantity, duration of smoking, time since ceasing smoking
- Allergy history: percentage of subjects with allergy history and allergy type
- Baseline height, weight, BMI, BSA
- Baseline vital signs SBP,DBP,pulse, temperature, respiratory
- Baseline ECOGS PS
- Baseline physical exam: N and percentage for each exam item
- Baseline virology exam and HBV, HBV DNA, HCV RNA
- Baseline anti-auto antibody

5.3.2 Medical History

- **Disease Diagnosis**
- Cancer related disease history: including time since first diagnose, disease stage, pathological stage, disease range, histological subtype.
- Anti-cancer therapy history: History of anti-cancer systemic therapy (number of chemotherapy regimens, treatment cycles, treatment type, best response), history of anti-cancer radiotherapy (site of radiotherapy, total dosage, treatment type and best response) and other therapies (treatment, best response)

- Baseline target lesion number and non-target lesion numbers, locations, sum of diameters

Following variables will be summarized by descriptive statistics: Disease duration=date of inform consent-earlier time between initial diagnosis and start of prior therapy+1

- **Other Medical History**

The disease will be coded according to the MedDRA term, and the proportion of subjects with each disease will be summarized according to the preferred term (PT), including: prior disease recovered: A disease that has been cured in a medical history, onging disease: a disease no cured, a disease undergoing treatment: a disease undergoing medical treatment.

- **Prior and Concomitant Medication (other than anti-cancer)**

Prior and concomitant medications will be coded using The World Health Organization Drug Dictionary (WHODD) and will be summarized by Anatomical Therapeutic Chemical (ATC) class 1, 2, 4 and preferred name (PN). One subject is only counted once for each corresponding category/PN.

Prior medications: medications which started and stopped prior to the first dose of study medication, stop date – date of first dose of study medication < 0;

Concomitant medications: start date – date of first dose of study medication < 0, and (start date-date of last dose+90)>=0 and stop date – date of first dose of study medication >= 0;

New concomitant medications: medications newly added or changed during the study period, start date – end date of first dose of study medication >= 0 and (start date-date of last dose+90)>=0.

Post study medications: medications started after last dose of study treatment+90 days.

If the start date is missing, the medication will be considered as “concomitant medication”, unless the stop date is non-missing and the stop date is prior to date of first dose of study medication

5.4 TREATMENT EXPOSURE AND COMPLIANCE

In SS, summarize exposure of study treatment.

5.4.1 Treatment Exposure

Summary of treatment exposure includes duration of exposure, number of cycles completed and total dose.

- **Duration of Exposure**

Duration of exposure (days)=last dose date-first dosedate+21.

- **Dosage**

Following variables are summarized descriptively:

- Total dose(mg)=total dose received during the study
- Average dose per cycle(mg) = actual total dose received/(duration of exposure in days /21)

5.5 EFFICACY ANALYSIS

Efficacy analyses will be based on FAS and PP. A sensitivity analysis based on all enrolled subjects may also be conducted. The efficacy analysis will be based on Lugano 2014.

5.5.1 Primary Analysis

The ORR is defined as the proportion of subjects with CR or PR as Best Overall Response (BOR).

$$ORR = \frac{CR + PR}{\text{Total Number of Subjects}} *100\%$$

For ORR, the point estimate and 95% confidence interval will be provided using exact binomial distribution.

5.5.2 Secondary Analysis

DCR

$DCR = \frac{CR + PR + SD}{\text{Total Number of Subjects}} *100\%$, and 95% CI will be calculated using binomial distribution.

PFS

PFS: the time from the date of the first dose to the date of first disease progression (imaging), if subjects died due to any reason prior to disease progression, PFS is defined as the time from the date of the first dose to the date of death. Subjects who did not die or had disease progressed will be censored on the date of the last imaging assessment date. Subjects with no post-baseline imaging assessment will be censored on the date of the first dose of study medication. Subjects treated with other anti-cancer therapy before PD will be censored at last non-missing tumor assessment date before starting of the new anti-cancer therapy.

Kaplan-Meier method will be used for the analysis of PFS to evaluate the median PFS (mPFS), PFS rate at 6 month and at 1 year, and its 95% CI and the survival curves will be provided accordingly.

DOR

For subjects with complete response or partial response, the duration of response is defined as the time from the date of first response to the date of disease progression or death whichever is earlier, and subjects with no disease progression or death will be censored on the date of the last imaging assessment.

Kaplan-Meier method will be used for the analysis of DOR to evaluate the median DOR and its 95% CI and the survival curves will be provided accordingly.

TTR

For subjects with complete response or partial response, the time to response is defined as time from the date of first dose to the date of the first objective response.

Kaplan-Meier method will be used for the analysis of TTR to evaluate the median TTR and its 95% CI and the survival curves will be provided accordingly.

5.5.3 Subgroup Analysis

Subgroup analysis will be conducted for subgroups including PD-L1 expression, EBV, LDH, B symptom.

5.5.4 Exploratory Analysis

Correlation between gene related cancer immunity and effiacay will be explored.

5.6 SAFETY ANALYSIS

Safety analysis will be conducted in safety set.

5.6.1 Adverse Events

All adverse events will be coded using MedDRA dictionary for lower level term (LLT), preferred term (PT), high level term (HLT), high level group term(HLGT) and system organ class(SOC). AE

reporting period will be further defined based on onset date/becoming serious/becoming more severe as:

- Pre-treatment AE: AE occurs/becomes serious/becomes more severe before first dose of treatment and after inform consent.

- Treatment-emergent AE: AE occurs/becomes serious/becomes more severe on or after date of first dose of treatment up to last dose of study treatment+90 days

- Post treatment AE: AE occurs/becomes serious/becomes more severe on or after date of last dose of study treatment+91 days

If onset date of AE is missing or partial missing, determination of AE reporting period will be based on rules in Section 4.3.

- **Overview of adverse event**

Listing will be provided for pre-treatment and post-treatment AE.

Number and percentage of subjects who experience AE and event frequency will be summarized for:

- Treatment emergent period

  - TEAE
  - Treatment related AE(TRAE)
  - Serious AE (TESAE)
  - AE leading to death
  - TRSAE
  - TRAE leading to death
  - TEAE leading to treatment discontinuation
  - TRAE leading to treatment discontinuation
  - Important AE (Chinese regulator specific requirement only)
  - Immune-related AE(irAE)

Unless otherwise stated, SOC/PT summary will be sorted according to descending order of frequency.

- **TEAE analysis**

Number and percentage of sunjects with AE will be summarized by:

  - SOC and PT and by highest CTCAE grade for TEAE

- SOC and PT and by highest CTCAE grade for TRAE
- SOC and PT and by highest CTCAE grade for TEAE leading to treatment discontinuation
- SOC and PT and by highest CTCAE grade for TRAE leading to treatment discontinuation
- SOC and PT and by highest CTCAE grade for important AE (Chinese regulator specific requirement only)
- PT for TESAE
- PT for infusion-related reactions(IRR)

- **Immune-related treatment emergent AE and AE of special interest**

Immune-related treatment emergent AE:

IBI308 mechanism of action includes T-cell activitaion and proliferation. It may cause overactivation of immune system, which leads to systemic immune disorders. In Other immune checkpoint inhibitors (ipilimumab, nivolumab, pembrolizumab and atezolizumab) clinical data, AEs such as immune-mediated pneumonitis, diarrhea/colitis adrenal insufficiency, rash, hepatitis, endocrines disorders and peripheral neuropathy have been observed. In this study, once a subject has above AE occurring, investigators should monitor subjects's status and take proper diagnosis actions. If no alternaive causes (such as disease progression, concomitant medication, other infection) and corticosteroid/other immune suppressant treatments are needed to treat the condition (except for related endocrine disorders such hypo/hyperthyroidism, hypophysitis, type 1 diabetes, adrenal insufficiency, which may not be given this treatment), the corresponding AE should be considered as potentially immune related.

AE of special interest:

AE of special interest (AESI) is defined as AE requiring special attention to understand the safety profile of the investigational product. A non-serious AE can also be considered as AESI.

AESI of this study include:

- IRR of grade 3 and above
- Diarrhea, colitis, uveitis, intestinal pneumonitis of grade 2 and above
- Suspected irAE of grade 3 and above

Number and percentage of subjects experiencing treatment emergent irAE and AESI will be summarized.

In above summaries, a subject will only be counted once accoding to the highest CTCAE grade and/or seriousness for each SOC or PT.

An AE with causilty reported as related, possibly related or missing/undetermined will be counted as treatment related. Handling of missing seriousness and CTCAE grade can be found in Section 4.3.

- **Death**

Death during the study will be listed.

Listing of AE will include all AE, SAE, TRAE, TEAE leading to treatment discontinuation, irAE and AESI. Treatment emergent flag will be provided.

5.6.2 Clinical Laboratory Evaluation

Clinical laboratory evaluation includes hematological exam, blood chemistry, urine test. Local lab is used in this study and results will be analyzed and reported using international standard unit. Invalid resultsif marked will not be included in the analysis. Non-protocol specified laboratory test or test out of study center will not be included in the summary analysis. If abnormal is observed, AE will be reported.

Laboratory results will be summarized as normal, abnormal low, abnormal high according to normal range of each center. Abnormal values will also be reported by investigators as clinically significant or not. If "<", "<=", ">" or ">=" limit of quantitation, limit of quantitation will be used for summary statistics. Original results will be displayed in listing.

In SS, by visit descriptive summary will be provided for quantitative clinical laboratory evaluation. For qualitative evaluations, shift summary of change from baseline will be provided based on normal/abnormal status and clinically significant/not clinically significant status.

Listing will be provided for clinical laboratory evaluation results. Virology and (or) pregnancy exam will be listed separately.

5.6.3 Vital Sign

Vital signs will be summarized by visit for absolute values and changes from baseline usingdescriptive statistics.

Shift table of normal/abnormal status from baseline to post-baseline will also be provided.

Listing will be provided for vital sign results.

5.6.4 ECG

Worst post baseline QTc will be summaried according to ≤450ms, >450-480ms, >480-500ms, >500ms categories and increase from baseline by≤30ms, >30-60ms, >60ms. On-treatment period is defined as the period from first dose of study treatment until the last dose of study treatment +90 days including both scheduled and unscheduled visits and repeated visits.

Listing will also be provided ECG results.

5.6.5 Other safety measurements

Listing will be provided for physical exam and ECOG.

5.7 IMMUNOGENECITY ANALYSIS

Immunogenicity is evaluated by ADA and NAb positive rates. Analyses of immunogenicity in SS include:

Baseline ADA/Nab positive rate and number of positive subjects

Post-baseline ADA/Nab positive rate and number of positive subjects at each timepoint

Further summary of post-baseline data by baseline status

Number and percentage of subjects with persistent/transient post-baseline positive ADA/NAb
Listing will also be provided for ADA titre values. Only subjects with at least one non-missing post-baseline ADA result will be included in post-baseline positive rate calculation.

5.8 PD/BIOMARKER ANALYSIS

A separate analysis plan will be provided.

5.9 QUALITY OF LIFE

The EORTC QLQ-C30 is a core questionnaire for patients with cancer consisting of 30 items which are divided into 15 scales: 5 functional scales (physical, role, cognitive, emotional, and social function), 3 symptom scales (fatigue, pain, and nausea/vomiting), 1 global health status/quality of life scale, and 6 single item scales. The value of EORTC QLQ-C30 score is between 0 and 100.

Definition of EORTC QLQ-C30 dimensions:

	Numbers of Items	**Item Range**	**Item numbers**
Overall health and Quality of Life	2	6	29, 30
Function dimension			
Physical function	5	3	1~5
Role function	2	3	6, 7
Emotional function	4	3	21~24
Cognitive function	2	3	20, 25
Social function	2	3	26, 27
Symptom dimension			

Weak	3	3	10, 12, 18
Nauseated and vomited	2	3	14, 15
Pain	2	3	9, 19
Short of breath	1	3	8
Poor sleep	1	3	11
Lacked appetite	1	3	13
Constipated	1	3	16
Diarrhea	1	3	17
Financial difficulties	1	3	28

Raw Score (RS) is the mean of each term, RS = (I1+I2+ ……+In) /n. Missing items are excluded from the calculation of the mean.

Function dimension: Score=$\left(1-\frac{RS-1}{range}\right)\times 100$.

For change from baseline, descriptive summary will be used.

5.10 INTERIM ANALYSIS AND DATA MONITORING COMMITTEE

No interim analysis planned.

6 References:

1 NMPA guidance on good clinical practice 2013
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3 NMPA guidance on statistical principles in clinical tirals, Mar 2016 .
4 ICH. *ICH E9 Guideline: Statistical Principles for Clinical Trials*, 1998. Available at https://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E9/Step4/E9_Guideline.pdf
5 ICH. *ICH E3 Guideline: Structure and Content of Clinical Study Reports Questions & Answers*, 2012. Available at http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E3/E3_QAs_R1_Step4.pdf

APPENDICES

APPENDIX 1 FLOWCHART

TABLE 1. Schedule of Visits

Phase	Screening	Treatment						End-of-Treatment Visit [22]	Safety Follow-Up	Survival Follow-up [23]
		Cycle 1	Cycle 2	Cycle 3	Cycle 4	Cycle 5	Cycle 6–N			
Visit	1	2	3	4	5	6	7 ~ N	Premature discontinuation/end-of-treatment visit		
Day	-28~-1	Day 1	Day 22 (±3 days)	Day 43 (±3 days)	Day 64 (±3 days)	Day 85 (±3 days)	Q3W (±3 days)		since the last dose 90 days (± 7 days)	after safety follow-up Q60D (±7 days)
General Study Procedures										
Written ICF [1]	X									
Inclusion/Exclusion Criteria	X									
Demographics /History / Previous Medication [2]	X									
Vital Signs [3]	X	X	X	X	X	X	X	X	X	
Weight/Height [4]	X							X		
Physical Examination	X		X	X	X	X	X	X		
ECOG PS Score	X	X	X	X	X	X	X	X		
12-Lead ECG [5]	X			X		X	X	X		
Count of Whole Blood	X		X	X	X	X	X	X	X	

Phase	Screening	Treatment						End-of-Treatment Visit [22]	Safety Follow-Up	Survival Follow-up [23]
		Cycle 1	Cycle 2	Cycle 3	Cycle 4	Cycle 5	Cycle 6–N			
Visit	1	2	3	4	5	6	7 ~ N	Premature discontinuation/end-of-treatment visit		
Day	-28~-1	Day 1	Day 22 (±3 days)	Day 43 (±3 days)	Day 64 (±3 days)	Day 85 (±3 days)	Q3W (±3 days)		since the last dose 90 days (± 7 days)	after safety follow-up Q60D (±7 days)
Cells / Blood Biochemistry / Routine Urinalysis [6]										
Pregnancy Test [7]	X							X		
Thyroid Function [8]	X		X	X	X	X	X	X	X	
Immunogenicity [9]		X	X		X				X	
EBV-DNA[10]		X	X	X	X	X	X	X		
HIV, HBV and HCV[11]	X									
AE Evaluation [12]	X	X	X	X	X	X	X	X	X	X
Concomitant Medication	X	X	X	X	X	X	X	X	X	X
Efficacy Evaluation										
Bone Marrow Biopsy [13]	X									

Phase	Screening	Treatment						End-of-Treatment Visit [22]	Safety Follow-Up	Survival Follow-up [23]
		Cycle 1	Cycle 2	Cycle 3	Cycle 4	Cycle 5	Cycle 6–N			
Visit	1	2	3	4	5	6	7 ~ N	Premature discontinuation/end-of-treatment visit		
Day	-28~-1	Day 1	Day 22 (±3 days)	Day 43 (±3 days)	Day 64 (±3 days)	Day 85 (±3 days)	Q3W (±3 days)		since the last dose 90 days (± 7 days)	after safety follow-up Q60D (±7 days)
Tumor Biopsy [14]										
CT/MRI Evaluation [15]	X						X			
PET-CT[16]	X			X			X	X		
Disease-Related Symptom Evaluation [17]		X	X	X	X	X	X	X		
Investigational Drug Infusion										
IBI308[18]		X	X	X	X	X	X			
Quality of Life Evaluation										
EQ-5D-5L/ EORTC QLQ-C30 [19]		X		X			X	X		
Biomarker Study										
Archival/Fresh Tumor Tissue Sample [20]	X									

Phase	Screening	Treatment						End-of-Treatment Visit [22]	Safety Follow-Up	Survival Follow-up [23]
		Cycle 1	Cycle 2	Cycle 3	Cycle 4	Cycle 5	Cycle 6–N			
Visit	1	2	3	4	5	6	7 ~ N	Premature discontinuation/end-of-treatment visit		
Day	-28~-1	Day 1	Day 22 (±3 days)	Day 43 (±3 days)	Day 64 (±3 days)	Day 85 (±3 days)	Q3W (±3 days)		since the last dose 90 days (± 7 days)	after safety follow-up Q60D (±7 days)
Peripheral Blood Sample [21]	X			X			X			

Note:

1. ICFs shall be signed by subjects prior to any procedures outlined in the protocol.
2. Previous medications: treatment for the initial diagnosis, including chemotherapy, radiotherapy, and surgery.
3. Vital signs: body temperature, pulse, respiratory rate, and blood pressure.
4. Screening: weight and height; end-of-treatment visit: weight.
5. 12-lead ECG schedule: during screening, prior to administration every other cycle, and during the end-of-treatment visit.
6. Count of whole blood cells: RBC, HGB, white blood cell (WBC), PLT, WBC differentials [lymphocyte (LYM), ANC]. Blood biochemistry include: hepatic function [TBIL, ALT, AST, γ-glutamyltransferase (γ-GT), alkaline phosphatase (ALP), albumin (ALB), total protein (TP), and lactic dehydrogenase (LDH)], renal function [(blood urea nitrogen (BUN) and Cr)], electrolytes (Na, K, Cl, Mg, Ca, and P), lipase, amylase, and fasting blood glucose (FBG). Routine urinalysis: pH, urinary albumin (UALB), urine protein (UPRO), urine red blood cell (URBC), and urine glucose (UGLU). The tests will be conducted within 7 days prior to the first dose of the investigational drug, within 3 days prior to the administration of the investigational drug from Cycle 2 onwards, and during safety follow-up. Tests shall be performed at the study sites.
7. Women of childbearing potential shall undergo urine or blood pregnancy test within 3 days prior to the first dose and during the end-of-treatment visit. If the urine pregnancy test is not conclusive, then blood pregnancy test shall be performed. The conclusion shall be based on the blood pregnancy test. Tests shall be performed at the study sites.
8. T3, T4, free thiiodothronine (FT3), free thiiodothronine (FT4), and TSH shall be tested during screening, prior to the administration of the investigational drug from Cycle 2 onwards, and during safety follow-up. Tests shall be performed at the study sites.
9. Immunogenicity assays will be carried out within 1 hour prior to IBI308 administration in Cycles 1, 2, 4 and then every 4 cycles thereafter (Cycle 8, 12, 16, and so on), and during safety follow-up. Tests shall be conducted at the central laboratory.
10. EBV DNA shall be tested on the day of IBI308 administration in each cycle, with 4 mL of blood collected each time, until the end of study treatment. Tests shall be conducted at the central laboratory. The investigator may add EBV-DNA testing at the study sites according to the efficacy assessment result.
11. Hepatitis B panel (HBsAg, HBsAB, HBcAB, HBeAg, and HBeAb), HCV antibody, and HIV antibody will be tested during screening. If the result shows HBsAg positive, then HBV DNA test shall be further conducted; if the result shows HCV antibody positive, then HCV RNA test shall be further conducted. For HBV DNA-positive subjects or HBV carriers, HBV

activity shall be monitored regularly, and prophylactic antiviral therapy is suggested to be performed according to the treatment guidelines for chronic hepatitis B during the trial. Tests shall be performed at the study sites.

12. AE and laboratory safety evaluation are performed according to NCI CTCAE v4.03. Refer to Section 7 for AE and SAE definitions, recording, determination of causal relationship, severity, reporting deadlines, and processing.
13. Subjects with positive bone marrow biopsy at baseline shall repeat the biopsy if a CR by imaging is achieved during the treatment (shall be completed within 2 weeks after imaging evaluation).
14. Tumor biopsy: The investigator may decide whether a biopsy is needed to confirm the results of an imaging evaluation during the study.
15. CT/MRI evaluation: contrast-enhanced CT will be used (MRI will be performed for subjects allergic to CT contrast media). Contrast-enhanced CT shall be performed at baseline, week 24 (± 7 days), every 12 weeks (± 14 days) after 24 weeks, and every 24 weeks (± 14 days) after 48 weeks or when it is needed during the study until initiation of new anti-tumor therapy, PD, withdrawal of ICF, or death.
16. PET-CT evaluation: PET-CT shall be performed at baseline, week 6 (± 7 days), week 15 (± 7 days), and week 24 (± 7 days) or when it is needed during the study. PET-CT evaluation shall be performed at the end of treatment for subjects who discontinue the treatment prematurely prior to week 24.
17. Disease-related symptom (including fever, night sweats, weight loss) evaluation shall be performed prior to administration in each cycle.
18. IBI308 200mg IV Q3W until PD, death, intolerable toxicity, withdrawal of ICF, or other reasons stated in the protocol up to 24 month. For subjects who develop PD for the first time and are clinically stable, the investigator can continue treatment until further PD, death, intolerable toxicity, withdrawal of ICF, or other reasons stated in the protocol up to 24 month.
19. Quality of life evaluation will be performed on the day of the first dose, during each imaging evaluation, and during the end-of-treatment visit as per EQ 5D-5L and EORTC QLQ-C30.
20. All the eligible subjects must provide archival tumor tissue at baseline or 8–10 unstained sections (4–5 μm) of fresh samples during screening for evaluations of PD-L1 expression and TIL. Tests shall be conducted at the central laboratory.
21. Ten mL whole blood samples are required to be provided by subjects for molecular tumor testing at the following time points: prior to the first dose, during efficacy evaluation but before the next treatment, and when PD is confirmed.
22. Treatment discontinuation: treatment discontinuation includes premature discontinuation (treatment discontinuation for reasons other than PD) and end of treatment (treatment discontinuation due to PD). The end-of-treatment visit shall be conducted when treatment is discontinued.
23. Survival follow-up: once Q60D (± 7 days) after the safety follow-up. Telephone visits is allowed.