Clinical Protocol

Study Title:	A Multicenter, Single Arm, Phase II Clinical Trial Evaluating the Efficacy and Safety of IBI308 Monotherapy for the Treatment of Relapsed or Refractory Extranodal NK/T-Cell Lymphoma, Nasal Type (ORIENT-4)
Protocol Number:	CIBI308D201
Version and Date:	July 8, 2019, Version 2.0
Product Name:	IBI308
Study Phase:	II
Sponsor:	Innovent Biologics (Suzhou) Co., Ltd. Room 201, Building C14, BioBay, No. 218 Xinghu Street, Suzhou Industrial Park, Suzhou, China
Sponsor Contact Information:	**Zhou Hui**, **Vice President, Medical Sciences and Strategic Oncology** + 86 021-31652896 hui.zhou@innoventbio.com

Protocol Synopsis

Protocol Number	CIBI308D201
Sponsor	Innovent Biologics (Suzhou) Co., Ltd.
Investigational Drug	IBI308
Active Ingredient	Recombinant fully human anti-PD-1 monoclonal antibody
Study Title	A Multicenter, Single Arm, Phase II Clinical Trial Evaluating the Efficacy and Safety of IBI308 Monotherapy for the Treatment of Relapsed or Refractory Extranodal NK/T-Cell Lymphoma, Nasal Type (ORIENT-4)
Trial Phase	II
Study Duration	Approximately 30 months
Study Objectives	Primary Objective: ● To evaluate the objective response rate (ORR) of IBI308 monotherapy for the treatment of relapsed or refractory extranodal natural killer (NK)/T-cell lymphoma, nasal type (ENKTL-NT). Secondary Objectives: ● To evaluate the complete response (CR) and partial response (PR) of IBI308 monotherapy for the treatment of relapsed or refractory ENKTL-NT; ● To evaluate the disease control rate (DCR) of IBI308 monotherapy for the treatment of relapsed or refractory ENKTL-NT; ● To evaluate the time to response (TTR) of IBI308 monotherapy for the treatment of relapsed or refractory ENKTL-NT; ● To evaluate the duration of response (DoR) of IBI308 monotherapy for the treatment of relapsed or refractory ENKTL-NT; ● To evaluate the progression-free survival (PFS) and 6-month PFS of IBI308 monotherapy for the treatment of relapsed or refractory ENKTL-NT;

	● To evaluate the overall survival (OS) and 6-month overall survival rate (OSR) of IBI308 monotherapy for the treatment of relapsed or refractory ENKTL-NT; ● To evaluate the safety of IBI308 monotherapy for 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). Exploratory Objectives: ● To evaluate the PD-L1 expression, number of tumor-infiltrating lymphocytes (TIL) in tissue samples of subjects with relapsed or refractory ENKTL-NT, RNA expression, dynamic changes in Epstein-Barr virus (EBV), DNA copy number in plasma and peripheral blood lymphocytes, immune cell phenotyping, and association between immune-related cytokines and efficacy of anti-PD-1 treatment.
Study Design	This is a multicenter, single-arm, phase II clinical trial evaluating the efficacy and safety of IBI308 monotherapy for the treatment of relapsed or refractory ENKTL-NT. Patients with relapsed or refractory ENKTL-NT will be enrolled to receive IBI308 200mg IV Q3W up to 24 months until progressive disease (PD), death, intolerable toxicity, withdrawal of ICF, or other reasons stated in the protocol. For subjects who develop PD for the first time and are clinically stable, the investigator can continue treatment up to 24 months until further PD, death, intolerable toxicity, withdrawal of ICF, or other reasons stated in the protocol.

	The primary endpoint is ORR, defined as the proportion of subjects who either experience CR or PR as the best overall response based on imaging evaluation. The primary endpoint will be analyzed after the last statistical and radiological evaluable subject completes a maximum of 24 weeks of follow-up. The tumor assessment is according to the Recommendations for Initial Evaluating, Staging, and Response Assessment of Hodgkin and non-Hodgkin Lymphoma: the Lugano Classification (Lugano 2014 Criteria) (see Appendix 3) as the evaluation criteria and then International Working Group (IWG) 2007 Criteria (see Appendix 4) after 24 weeks. The safety follow-up will be performed until 90 days after the last dose.
Inclusion Criteria	1. Histologically confirmed ENKL-NT. 2. Relapsed or refractory ENKTL-NT. Being relapsed is defined as presence of new lesions at the primary location or other sites after achieving CR; being refractory is defined as any one of the followings: PD after 2 treatment cycles, PR not achieved after 4 treatment cycles, or CR not achieved after 6 treatment cycles. Patients who do not response or patients with relapsed disease or PD after autologous stem cell transplantation can enroll. 3. Must have been treated with asparaginase-based regimen (radiotherapy must be performed for stage I/II disease). 4. Long axis of a lesion > 15 mm or ^{18}FDG-PET uptake by lesion. 5. Eastern Cooperative Oncology Group Performance Status (ECOG PS) scores of 0–2. 6. Signed the inform consent form (ICF) and able to comply with the scheduled follow-up visits and related procedures required in the protocol. 7. Between the ages of ≥18 to ⩽70 years. 8. Life expectancy⩾ 12 weeks.

	9. Patients (female patients at childbearing age or male patients whose partners are at childbearing age) must take effective contraceptive measures during the entire course of the trial and within 90 days since the last dose of treatment (see Section 4.3). 10. Adequate organs and bone marrow functions, as defined below: ● Count of whole blood cells: absolute neutrophil count (ANC) ⩾ 1.0×10^9/L, platelets (PLTs) count ⩾ 50×10^9/L, hemoglobin (HGB) ⩾ 8.0 g/L; granulocyte colony-stimulating factor, PLT, or red blood cell (RBC) transfusion has not been performed within 7 days prior to the test. ● Hepatic function: total bilirubin (TBIL) ⩽ 1.5 ×upper limit of normal (ULN), alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ⩽ 2.5 ×ULN. ● Renal function:serum creatinine (Cr) ⩽ 1.5 ×ULN. ● Thyroid function: normal thyroid stimulating hormone (TSH) at baseline, or abnormal TSH at baseline with normal thiiodothronine (T3)/thiiodothronine (T4) and no symptoms.
Exclusion Criteria	1. Patients with aggressive NK cell leukemia. 2. Patients with primary or secondary central nervous system (CNS) lymphoma. 3. Patients with severe hemophagocytic syndrome at initial diagnosis of ENKTL-NT. 4. Patients with pulmonary great vessel invasion. 5. Previous exposure to any anti-PD-1, anti-PD-L1, or anti-CTLA-4 antibodies. 6. Enrolled in another interventional clinical study, unless only involved in an observational study (non-interventional) or in the follow-up phase of an interventional study.

	7. Received any investigational drug within 4 weeks prior to the first dose of study treatment. 8. The last dose of radiation or anti-tumor therapy (chemotherapy, targeted therapy or tumor embolization) was within 3 weeks prior to receiving the first dose of study treatment; the last dose of nitrosourea or mitomycin C treatment was within 6 weeks prior to receiving the first dose of study treatment. 9. Received immunosuppressants within 4 weeks prior to the first dose of study treatment, excluding local glucocorticoids administered by nasal, inhaled, or other topical routes, or systemic glucocorticoids of physiological doses (no more than 10 mg/day of prednisone or equivalents). 10. Received any live attenuated vaccine within 4 weeks prior to the first dose of study treatment, or is scheduled to receive live attenuated vaccine during the study period. 11. Received major surgery (craniotomy, thoracotomy, or laparotomy) within 4 weeks prior to the first dose of study treatment, or has unhealed wounds, ulcers, or fractures. 12. Active, known, or suspected autoimmune disease (see Appendix 6) or previous medical history of these diseases within 2 years (patients with vitiligo, psoriasis, alopecia, or Graves' disease not requiring systemic treatment, hypothyroidism only requiring thyroid replacement, or type I diabetes only requiring insulin can enroll). 13. Known history of primary immunodeficiency diseases. 14. Known active pulmonary tuberculosis. 15. Known history of allogeneic organ transplantation or allogeneic hem atopoietic stem cell transplantation. 16. Known to be allergic to any ingredients of monoclonal antibodies. 17. Uncontrolled concurrent diseases including but not limited to:

	● HIV-infected patients (positive anti-HIV antibody). ● Active or poorly controlled severe infections. ● Symptomatic congestive heart failure (NYHA Class III-IV) or symptomatic or poorly controlled arrhythmia. ● Uncontrolled hypertension (systolic blood pressure ⩾ 160 mmHg or diastolic blood pressure ⩾ 100 mmHg) despite of standard treatment. ● Any arterial thromboembolic events occurred within 6 months prior to enrollment, including myocardial infarction, unstable angina, cerebrovascular accident, or transient cerebral ischemic attack. ● Life-threatening hemorrhagic events or grade 3–4 gastrointestinal /variceal hemorrhage requiring blood transfusion, endoscopy, or surgical treatment within 3 months prior to enrollment. ● History of deep venous thrombosis, pulmonary embolism, or other serious thromboembolic events within 3 months prior to enrollment (implantable port or catheter-related thrombosis, or superficial venous thrombosis are not considered as serious thromboembolisms). ● Uncontrolled metabolic disorders, non-malignant organ or systemic diseases, or cancer-related secondary diseases that may lead to higher medical risks and/or survival evaluation uncertainties. ● Hepatic encephalopathy, hepatorenal syndrome, or cirrhosis with Child-Pugh grade B or C. ● Bowel obstruction or history of the following diseases: inflammatory bowel disease or extensive bowel resection (partial

	colectomy or extensive small bowel resection accompanied with chronic diarrhea), Crohn's disease, and ulcerative colitis. ● Acute or chronic diseases, psychiatric disorders, or laboratory abnormalities that may lead to the following consequences: increased investigational drug-related risks, or interference with interpreting trial results, and considered ineligible for participating in the trial by the investigators. 18. Known acute or chronic active hepatitis B (chronic HBV carriers or inactive HBsAg-positive patients can enroll if the HBV DNA < 1×10^3 copies/mL), or acute or chronic active hepatitis C (patients with negative HCV antibody can enroll; HCV RNA test is required for patients with positive HCV antibody, those test negative can enroll). 19. History of GI perforation and/or fistula without radical treatment within 6 months prior to the enrollment. 20. Known interstitial lung disease. 21. Clinically uncontrollable third spacing, such as pleural effusion and ascites that cannot be controlled by drainage or other methods prior to enrollment. 22. History of other primary malignant tumors, excluding: ● History of radical treatment for malignant tumors with no evidence of tumor recurrence for more than 5 years prior to enrollment and with a very low risk of recurrence. ● Adequately treated nonmelanoma skin cancer or lentigo maligna with no signs of disease recurrence. ● Adequately treated carcinoma in situ with no signs of disease recurrence. 23. Pregnant or breastfeeding female patients.
Investigational Drug, Strengths, and Administration	IBI308 100mg/10mL/vial 200 mg IV Q3W

Evaluation Criteria	**Efficacy evaluation:** ● Imaging evaluations will be performed based on Lugano 2014 Criteria (see Appendix 3) and IWG 2007 Criteria (see Appendix 4), evaluating the ORR, CR, PR, DCR, TTR, DoR, PFS, OS, 6-month PFS, and 6-month OS after treatment. **Safety evaluation:** ● Incidence, relationship with investigational drug, and severity of all adverse events (AEs), treatment-emergent adverse events (TEAEs), adverse events of special interest (AESIs), and serious adverse events (SAEs) will be evaluated. ● Changes in vital signs, physical examination, and laboratory tests results before, during, and after treatment will be evaluated. **Immunogenicity evaluation：** ● Detection of anti-drug antibodies (ADAs) and neutralizing antibodies (NAbs) will be performed. **Biomarker evaluation:** ● Tumor tissue samples will be collected for cancer biomarker analysis, including PD-L1 expression, RNA expression and number of TIL in tissue samples of subjects with ENKTL-NT. ● Blood samples will be collected for biomarker analysis, including dynamic changes in EBV DNA copy number in peripheral blood, immune cell phenotyping, and association between immune-related cytokines and efficacy of anti-PD-1 treatment. **Quality of life evaluation:** ● The quality of life and health status during IBI308 treatment will be evaluated based on EQ 5D-5L and EORTC QLQ-C30.
Statistics	**Sample size estimation:** This is a single-arm trial. The primary objective is to evaluate the efficacy

	of IBI308 monotherapy for the treatment of relapsed or refractory extranodal NK/T-Cell Lymphoma. 20-60 subjects will be enrolled. Assuming a null hypothesis of 30% ORR, α of 0.05 (two-sided), power of 80%, a 50% ORR after IBI308 treatment will be achieved and the minimum sample size will thus be 43. The sponsor will evaluate the safety data from the first 20 subjects to determine whether the study shall be discontinued prematurely due to safety concerns. Hypothesis for superiority: H0: ORR ≤ 30% H1: ORR > 30% The total α is set at 0.05 (two-sided), and the superiority is determined using confidence intervals (CIs). Interim analysis: One interim analysis is planned for this study. It will be conducted after the first 20 subjects have completed the protocol-specified treatment to evaluate the safety. Primary efficacy endpoint: ORR and the corresponding 1-α% CI is estimated using binomial distribution to test for superiority. Secondary efficacy endpoints: TTR, DoR, PFS, and OS will be estimated through the median values and the corresponding 95% CIs using the Kaplan-Meier method. PFS and 6-month PFS curves will be plotted. CR, PR, and DCR and the corresponding 95% CIs will be estimated using binomial distribution. Safety analysis:

	The incidence and severity of AEs will be summarized for each treatment arm, and the abnormal changes in laboratory measurements will be presented. Immunogenicity analysis: The positive rates of ADAs and NAbs will be summarized. Quality of life analysis: Data based on EQ-5D-5L and EORTC QLQ-C30 will be analyzed using descriptive statistics. Biomarker analysis: PD-L1 expression and number of TIL in tissue samples of subjects with relapsed or refractory ENKTL-NT, dynamic changes in EBV DNA copy number in plasma and peripheral blood lymphocytes, immune cell phenotyping, and association between immune-related cytokines and efficacy of anti-PD-1 treatment will be analyzed using descriptive statistics.

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 to -1	Day 1	Day 22 (±3 days)	Day 43 (±3 days)	Day 64 (±3 days)	Day 85 (±3 days)	Q3W (±3 days)		90 days (±7 days) since the last dose	Q60D (±7 days) after safety follow-up
General Study Procedures										
SignedICF[1]	X									
Inclusion/Exclusion Criteria	X									
Demographics/Medical 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 Cells/Blood Biochemistry/Routine Urinalysis[6]	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 to -1	Day 1	Day 22 (±3 days)	Day 43 (±3 days)	Day 64 (±3 days)	Day 85 (±3 days)	Q3W (±3 days)		90 days (±7 days) since the last dose	Q60D (±7 days) after safety follow-up
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									
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										

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 to -1	Day 1	Day 22 (±3 days)	Day 43 (±3 days)	Day 64 (±3 days)	Day 85 (±3 days)	Q3W (±3 days)		90 days (±7 days) since the last dose	Q60D (±7 days) after safety follow-up
EQ-5D-5L/ EORTC QLQ-C30[19]		X		X			X	X		
Biomarker Study										
Archival/Fresh Tumor Tissue Sample[20]	X									
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. According to the changes of patients' condition and the needs of efficacy evaluation, EBV DNA test may be added by investigators at the centre.
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, every 24 weeks (±14 days) after 48 weeks and when clinical need arises 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), week 24 (±7 days) , and when clinical need arises. 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. For subjects who develop PD for the first time and are clinically stable, the investigator can continue treatment up to 24 months until further PD, death, intolerable toxicity, withdrawal of ICF, or other reasons stated in the protocol.
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 biomarkers. 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.

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List of Tables

List of Abbreviations and Definitions

ADA	Anti-drug antibody
AE	Adverse event
AESI	Adverse event of special interest
ALB	Albumin
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
ANC	Absolute neutrophil count
APTT	Activated partial thromboplastin time
AST	Aspartate aminotransferase
AUC	Area under the curve
BASO	Basophil count
BUN	Blood urea nitrogen
CCr	Creatinine clearance
ENKTL	Extranodal natural killer/T-cell Lymphoma, nasal type
CHO	Chinese hamster ovary cell
CI	Confidence interval
C_{max}	Maximum observed concentration
Cr	Serum creatinine
CR	Complete response
CRO	Contract research organization
CRA	Clinical Research Associate
CSR	Clinical study report
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTLA-4	Cytotoxic T-lymphocyte antigen 4
DCR	Disease control rate
DLT	Dose-limiting toxicity
DoR	Duration of response
EBV	Epstein-Barr virus; human herpesvirus 4
EBER	Epstein-Barr virus Encoded RNA
EBNA1	Epstein-Barr virus nucleus antigen 1
EC	Ethics committee
ECG	Electrocardiogram
ECOG PS	Eastern Cooperative Oncology Group Performance Status

eCRF	Electronic case report form
EOS	Eosinophil count
EDC	Electronic data capture
ENKTL	Extranodal NK/T-celllymphoma
FAS	Full analysis set
FBG	Fasting blood glucose
FFPE	Formalin fixed paraffin-embedded
FT3	Free triiodothyronine
FT4	Free thyroxine
GCP	Good Clinical Practice
HBV	Hepatitis B virus
HCT	Hematocrit
HCV	Hepatitis C virus
HGB	Hemoglobin
HIV	Human immunodeficiency virus
HDACi	Histone deacetylase inhibitor
HDC	High dosage chemotherapy
ICF	Informed consent form
ICH	International Conference on Harmonization
IgG	Immunoglobulin G
INR	International normalized ratio
irAE	Immune-related adverse event
IRR	Infusion-related reaction
IV	Intravenous infusion
LDH	Lactate dehydrogenase
LYM	Lymphocyte count
LMP1	Latent membrane protein1
MedDRA	Medical Dictionary for Regulatory Activities
MONO	Monocyte count
mOS	Median overall survival
mPFS	Median progression-free survival
MTD	Maximum tolerated dose
NAb	Neutralizing antibody
NCI	National Cancer Institute
NHL	Non-Hodgkin lymphoma

NSCLC	Non-Small cell lung carcinoma
NOAEL	No-observed-adverse-effect level
NOEL	No-observed-effect level
ORR	Objective response rate
OS	Overall survival
PTCL	Peripheral T-cell lymphoma
PD	Progressive disease
PD-1	Programmed cell death-1
PD-L1	Programmed cell death ligand 1
PFS	Progression-free survival
pH	Potential of hydrogen
PK/PD	Pharmacokinetics/pharmacodynamics
PLT	Platelet
PPS	Per protocol set
PR	Partial response
PT	Preferred ter
Q2W	Every 2 weeks
Q3W	Every 3 weeks
RBC	Red blood cell
SAE	Serious adverse event
SAP	Statistical analysis plan
SCT	Sterm cell transplantation
SD	Stable disease
SOC	System organ classification
SS	Safety set
$t_{½}$	Half-life
T3	Triiodothyronine
T4	Thyroxine
TBIL	Total bilirubin
TEAE	Treatment-emergent adverse event
TGF	Tumor growth factor
TIL	Tumor infiltrating lymphocyte
TNFR	Tumor necrosis factor receptor
TP	Total protein
TSH	Thyroid stimulating hormone

TT	Thrombin time
TTR	Time to response
UALB	Urinary albumin
UGLU	Urine glucose
ULN	Upper Limit of Normal
UPRO	Urine protein
URBC	Urine red blood cell
VAS	Visual analogue scale
WBC	White blood cell
γ-GT	γ-glutamyltransferase

1 Background

1.1 Disease Background

Extranodal natural killer (NK)/T-cell lymphomas, nasal type (ENKTL-NT) is a subtype of peripheral T-cell lymphoma (PTCL) with a distinctive geographical distribution. The incidence is higher in Asia than in Europe and America (22% vs. 5% of all the PTCLs) [1]. In 2012, a multi-center analysis of pathological classification of 10002 lymphoma subjects in China showed that ENKTL-NT accounted for 6.6% of all the non-Hodgkin lymphomas (NHLs) and 28.1% of all the PTCLs [2]. The 5-year overall survival rate (OSR) is approximately 32%, and the median overall survival (OS) is around 8 months [3, 4].

The Epstein-Barr virus (EBV) is a known cause and contributing factor to ENKTL-NT. EBV infection is always present in ENKTL-NT cases. Epstein–Barr encoding region (EBER) in situ hybridization (EBV encoded RNA) has become a routine test for pathological diagnosis of ENKTL-NT [1]. Data indicate that positive-EBER and high EBV DNA copy numbers in peripheral blood ($> 6.1 \times 10^7$copies/mL) are associated with poor PTCL prognosis [5, 6] and high EBV DNA copy number ($> 10^5$copies/mL) indicates poor treatment efficacy [7]. EBV promotes the development of tumors by activating the STAT1 signaling pathway, inhibiting the TGFβ-1 signaling pathway, and up-regulating survivin with EBV nuclear antigen 1 (EBNA1), and the proliferation of tumors by activating NF-κB and MAPK signaling pathways with latent membrane protein 1 (LMP1) and tumor necrosis factor receptor (TNFR) [8, 9]. Immunotherapy is more suitable for lymphomas associated with EBV, possibly because these tumor cells express more EBV antigens that are recognized by $CD8^+$ T-cells [9].

PD-L1 positive expression is detected in approximately 70–75% and PD-1 in approximately 10–30% of all the ENKTL-NT patients. High PD-L1 expression suggests relative good prognosis of PTCL [10–13]. EBV can up-regulate PD-L1 expression on tumor cells, which results in immune tolerance. The main mechanisms are: 1. innate immunity: up-regulation of PD-1 by activating the NF-κB signaling pathway with LMP1 and continuously activating oncogenic pathways. This mechanism does not rely on inflammatory signals in the tumor microenvironment; 2. adaptive immunity: up-regulation of PD-L1 induced by tumor microenvironment or anti-inflammatory cytokines associated with viral infections such as IFN-γ. In vitro experiments have confirmed that PD-1 monoclonal antibody can restore the activity of T-cells inhibited by diffuse large B-cell lymphoma [14, 15]. In clinical practice, nivolumab has been approved by the US Food and Drug Administration (FDA) for the treatment of Hodgkin lymphoma (HL). High expression of PD-L1 is observed in HL due to the copy number amplification of 9p24.1(loci for PD-L1, PD-L2, and JAK2 genes) [16, 17]. The above studies provide theoretical bases for the inhibition of the PD-1/PD-L1 axis for the treatment of EBV-associated PTCL.

Anthracycline-based chemotherapies are not used in patients with ENKTL-NT due to the high expression of multidrug-resistant (MDR) P-glycoproteins. The objective response rate (ORR) and complete response (CR) of L‑ asparaginase‑ based regimen, SMILE or AspaMetDex, as first-line treatment for ENKTL-NT was 79–80% and 45–66%, respectively [18–20]. However, internationally there is currently no treatment recommendation for ENKTL-NT refractory to L-asparaginase-based regimens. Prognosis is extremely poor in these patients.

High-dose chemotherapy (HDC)/autologous or allogeneic hematopoietic stem cell transplantation (ASCT or HSCT) are currently used as first-line consolidation therapy or second-line salvage therapy. However, there is limited data. Some small sample size reports showed that the subjects with relapsed or refractory ENKTL-NT have a better long-term outcome after HDC/SCT, and sustained response can be achieved for 3–5 years [21, 22]. A retrospective study conducted by the NK-Cell Tumor Study Group showed that 7 of 15 subjects with ENKTL survived and achieved CR after HDT/ASCT [duration of response (DoR): 25+ to 87+ months]. However, 6 of these subjects died within 5 months after the transplantation [23]. Due to the low acceptance of transplant therapy and limited medical resources in China, few patients receive hematopoietic stem cell transplantation. Patients with relapsed or refractory ENKTL in China usually choose to continue with drug treatment.

There is currently no valid prospective clinical data in subjects with ENKTL-NT refractory to L-asparaginase. Guidelines have suggested combination chemotherapy replacing L-asparaginase with pegaspargase for refractory ENKTL-NT may be beneficial [1]. The DeVIC regimen, which is comprised of non-MDR agents, is also recommended in literature[24]. However, this regimen is currently used sequentially after radiation for early ENKTL-NT, and there is no data in advanced, relapsed/refractory ENKTL-NT. The efficacy of gemcitabine for the treatment of PTCL has received attention. Data from a Korean study with small sample size showed that regimens containing gemcitabine achieved an ORR of approximately 40% in subjects with ENKTL-NT, with 20% achieving CR and 20% partial response (PR) [25]. Other drugs such as histone deacetylase inhibitors (HDACi) and anti-CD30 monoclonal antibody have demonstrated efficacy in PTCL but have not been studied in ENKTL-NT treatment. Therefore, there is a significant clinical need to find an effective drug for patients with relapsed or refractory ENKTL-NT.

In Feb. 2017, Yok-Lam Kwong et al. published a small-sample-size study of pembrolizumab for the treatment of 7 subjects with NK/T-cell lymphoma refractory to L-asparaginase regimens in Blood. The ORR was 100%, with 5 cases of CR (71%, among which 2 had undetectable EBV) and 2 cases of PR (29%). The 5 subjects who achieved CR remained in response during a follow-up of 6 months. The treatment was well-tolerated, with only 1 subject developing a grade 2 skin reaction during the study [26]. Compared to other medications, the treatment of relapsed/refractory

NK/T-cell lymphoma with pembrolizumab was characterized by excellent efficacy and mild adverse reactions. On this basis, the investigator will continue to increase the number of subjects and other PTCL subtypes.

In summary, immunotherapy that inhibits the PD-1/PD-L1 axis is very likely to achieve good results in patients with relapsed or refractory ENKTL-NT. This study is thus conducted to evaluate the efficacy and safety of IBI308 in relapsed/refractory ENKTL-NT.

1.2 Investigational Drug (IBI308)

1.2.1 Mechanism of action

Immune checkpoints are a type of immune inhibitory molecules, whose physiological function is to regulate the the immune response, avoiding the damage and destruction of normal tissues. Cancer cells often use these immune checkpoints to avoid being attacked by immune cells. Currently, immune checkpoints CTLA-4 and PD-1/PD-L1 have been validated clinically. Immune checkpoint inhibitors that target PD-1/PD-L1 have better prospects for clinical applications due to better safety and a broader range of indications.

PD-1 is primarily expressed on activated T-cells and has two ligands, PD-L1 and PD-L2. PD-L1 is the main ligand that is expressed on activate T-cells, antigen-presenting cells, and tumor cells[19]. The binding of PD-1 with PD-L1 plays an important role in regulating the activation of T cells and maintaining peripheral immune tolerance. When T cells do not express PD-1, they interact with antigen-presenting cells to enable the activation and proliferation of T cells as well as the activation of cytokine secretion, which can kill the tumor cells. The activated T cells begin to express PD-1. After PD-1 binds to the ligand PD-L1 expressed on the surface of antigen-presenting cells or tumor cells, the inhibitory signal transmitted by PD-1 inhibits the proliferation of T cells and activates the secretion of cytokines, thus weakens the function of T cells. Most tumor cells evade the attack of immune cells through this mechanism. The activity and ability to kill cancer cells of T cells can be restored by blocking the PD-1/PD-L1 interaction with drugs [20].

The US FDA has currently approved 3 PD-1/PD-L1 products, namely, anti-PD-1 antibodies by BMS——nivolumab (brand name: OPDIVO), by Merck——pembrolizumab (brand name: KEYTRUDA), and by Genetech——atezolizumab (brand name: Tecentriq), indicated for advanced melanoma, advanced non-small-cell lung cancer, advanced ENKTL-NT, advanced renal cell carcinoma, urothelial carcinoma, and advanced head and neck cancer. In addition,

many indications have been in phase III clinical studies or have been submitted for approval. The approval of these drugs confirms the important role of PD-1/PD-L1 immune checkpoint inhibitors in cancer immunotherapy. There is no available PD-1/PD-L1 immune checkpoint inhibitors approved for marketing in China. It is of great significance to actively develop such inhibitors to provide better treatment options for domestic patients with advanced cancer.

Recombinant fully human anti-PD-1 monoclonal antibody (R&D code: IBI308) injection is a recombinant fully human IgG4 monoclonal antibody. Multiple preclinical in vitro trials have shown the blockade function of IBI308 of the PD-1 pathway, and the anti-tumor activity of murine analogs of IBI308 has also been indicated in various murine tumor models (refer to the Investigator's Brochure for details regarding study results). The preclinical study results demonstrate the promising use of IBI308 for PD-1 blockade.

1.2.2 Clinical study results

A phase Ia dose-escalation trial was initiated in Sep. 2016. Around 12–24 patients with advanced solid tumors who had failed standard treatment were enrolled. This dose escalation study used the standard "3 + 3" design to evaluate 4 dose levels (1 mg/kg, 3 mg/kg, 200 mg, and 10 mg/kg) of IBI308. After the completion of 1 mg/kg dose administration, subjects were randomized in a 1:1 ratio to either 3 mg/kg or 200 mg arm for independent evaluations. Dose-limiting toxicity (DLT) was observed for 28 days after the first dose for each dose arm. After completion of DLT observation, subjects were treated with IBI308 once Q2W (1 mg/kg, 3 mg/kg, or 10 mg/kg) or Q3W (200 mg) up to 24 months until progressive disease (PD), intolerable toxicity, withdrawal of ICF, or other reasons requiring treatment discontinuation (whichever occurs first).

Pharmacokinetic (PK) evaluation of IBI308 1 mg/kg was conducted in subjects with multiple tumors (n = 3). Preliminary results after a single-dose administration showed that IBI308 1 mg/kg reached the maximum drug exposure right after the completion of the single-dose infusion. The drug distribution was rapid after reaching the peak concentration, followed by a slow elimination ($t1/2 \approx 17.3$ d), which is the typical two-compartment PK characteristics of a monoclonal antibody. The elimination half-life is similar to the physiological half-life of IgG4.

The pharmacodynamic (PD) results showed that: a dosed of IBI308 1 mg/kg rapidly (24 h) saturated the peripheral PD-1 (95.8 ± 2.3%) and m aintained the receptor occupancy with decreasing concentrations throughout the study (28 d, C28d: 3.70 ± 0.15 μg/mL). It is estimated that the steady state can be reached after 84 days with 6 continuous doses of IBI308 1 mg/kg

administered Q2W. If there are no significant changes in drug clearance, the steady-state trough concentration will be around 13 μg/mL and the peripheral PD-1 receptor occupancy will be maintained.

Up to Apr. 16, 2017, the phase Ia study has enrolled 12 patients (3 for each cohort) in 4 treatment cohorts (1 mg/kg, 3 mg/kg, 200 mg, and 10mg), and evaluated the DLTs for each arm. No DLTs were observed. A total of 4 serious adverse events (SAEs) ⩾ grade 3 were observed in the phase Ia study, among which 3 cases of immune-related pneumonitis and lung infections are possibly related to the investigational drug.

1.3 Risk/Benefit Assessment

Considering the mechanism of action of IBI308 and the clinical safety information of products with similar mechanisms, the main adverse events (AEs) during this clinical trial will possibly be the immune-mediated inflammatory resulted from the activation of immune system, e.g. pneumonitis, colitis, hepatitis, renal insufficiency, and endocrine events. According to the available clinical data, anti-PD-1 monoclonal antibodies are well-tolerated despite of high incidence of adverse reactions. Treatment discontinuation due to adverse reactions only occur in a small number of subjects, and most events resolve after appropriate interventions. Early symptoms of immune-related adverse events (irAEs) vary. Therefore, investigators must closely monitor early signs and symptoms of irAEs during the trial, make correct judgments timely, adjust the dose according to Section 5.4 in the protocol, and provide effective treatment measures to reduce the subject risks. Besides, subjects with autoimmune diseases shall be excluded from the trial to avoid exacerbation of the original disease due to the activation of immune system.

Pharmacological and safety data from the phase Ia clinical trial showed that IBI308 is of clear pharmacological activity and good safety in subjects with advanced cancers.

The preliminary data of the above study show that IBI308 has good pharmacological activity and safety. Since other anti-PD-1 monoclonal antibodies have demonstrated significant efficacy in ENKTL-NT, it is reasonable to conduct a clinical study of IBI308 in Chinese patients with relapsed or refractory ENKTL-NT.

2 Study Objectives

2.1 Primary Objective

- To evaluate the ORR of IBI308 monotherapy for the treatment of relapsed or refractory ENKTL-NT.

2.2 Secondary Objectives

- To evaluate the CR and PR of IBI308 monotherapy for the treatment of relapsed or refractory ENKTL-NT;
- To evaluate the disease control rate (DCR) of IBI308 monotherapy for the treatment of relapsed or refractory ENKTL-NT;
- To evaluate the time to response (TTR) of IBI308 monotherapy for the treatment of relapsed or refractory ENKTL-NT;
- To evaluate the DoR of IBI308 monotherapy for the treatment of relapsed or refractory ENKTL-NT;
- To evaluate the progression-free survival (PFS) and 6-month PFS of IBI308 monotherapy for the treatment of relapsed or refractory ENKTL-NT;
- To evaluate the OS and 6-month OSR of IBI308 monotherapy for the treatment of relapsed or refractory ENKTL-NT;
- To evaluate the safety of IBI308 monotherapy for 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).

2.3 Exploratory Objectives:

- To evaluate the PD-L1 expression and number of tumor-infiltrating lymphocytes (TIL) in tissue samples of subjects with relapsed or refractory ENKTL-NT, RNA expression, dynamic changes in Epstein-Barr virus (EBV) DNA copy number in plasma and peripheral blood lymphocytes, immune cell phenotyping, and association between immune-related cytokines and efficacy of anti-PD-1 treatment.

3 Study Design

3.1 Overall Design

This is a multicenter, single-arm, phase II clinical trial evaluating the efficacy and safety of IBI308 monotherapy for the treatment of relapsed or refractory ENKTL-NT. Patients with relapsed or refractory ENKTL-NT will be enrolled to receive IBI308 200mg IV Q3W up to 24 months until PD, death, intolerable toxicity, withdrawal of ICF, or other reasons stated in the

protocol. For subjects who develop PD for the first time and are clinically stable, the investigator can continue treatment up to 24 months until further PD, death, intolerable toxicity, withdrawal of ICF, or other reasons stated in the protocol.

The primary endpoint is ORR, defined as the proportion of subjects who either experience CR or PR as the best overall response based on imaging evaluation. The primary endpoint will be analyzed after the last statistical and radiological evaluable subject completes a maximum of 24 weeks of follow-up. The tumor assessment is according to Lugano 2014 Criteria (see Appendix 3) and IWG 2007 Criteria after week 24 (see Appendix 4).

The safety follow-up will be performed until 90 days after the last dose.

3.2 Design Principles

3.2.1 Rationale for a single-arm design

It is recommended the DeVIC regimen, which is comprised of non-MDR agents [24], and sequential radiotherapy for the treatment of early ENKTL-NT. There is no data in advanced, relapsed/refractory ENKTL-NT. Data from a Korean study with small sample size showed that regimens containing gemcitabine achieved an ORR of approximately 40% in subjects with ENKTL-NT, with 20% achieving CR and 20% PR [25]. Other drugs such as HDACi and anti-CD30 monoclonal antibody have demonstrated efficacy in PTCL, but have not been used in ENKTL-NT treatment. Therefore, there is a significant clinical need to find an effective drug for patients with relapsed or refractory ENKTL-NT.

In Feb. 2017, Yok-Lam Kwong et al. published a small-sample-size study of pembrolizumab for the treatment of 7 subjects with NK/T-cell lymphoma refractory to L-asparaginase regimens in Blood. The ORR was 100%, with 5 cases of CR (71%, among which 2 had undetectable EBV) and 2 cases of PR (29%). The 5 subjects who achieved CR remained in response during a follow-up of 6 months. The treatment was well-tolerated, with only 1 subject developing a grade 2 skin reaction during the study [34]. Compared to other medications, the treatment of relapsed/refractory NK/T-cell lymphoma with pembrolizumab was characterized by excellent efficacy and mild adverse reactions. The data of the above studies indicate that anti-PD-1 monoclonal antibodies may have significant efficacy in patients with relapsed or refractory ENKTL-NT who have failed multiple lines of treatment and are better tolerated compared to other drugs. A single-arm design will be used because there is no standard treatment for relapsed/refractory ENKTL-NT in China.

3.2.2 Rationale for a treatment regimen of 200 mgQ3W

In this study，IBI308 will be administrated as 200 mg Q3W. This method of administration is used primarily due to the safety and exposure (concentration)-response (PD-1 receptor occupancy) correlation data from the ongoing phase I study (CII308A101) as well as the preclinical in vitro/in vivo PD comparisons with drugs of the same class.

In vivo PD studies involving SCID-Winn mice model and MC38 mice colon cancer model showed that the anti-tumor effect of IBI308 increased with dose, and IBI308 10 mg/kg significantly inhibited cancer growth. The human equivalent dose is 0.8 mg/kg. IBI308 1 mg/kg rapidly (24 h) saturated the peripheral PD-1 (95.8 ±2.3%) and maintained the receptor occupancy with decreasing concentrations throughout the study (28d, C28d: 3.70 ± 0.15 μg/mL). Tissue distribution of IBI308 in cynomolgus monkeys showed that IBI308 exposure in lungs, liver, colon, small intestine, lymph nodes were 3.5–1/10 of its serum concentration. Given there are no significant changes in drug clearance, it is estimated that steady state can be reached after 84 days with 6 continuous doses of IBI308 200 mg Q3W. The steady-state trough concentration would be around 26 μg/mL and peripheral PD-1 receptor occupancy would still be maintained. The above data support the use of IBI308 200 mg Q3W as the treatment regimen of this study.

3.2.3 Rationale for a primary endpoint analysis after the maximum of 24 weeks

There are currently no large-scale and long-term follow-up clinical trials evaluating PD-1/PD-L1 monoclonal antibodies for the treatment of ENKTL-NT. In the latest small-sample-size study of pembrolizumab for the treatment of 7 subjects with NK/T-cell lymphoma refractory to L-asparaginase regimens, the ORR was 100%, with 5 cases of CR remained in response during a follow-up of 6 months [26]. Therefore, it is expected that most ORR events will be observed if the primary endpoint analysis is conducted after the last subject has completed up to 24 weeks of treatment.

3.2.4 Rationale for choosing ORR as the primary endpoint

There are currently no similar large-scale clinical trials available for reference in China or abroad. The ORR is 40%, CR is approximately 20% [25], and 5-year OSR is around 32% in subjects with relapsed/refractory ENKTL-NT with monotherapy [3, 4]. Therefore, there is a significant clinical need to find an effective drug for patients with ENKTL-NT. There is only one small-sample-size study of pembrolizumab for the treatment of 7 subjects with NK/T-cell lymphoma refractory to L-asparaginase regimens. The ORR was 100%, with 5 cases of CR (71%,

among which 2 had undetectable EBV) and 2 cases of PR (29%). The 5 subjects who achieved CR remained in response during a follow-up of 6 months [26]. Since it is likely that IBI308 will yield similar results in the relapsed/refractory ENKTL subtype, ORR is chosen as the primary endpoint for this study.

3.2.5 Rationale for treatment after PD

Clinical data from approved products showed that a small number of subjects receiving immunotherapy may benefit clinically despite of preliminary evidence of PD (based on routine response criteria) prior to achieving objective response and/or stable disease [27, 28]. This phenomenon can be explained by two possibilities. First, increased inflammation in tumors may lead to increase of tumor volume, manifested as elevated measurable lesions and emergence of new, visible, non-measurable lesions. Over time, the malignant and inflammatory parts of the mass may shrink, resulting in significant imaging response and improvement in clinical signs. Second, in some patients, the initiation of anti-tumor immune response is slow, and tumor inhibition in the early stages is less than the tumor growth. Over time, anti-tumor activity will dominate, giving rise to imaging response and improvement in clinical signs. In Checkmate 205, a reduction in tumor burden after continuing treatment was observed in 6 of 9 cHL subjects with PD [27]. Response after pseudo-progression has also been seen in subjects with renal carcinoma during treatment with immune checkpoint inhibitors [28]. A small--sample-size study conducted at the University of Hong Kong involving pembrolizumab for the treatment of ENKTL-NT also had 1 subject who achieved CR after pseudo-progression [26]. Thus, subjects treated with IBI308 treatment may continue to receive the study treatment after being initially assessed to have PD by the investigator according to the Lugano 2014 Criteria, provided the subject is will benefit clinically and can tolerate the drug (see Section 5.1.2). Subjects must discontinue the study treatment if there are further evidence of PD.

4 Study Population

4.1 Inclusion Criteria

1. Histologically confirmed ENKL-NT.
2. Relapsed or refractory ENKTL-NT. Being relapsed is defined as presence of new lesions at the primary location or other sites after achieving CR; being refractory is defined as any one of the followings: PD after 2 treatment cycles, PR not achieved after 4 treatment cycles, or

CR not achieved after 6 treatment cycles. Patients who do not response or patients with relapsed disease or PD after autologous stem cell transplantation can enroll.

3. Must have been treated with asparaginase-based regimen (radiotherapy must be performed for stage I/II disease).
4. Long axis of a lesion > 15 mm or ^{18}FDG-PET uptake by lesion.
5. Eastern Cooperative Oncology Group Performance Status (ECOG PS) scores of 0–2.
6. Signed the ICFs and able to comply with the scheduled follow-up visits and related procedures required in the protocol.
7. Between the ages of ≥18 to ≤70 years.
8. Life expectancy ≥ 12 weeks.
9. Patients (female patients at childbearing age or male patients whose partners are at childbearing age) must take effective contraceptive measures during the entire course of the trial and within 90 days since the last dose of treatment (see Section 4.3).
10. Adequate organs and bone marrow functions, as defined below:
    - Count of whole blood cells: absolute neutrophil count (ANC) ≥ 1.0×10^9/L, platelets (PLTs) count ≥ 50×10^9/L, hemoglobin (HGB) ≥ 8.0 g/L; granulocyte colony-stimulating factor, PLT, or red blood cell (RBC) transfusion has not been performed within 7 days prior to the test.
    - Hepatic function: total bilirubin (TBIL) ≤ 1.5 × upper limit of normal (ULN), alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ≤ 2.5 ×ULN.
    - Renal function:serum creatinine (Cr) ≤ 1.5 ×ULN.
    - Thyroid function: normal thyroid stimulating hormone (TSH) at baseline, or abnormal TSH at baseline with normal T3/T4 and no symptoms.

4.2 Exclusion Criteria

1. Patients with aggressive NK cell leukemia.
2. Patients with primary or secondary central nervous system (CNS) lymphoma.
3. Patients with severe hemophagocytic syndrome at initial diagnosis of ENKTL-NT.
4. Patients with pulmonary great vessel invasion.
5. Previous exposure to any anti-PD-1, anti-PD-L1, or anti-CTLA-4 antibodies.

6. Enrolled in another interventional clinical study, unless only involved in an observational study (non-interventional) or in the follow-up phase of an interventional study.
7. Received any investigational drug within 4 weeks prior to the first dose of study treatment.
8. The last dose of radiation or anti-tumor therapy (chemotherapy, targeted therapy, or tumor embolization) was within 3 weeks prior to receiving the first dose of study treatment; the last dose of nitrosourea or mitomycin C treatment was within 6 weeks prior to receiving the first dose of study treatment.
9. Received immunosuppressants within 4 weeks prior to the first dose of study treatment, excluding local glucocorticoids administered by nasal, inhaled, or other topical routes, or systemic glucocorticoids of physiological doses (no more than 10 mg/day of prednisone or equivalents).
10. Received any live attenuated vaccine within 4 weeks prior to the first dose of study treatment, or is scheduled to receive live attenuated vaccine during the study period.
11. Received major surgery (craniotomy, thoracotomy, or laparotomy) within 4 weeks prior to the first dose of study treatment, or has unhealed wounds, ulcers, or fractures.
12. Active, known, or suspected autoimmune disease (see Appendix 6) or previous medical history of these diseases within 2 years (patients with vitiligo, psoriasis, alopecia, or Graves' disease not requiring systemic treatment, hypothyroidism only requiring thyroid replacement, or type I diabetes only requiring insulin can enroll).
13. Known history of primary immunodeficiency diseases.
14. Known active pulmonary tuberculosis.
15. Known history of allogeneic organ transplantation or allogeneic hematopoietic stem cell transplantation.
16. Known to be allergic to any ingredients of monoclonal antibodies.
17. Uncontrolled concurrent diseases including but not limited to:
    - HIV-infected patients (positive anti-HIV antibody).
    - Active or poorly controlled severe infections.
    - Symptomatic congestive heart failure (NYHA Class III-IV) or symptomatic or poorly controlled arrhythmia.
    - Uncontrolled hypertension (systolic blood pressure $\geqslant$ 160 mmHg or diastolic blood pressure $\geqslant$ 100 mmHg) despite of standard treatment.

- Any arterial thromboembolic events occurred within 6 months prior to enrollment, including myocardial infarction, unstable angina, cerebrovascular accident, or transient cerebral ischemic attack.
- Life-threatening hemorrhagic events or grade 3–4 gastrointestinal /variceal hem orrhage requiring blood transfusion, endoscopy, or surgical treatment within 3 months prior to enrollment.
- History of deep venous thrombosis, pulmonary embolism, or other serious thromboembolic events within 3 months prior to enrollment (implantable port or catheter-related thrombosis, or superficial venous thrombosis are not considered as serious thromboembolisms).
- Uncontrolled metabolic disorders, non-malignant organ or systemic diseases, or cancer-related secondary diseases that may lead to higher medical risks and/or survival evaluation uncertainties.
- Hepatic encephalopathy, hepatorenal syndrome, or cirrhosis with Child-Pugh grade B or C.
- Bowel obstruction or history of the following diseases: inflammatory bowel disease or extensive bowel resection (partial colectomy or extensive small bowel resection accompanied with chronic diarrhea), Crohn's disease, and ulcerative colitis.
- Acute or chronic diseases, psychiatric disorders, or laboratory abnormalities that may lead to the following consequences: increased investigational drug-related risks, or interference with interpreting trial results, and considered ineligible for participating in the trial by the investigators.

18. Known cute or chronic active hepatitis B (chronic HBV carriers or inactive HBsAg-positive patients can enroll if the HBV DNA $< 1 \times 10^3$ copies/mL), or acute or chronic active hepatitis C (patients with negative HCV antibody can enroll; HCV RNA test is required for patients with positive HCV antibody, those test negative can enroll).
19. History of GI perforation and/or fistula without radical treatment within 6 months prior to the enrollment.
20. Known interstitial lung disease.
21. Clinically uncontrollable third spacing, such as pleural effusion and ascites that cannot be controlled by drainage or other methods prior to enrollment.

22. History of other primary malignant tumors, excluding:
    - History of radical treatment for malignant tumors with no evidence of tumor recurrence for more than 5 years prior to enrollment and with a very low risk of recurrence;
    - Adequately treated nonmelanoma skin cancer or lentigo maligna with no signs of disease recurrence;
    - Adequately treated carcinoma in situ with no signs of disease recurrence.
23. Pregnant or breastfeeding female patients.

4.3 Restrictions During the Study

For women of childbearing potential who are sexually active with male partners who have not undergone surgical sterilization, the subjects must use 1 acceptable and effective methods of contraception (see Table 2) starting from the screening, and agree to continue these measures during the 90 days since the last dose of study treatment. Besides, the subjects shall discuss with a responsible physician about the discontinuation of contraception after this time point. Periodic abstinence, calendar-based method, and withdrawal method are not the acceptable forms of contraception.

Women of childbearing potential is defined as any female who has not undergone surgical sterilization (bilateral tubal ligation, bilateral oophorectomy, or hysterectomy) or is not postmenopausal (defined as 12 months of amenorrhea without alternative medical causes).

Menopause is defined as 12 months of amenorrhea of a woman without any other medical reasons. Age requirement are as follows:

- Females ⩾50 years old who have at least 12 months of amenorrhea after stopping hormone replacement therapy, and luteinizing hormone and follicle stimulating hormone levels within the postmenopausal range, are considered menopausal;
- Females < 50 years old who have at least 12 months of amenorrhea after stopping hormone replacement therapy, radiation-induced ovariectomy and the time from the last menorrhea > 1 year, chemotherapy-induced amenorrhea and the time from the last menorrhea > 1 year, or surgical sterilization (bilateral ovariectomy or hysterectomy), are considered menopausal.

Table 2**.** Effective methods of contraception (one of the followings must be used)

Barrier Method	Intrauterine Devices (IUDs)	Hormonal Methods
Male condom with spermicide	Copper-T IUD	Implant

Barrier Method	Intrauterine Devices (IUDs)	Hormonal Methods
Cervical cap with spermicide	Progesterone-T IUD[a]	Hormonal injection
Diaphragm with spermicide	Levonorgestrel-releasing intrauterine system (e.g. Mirena®)[a]	Combined oral contraceptive pill
		Low-dose oral contraceptive pill
		Contraceptive patch

[a]Also considered as a hormonal method.

4.4 Treatment Discontinuation/Withdrawal from the study

Subjects should discontinue treatment/withdrawal from the study in any of the following circumstances:

1. Subjects do not meet the inclusion/exclusion criteria, and are deemed unsuitable to continue in this study by the sponsor and investigator.
2. Subjects seriously violate the study protocol, and deemed unsuitable to continue in this study by the sponsor and investigator.
3. Subjects are enrolled in another clinical trial that is considered scientifically or medically incompatible with this study.
4. Subjects are lost to follow-up (study site personnel shall regain contact with the subjects to determine the cause of loss to follow-up and reschedule study visits if possible. The date and method of contact shall be documented in the study documents).
5. Decided by the investigator

- Subjects should discontinue the treatment or withdraw from the study based on the safety and benefits of the subjects.
- If the subjects require treatment with another drug for any reason, and the drug has been demonstrated to be effective for the indication of this study, then the subject shall withdraw from this study prior to starting the new drug.
- PD is developed or the investigator believes that continuing with study treatment is not appropriate.
- A life-threatening event that is treatment-related occurred, regardless of the severity of the event.
- The investigational drug shall be discontinued due to toxicities (see Section 5.4).

6. Subjects or their representatives (such as parents or legal guardians) requests to withdrawal from the study or discontinue the investigational drug (subjects may be

eligible for long-term follow-up if he/she withdraws ICF for treatment but not for follow-up).

7. The sponsor may terminate the study or discontinue a subject from participating in the study due to medical, safety, regulatory, or other reasons related to the applicable laws, regulations, and Good Clinical Practice (GCP).
8. Subjects who delay the treatment for 6 weeks due to adverse reactions shall withdraw from the study.
9. Subjects may withdraw from the study if the investigator believes that the local lesions should also be treated with radiation or other therapies after the subject reaches the primary endpoint.

The reasons and dates of discontinuation for all the subjects shall be documented. Subjects who discontinue the treatment shall undergo other study procedures as specified in the schedule of visits.

5 Investigational Drug and Other Treatments

5.1 Treatment Regimen

5.1.1 Treatment Regimen

The investigational drug is IBI308, given at the dose of 200mg IV Q3W up to 24 months until PD, death, intolerable toxicity, withdrawal of ICF, or other reasons stated in the protocol. Other drugs used in this study are non- investigational drugs.

5.1.2 Continuing Treatment After PD

During the treatment with IBI308, if subjects must meet all of the following criteria, he/she couldcontinueto receive IBI308 after initial PD (first PD):

1. The investigator believes that continuing treatment may yield clinical benefits, and the disease is not progressing rapidly;
2. Subjects are able to the tolerate investigational drug;
3. Stable ECOG PS score;
4. The treatment of serious complications requiring urgent interventions (such as CNS metastasis)could be managed on time;
5. Before continuing treatment with IBI308, subjects must be fully informed and the investigator must elucidate the foreseeable risks or discomforts and alternative treatments.

If the above criteria are met, the investigator and sponsor's medical manager will decided whether the subjects shall continue the treatment after PD, and document in the study records.

Data from subjects who continue IBI308 treatment after initial PD shall be collected. Refer to Table 1 for collection of data variables.

If the subjects continue to receive the investigational drug, imaging evaluation shall also be continued at the specified interval. Treatment is continued up to 24 months until further PD, death, intolerable toxicity, withdrawal of ICF, or other reasons stated in the protocol.

For subjects who continue IBI308 treatment after initial PD, treatment shall be discontinued if clinical symptoms worsen, even if there are no imaging evidence of further PD. It should be documented as "exacerbation of clinical symptoms".

5.2 Investigational Drug (IBI308)

5.2.1 Description

The investigational drug is a recombinant fully human anti-PD-1 monoclonal antibody injection, IBI308.

The main active ingredient of IBI308 is the recombinant fully human anti-PD-1 monoclonal antibody. The strength of IBI308 is 10 ml: 100 mg. IBI308 does not contain any preservatives. The concentration is 10 mg/mL, with excipients including 140 mmol/L mannitol, 25 mmol/L histidine, 20 mmol/L sdihydrate sodium citrate, 50 mmol/L sodium chloride, 0.02 mmol/L disodium edetate (ethylenediaminetetraacetic acid disodium salt), and 0.2 mg/mL polysorbate 80, pH 6.0.

This product is a clear, colorless liquid, no foreign matter, flocs, and precipitation.

Manufactured by: Innovent Biologics (Suzhou) Co., Ltd..

5.2.2 Labels

The smallest packaging unit is a box. Each box contains two vials of IBI308 injection. The package label shoude contains the drug name, medication number, dosage form, strengths, drug code, batch number, expiration date, storage conditions, dosage and administration, precautions, and sponsor's information. The label on the vial contains the same information as the outer package except for dosage form and precautions. The package and vial shall be both labeled "use for clinical study only".

5.2.3 Storage

Store at 2–8℃away from light. The shelf life is 24 months. If quality issues such as turbidity and precipitation are observed in the injection, seal the vial immediately and notify the sponsor.

5.2.4 Preparation and administration

The preparation and administration of IBI308 is as follows:

1. Completely draw the contents of two vials of IBI308 injection and transfer them into a 100-mL IV infusion bag containing 0.9% (w/v) sterile sodium chloride solution, then document the start time of the preparation.

2. Gently invert the infusion bag to mix the solution, ensuring the uniformity of the contents. Do not violent shake t to avoid foam.

3. Administer with a 0.2–1.2 μm in-line filter (suggested infusion time is around 30~60 min). Document the start and stop time of infusion.

Note: For each dose infusions, do not mix the drugs of different batches; make sure that the IBI308 injection is clear without any quality issues such as turbidity or precipitation. Make sure that the time from drawing IBI308 from the first vial to the end of infusion is no more than 24 hours (storage conditions for the prepared solution is at 2－8 ℃ in the fridge or at the room temperature/under the light). Avoid mixing with other drugs. Do not administer as an IV bolus.

5.3 Administration Adjustments of Investigational Drug

5.3.1 General principles

- The subject's hematologic, hepatic, and renal function must meet the requirements for administration of study treatment prior to each dose. All the toxicities must resolve to NCI CTCAE v4.03 grade 0–1 or baseline levels (excluding alopecia, fatigue, etc.).
- Reasons for administration adjustments and actual changes shall be documented in the original medical records and electronic case report forms (Electronic case report form ， eCRFs).

5.3.2 Administration adjustments of IBI308

Dose adjustments of IBI308 are not permitted throughout the trial. Refer to the following table for administration adjustments of IBI308 (only for AEs related to IBI308 as determined by the investigator).

Table 3. Administration adjustments of IBI308

AEs	**Severity**	**Administration Adjustments**
Pneumonitis	Grade 2 pneumonitis	Interrupt[a]
	Grade 3 or 4 pneumonitis	Permanently discontinue
Diarrhea or Enterocolitis	Grade 2 or 3 diarrhea or enterocolitis	Interrupt[a]
	Grade 4 diarrhea or enterocolitis	Permanently discontinue
Dermatitis	Grade 3 dermatitis	Interrupt[a]
	Grade 4 dermatitis	Permanently discontinue
Hepatitis	Grade 2 AST, ALT, or TBIL elevation for subjects with normal AST, ALT or TBIL at baseline; AST, ALT, or TBIL elevation of ≥ 50% for < 7 days for subjects with AST, ALT, or TBIL > ULN at baseline	Interrupt[a]
	Grade 3 or 4 AST, ALT, or TBIL elevation for subjects with normal AST, ALT or TBIL at baseline; AST, ALT, or TBIL elevation of ≥ 50% for ≥ 7 days for subjects with AST, ALT, or TBIL > ULN at baseline	Permanently discontinue
Hypophysitis	Grade 2 hypophysitis	Interrupt[b]
	Grade 3 or 4 hypophysitis	Permanently discontinue
Adrenocortical insufficiency	Grade 2 adrenocortical insufficiency	Interrupt[b]
	Grade 3 or 4 adrenocortical insufficiency	Permanently discontinue
Hyperthyroidism	Grade 3 or 4 hyperthyroidism	Permanently discontinue
Type I Diabetes	Grade 3 hyperglycemia	Interrupt[b]
	Grade 4 hyperglycemia	Permanently discontinue
Renal insufficiency	Grade 2 or 3 Cr elevation	Interrupt[a]
	Grade 4 Cr elevation	Permanently discontinue
Neurotoxicity	Grade 2 neurotoxicity	Interrupt[a]

AEs	Severity	Administration Adjustments
	Grade 3 or 4 neurotoxicity	Permanently discontinue
Infusion Reactions	Grade 3 or 4 infusion reaction	Permanently discontinue
Other AEs	First occurrence of other grade 3 AEs	Interrupt[a]
	Second occurrence of other grade 3 AEs	Permanently discontinue
	Grade 3 AE that cannot resolve to grade 0–2/baseline levels within 7 days or grade 0–1/baseline levels within 14 days	Permanently discontinue
	Grade 4 AE	Permanently discontinue[c]

a: Resume the investigational drug after symptoms resolve to grade 0–1 or baseline levels.

b: Resume the investigational drug if hypophysitis, adrenocortical insufficiency, or type I diabetes is adequately controlled and require only physiological hormone replacement.

c: For grade 4 laboratory abnormalities, the event shall be determined based on clinical signs/symptoms and the clinical judgment of the investigator.

Investigational drug is allowed to be interrupted for up to 6 weeks. If the symptoms do not resolve within 6 weeks and treatment cannot be resumed, the subject must permanently discontinue IBI308 treatment and enter the follow-up phase of the study. Except for the following two cases:

- IBI308 interruption > 6 weeks due to glucocorticoid reduction for irAEs: Consult the sponsor's medical manager prior to resuming IBI308. Tumor imaging evaluation for efficacy shall not be affected by treatment interruption and will be performed as scheduled.
- IBI308 interruption > 6 weeks due to AEs possibly related or unrelated to IBI308: Consult the sponsor's medical manager prior to resuming IBI308. Tumor imaging evaluation for efficacy shall not be affected by treatment interruption and will be performed as scheduled.

5.4 Principles of Managing Immune Checkpoint Inhibitor Toxicities

The mechanism of action of IBI308 is to stimulate T-cell activation and proliferation. The result is an immune hyperfunction leading to autoimmune disease involving multiple systems. Autoimmune AEs such as immune-related pneumonitis, diarrhea/enterocolitis, renal insufficiency, rash, hepatitis, endocrine disorders, and peripheral or central neuritis have been observed with the clinical application of other immune checkpoint inhibitors including ipilimumab, nivolumab,

pembrolizumab, and atezolizumab. If subjects experience the AEs described above, the signs and symptoms shall be monitored, relevant examinations shall be performed, and the cause shall be identified. If an alternative cause is not found (such as PD, concomitant medications, or infections) and glucocorticoids and/or other immunosuppressants are required, then any AE described above is considered related to IBI308-induced immune hyperfunction, and should be diagnosed as an irAE (except for endocrine events such as hyperthyroidism/hypothyroidism, hypophysitis, type I diabetes, and adrenal insufficiency which may not require immunosuppressants but are still considered as immune hyperfunction related to IBI308).

See Appendix 7 for dose adjustments and toxicity management of major potential irAEs, other potential irAEs, and infusion reactions.

5.5 Concomitant Treatments

5.5.1 Prohibited treatments

- Other anti-tumor therapy (except for palliative radiotherapy), chemotherapy, immunotherapy, targeted therapy, or hormone therapy.
- Immunosuppressants and high-dose glucocorticoids (except for treatments of AEs at a dose of no more than 10 mg daily prednisone or equivalents).
- Immunoglobulins.
- Live attenuated vaccine.
- Autologous hematopoietic stem cell transplantation.

5.5.2 Permitted treatments

- Medications that meet the protocol requirements, as determined by the investigator (e.g. concomitant medication used for disease-related symptoms and treatment-related AEs).
- Long-term medication for underlying diseases such as high blood pressure and diabetes..
- Supportive care for relieving tumor-related symptoms.
- Use of topical, such as dermal, ocular, nasal, and inhaled, corticosteroids.

5.5.3 Drug-drug interactions

- IBI308: No interaction information is currently available.

5.6 Treatment Compliance

Study treatment is given at the study sites. Treatment compliance is monitored by medication dispensing and return records, medical records, and eCRFs.

5.7 Medication Return and Destruction

The packages and vials of used or partially used investigational drugs for this study shall be verified by the Clinical Research Associate (CRA) and returned to the sponsor for destruction. Arrangements for the return of investigational drug will be made by the designated CRA.

Upon the completion or discontinuation of the study, all unused or expired investigational drugs must be returned to the sponsor for destruction. Arrangements for the return of investigational drug will be made by the designated CRA.

5.8 Investigational Drug Records

The designee of the study sites shall make timely records of receiving, dispensing, using, storing, returning, and destroying the study drugs in accordance with the relevant regulations and guidelines and the operation requirements of this study.

5.9 Complaint Handling

To ensure the safety and proper monitoring of the subjects and facilitate the improvement of trial process and drug product, the sponsor will collect complaints related to the investigational drug.

Complaints regarding concomitant medications will be directed to the manufacturer according to the prescribing information of the drugs.

The investigator or designee must complete the following procedures for product complaints in accordance with applicable requirements of the study:

- A drug complaint form specific for clinical trials will be used to document product complaints and relevant description completely.
- The completed product complaint form shall be submitted to the sponsor or designee by fax within 24 hours.

If the investigator is asked to return the product for further investigation, the investigator shall return the product along with a copy of the complaint form.

6 Study Evaluations and Relevant Procedures

6.1 Subject Enrollment

6.1.1 Subject enrollment

The investigator will enroll subjects by the following steps:

1. Obtain the ICF signed by the subjects prior to any study-related procedures.

2. Confirm the subjects' eligibility by the principal investigator or trained designee after reviewing the inclusion/exclusion criteria.
3. Prior to enrollment, the trained designee must mail the subjects' medical information including those regarding the inclusion/exclusion to the sponsor's medical manager for review. The subject can only be enrolled after confirmation by the sponsor's medical manager.

Subjects who do not meet the criteria (screen failures) may be re-screened. If re-screening is considered, the investigator must contact the sponsor's medical manager. Each subject can be re-screened once. The subject must sign the ICF again and receive a new identification number when re-screening.

6.1.2 Enrollment error handling

The inclusion/exclusion criteria must be followed strictly. If an ineligible subject is enrolled, the sponsor's medical manager and investigator must discuss whether to allow the subject to continue participating in the study and whether to use the investigational drug. If the subject is appropriate medically to continue with the study judged by the investigator, which is also agreed with by the sponsor's medical manager, then the subject will continue participating in the study and receive the investigational drug; if the subject is appropriate medically to continue with the study judged by the investigator,, which is not agreed with by the sponsor's medical manager, then the subject shall not continue participating in the study (regardless of receiving the investigational drug or not). The investigator must not allow the improperly enrolled subject to continue with the study until receive the written approval from the sponsor.

6.2 Study Plan and Schedule

6.2.1 Screening

The following procedures must be completed during the screening (Day -28 to -1) to ensure subject eligibility:

- Signing of the ICF
- Confirming the inclusion/exclusion criteria
- Recording the demographics, medical history, and prior medications
- Recording the vital signs, height and weight.
- Physical examination
- ECOG PS score

- 12-lead ECG
- Count of whole blood cells/blood biochemistry/routine urinalysis (within 7 days prior to the first dose)
- Pregnancy test (within 3 days prior to the first dose)
- Thyroid function
- HIV antibody, hepatitis B panel, HCV antibody (patients testing positive for HCV antibody shall also be tested for HCV RNA)
- EBV DNA copy number in peripheral blood
- AE evaluation
- Concomitant medication
- Bone marrow biopsy
- Tumor imaging evaluation (PET-CT and contrast-enhanced CT)
- Archival or fresh tumor tissue sample

Refer to Table 1 for schedule of visits during screening.

Refer to Sections 6.3 and 6.4 for details regarding tumor evaluation and safety evaluation.

6.2.2 Baseline (prior to Day 1 of Cycle 1)

- Recording the vital signs□
- ECOG PS score□
- Immunogenicity
- AE evaluation
- Concomitant medication
- Disease-related symptom evaluation
- EQ-5D-5L and EORTC QLQ-C30
- Blood sampling for biomarkers

6.2.3 Treatment period

- Recording the vital signs
- Physical examination
- ECOG PS score
- 12-lead ECG
- Count of whole blood cells/blood biochemistry/routine urinalysis
- Thyroid function

- EBV DNA copy number in peripheral blood
- Immunogenicity
- AE evaluation
- Concomitant medication
- Tumor imaging evaluation
- Bone marrow biopsy: repeat the bone marrow biopsy if the imaging shows CR
- Tumor biopsy: perform a tumor biopsy if clinically indicated
- Disease-related symptom evaluation
- Investigational drug administration
- Blood sampling for biomarkers
- EQ-5D-5L and EORTC QLQ-C30

Refer to Table 1 for schedule of visits during treatment.

Refer to Sections 6.3, 6.4, and 6.5 for details regarding tumor evaluation, safety evaluation, blood sampling for immunogenicity.

6.2.4 End-of-treatment visit

If the treatment ends or the investigational drug is discontinued prematurely for any reasons, an end-of-treatment visit shall be carried out as soon as possible after the investigational drug is discontinued and before the subject receives new anti-tumor therapy. The visit shall include the followings:

- Recording the vital signs and weight
- Physical examination
- ECOG PS score
- 12-lead ECG
- Count of whole blood cells/blood biochemistry/routine urinalysis
- EBV DNA copy number in peripheral blood
- Thyroid function
- Pregnancy test
- AE evaluation
- Concomitant medication
- PET-CT (if applicable)
- EQ-5D-5L and EORTC QLQ-C30

6.2.5 Safety follow-up

The safety follow-up should be performed on 90 ± 7 days after the last dose or before initiation of a new anti-tumor therapy (whichever comes first). Subjects with drug-related AEs that result in treatment discontinuation will be followed up until the AE resolves to grade 0 or 1, symptoms are stable, subject withdraws ICF, or a new anti-tumor therapy is started (whichever comes first).

- Vital signs
- Count of whole blood cells/blood biochemistry/routine urinalysis
- Thyroid function
- AE evaluation
- Immunogenicity
- Concomitant medication

6.2.6 Survival Follow-Up

After completing the safety follow-up, the subject shall be contacted with (telephone visits is allowed) once 60 days (±7 days) to obtain the survival information, any subsequent systemic anti -tumor therapy, and PD information (for subjects with no imaging PD). Long-term follow-up shall be continued until death or end of study.

6.3 Imaging Evaluation

Baseline evaluation is conducted within 28 days prior to the first dose of the study treatment. The investigator can evaluate the imaging results within 28 days prior to the enrollment.

PET-CT and contrast-enhanced CT will be used (MRI will be performed for subjects allergic to CT contrast media). PET-CT shall be performed at baseline, week 6 (±7 days), week 15 (±7 days), and week 24 (±7 days). PET -CT evaluation shall be performed at the end of treatment for subjects who discontinue the treatment prematurely prior to week 24 (unless the previous PET-CT scan is done within the past month). 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 initiation of new anti-tumor therapy, PD, withdrawal of ICF, or death. Unplanned PET-CT and contrast-enhanced CT shall be added to evaluate the efficacy when investigators deem appropriate, if the subjects agree. The examinations will be taken at sponsor’s expense. First PD shall be confirmed after 4–6 weeks. For subject who discontinue the treatment for reasons other

than PD, tumor imaging evaluation shall be continued according to the study protocol until initiation of new anti-tumor therapy, PD, withdrawal of ICF, or death.

Imaging data shall be copied or saved according to the requirements of the sponsor.

6.4 Safety Evaluation

6.4.1 Routine laboratory safety evaluations

Table 4. Routine laboratory safety evaluations

Count of Whole Blood Cells	RBC, HGB, WBC, PLT, LYM, and ANC
Blood Biochemistry	TBIL, ALT, AST, γ-GT, ALP, ALB, TP, LDH, BUN, Cr, Na, K, Cl, Mg, Ca, P, lipase, amylase, and FBG
Routine Urinalysis	PH, UALB, UPRO, URBC, and UGLU

6.4.2 Physical examination

A comprehensive physical exam includes general conditions, respiratory tract, cardiovascular system, abdomen, skin, head and neck (including ears, eyes, nose, and throat), lymph nodes, thyroid, musculoskeletal system (including spine and limbs), genitalia/anus, and nervous system.

Refer to the schedule of visits in Table 1 for examination time. Refer to Appendix 2 for ECOG PS criteria.

6.4.3 12-lead ECG

A resting 12-lead ECG is performed at the local laboratory in accordance with the schedule of visits in Table 1.

A 12-lead ECG examination will be performed after the subject rested for at least 5 minutes in the supine position. All 12-lead ECGs should be recorded while the subject is resting in a supine position. Further ECG shall be performed if clinically indicated, such as a cardiac AE. The investigator shall review the ECG on the day it is performed, and document the results on the ECG. The same method of evaluation shall be used throughout the trial.

The investigator shall evaluate all the ECG as either a clinically significant/insignificant abnormality. If it is a clinically significant abnormality, the investigator shall document the results as an AE in the eCRF.

6.4.4 Vital signs

Vital signs are examined in accordance with the schedule of visits in Table 1, including body temperature, pulse, respiratory rate, and blood pressure.

Additional monitoring of vital signs is allowed based on standard clinical practice or clinical need,and shall be documented in the eCRF when an AE/SAE occurs (if applicable).

The time and date of measurement shall be documented in the appropriate section of the eCRF.

6.4.4.1 Pulse and blood pressure

The subject's blood pressure and pulse in the supine position is measured after rest for at least 5 minutes. Two or more readings shall be done with 2-minute intervals and the readings shall be averaged. If the first two systolic blood pressure readings differ by more than 5 mmHg, measure again and average the readings. The time and date of measurement shall be documented in the appropriate section of the eCRF.

Pulse and blood pressure shall be measured prior to the administration of investigational drug.

6.4.4.2 Body temperature and respiratory rate

Collect the body temperature and respiratory rate prior to the infusion on the scheduled administration day.

6.4.5 Weight and height

Height is only measured during screening. Weight is measured during screening and at the end of treatment.

6.4.6 Pregnancy test

Urine or serum β human chorionic gonadotropin (β-HCG) pregnancy test must be performed in women of childbearing potential (refer to Section 4.3 for definition) within 3 days prior to the first dose of study treatment. If the result of urine β-HCG is positive or inconclusive, then serum β-hCG pregnancy test shall be performed. The conclusion shall be based on the serum pregnancy test. If the β-hCG result is positive, the subject is not eligible or must discontinue participating in the study. A repeated test shall be performed if pregnancy is suspected during the study.

6.4.7 Other safety examinations include the followings:

- Hepatitis B panel (HBsAg, HBsAb, HBcAb, HBeAg, and HBeAb).
- HIV antibody, HCV antibody (if the result shows HCV antibody positive, then HCV RNA test shall be further conducted).
- Thyroid function: T3, T4, TSH, FT3, and FT4. T3, T4, FT3, FT4, and TSH shall be tested during screening and prior to the administration of IBI308 from Cycle 2 onwards.

6.5 Immunogenicity

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.

Anti-drug antibody (ADA) titer shall be tested for each subject. ADA-positive specimens shall be further tested for neutralizing antibodies (NAbs).

For ADA and NAb assays, 4 mL of whole blood is collected using vacutainers with clot activator. Serum is then separated, dispensed in aliquots, and frozen.

Refer to the Laboratory Manual provided by the sponsor-designated central laboratory for sampling methods, sample storage, transport, and analysis.

6.6 Quality of Life Evaluation

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.

EQ-5D-5L is a standardized tool used for patients to self-report their health status. Subjects will fill out a questionnaire that consists of 5 levels (no problems, slight problems, moderate problems, severe problems, and extreme problems) and 5 dimensions (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression). A single EQ-5D health status is defined after combining the different levels of all 5 dimensions. In addition, subjects will mark on a visual analog scale (VAS) for their health status, which ranges from 0 (the imaginable worse state) to 100 (the best imaginable state).

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.

6.7 Biomarker analysis

If permitted by the EC, all the eligible subjects must provide tumor tissue during screening. Acceptable tumor tissue include 8–10 unstained sections (4–5 μm) of archival specimen or fresh specimens for evaluations of PD-L1 expression, RNA expression and number of TIL.

EBV DNA copy number in plasma and peripheral blood lymphocytes 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. According to the changes of

patients' condition and the needs of efficacy evaluation, EBV DNA test may be added by investigators at the centre.Ten mL whole blood samples are required to be provided by subjects for molecular tumor testing at the following time points: during screening, during efficacy evaluation but before the next treatment, and when PD is confirmed. The followings may be tested to predict anti-PD-1 treatment efficacy and prognosis of subjects: lymphocyte (T cell and NK cell) phenotyping and immune-related cytokines (TNF-α, IL-6, IL-15, soluble PD-L1 et al.) in different subtypes.

Refer to Laboratory Manual for details regarding sample processing, handling, and transport.

6.8 Storage and Destruction of Biological Samples

Samples will be disposed or destroyed, pooled and anonymized. Additional analyses of pooled and anonymized samples may be performed to further evaluate and validate the analytical method. Results of these analyses may be published separately from the Clinical Study Report (CSR).

Reproducibility (if performed) will be assessed simultaneously with the biological analysis of the samples. The results of these evaluations will not be published in the clinical study report, but will be presented separately in a biological analysis report.

7 Safety Reports and AE Management

7.1 Definition of AEs

An AE is defined as any adverse medical event that occurs after the signing of the informed consent form within 90 days since the last dose of the study treatment, regardless of whether or not considered as related to the study drugs. AEs include but are not limited to the followings:

- Worsening of pre-existing (prior to enrollment) medical conditions/diseases (including symptoms, signs, and laboratory abnormalities);
- Any new adverse medical conditions (including symptoms, signs, and newly diagnosed diseases);
- Clinically significant laboratory abnormalities.

7.2 Definition of SAEs

An SAE refers to an AE meeting at least one of the followings:

- Results in death, except for death caused by PD.

- Life-threatening (a life-threatening event is defined as an AE when the subject is at immediate risk of death at the time, but does not include the one that may lead to death only when the event worsens).
- Requires hospitalization or prolonged hospitalization, excluding the followings:
  - ✓ Hospitalization at a rehabilitation institution
  - ✓ Hospitalization at a sanatorium
  - ✓ General emergency admission
  - ✓ Day surgery (e.g. outpatient/same-day/ambulatory surgery)
  - ✓ Hospitalizations or prolonged hospitalizations unrelated to worsening of an AE are not considered as an SAE. For example: hospitalization due to pre-existing disease, without new AEs and exacerbation of pre-existing disease (e.g. hospitalization to examine laboratory abnormalities that have been persistent before the study starts); hospitalization for administrative reasons (e.g. annual routine physical examinations); hospitalizations during the study as specified in the protocol (e.g. hospitalization performed in accordance study protocol); elective hospitalization unrelated to worsening of AEs (e.g. elective surgery); scheduled treatment or surgical procedures, which shall be documented in the entire study protocol and/or individual subject's baseline information; and hospitalization merely due to the use of blood products.
- Results in permanent or serious disability/incapacity.
- Results in congenital anomalies/birth defects
- Other important medical events: defined as events that may jeopardize the subjects and require medical or surgical interventions to prevent one of the other outcomes listed in the definition above.

7.3 AE Severity Grading Scale

The severity of AEs is evaluated using the 5-level criteria of NCI CTCAE v4.03.

For adverse event terms not included in NCI CTCAE version 4.03, graded according to the following CTCAE classification principles:

- Grade 1 Mild; asymptomatic or mild sings; clinical or diagnostic observations only; medical intervention not indicated.

- Grade 2 Moderate; minimal, local or non-invasive intervention required; limiting age-appropriate instrumental activities of daily living (e.g., cooking, shopping, using the telephone and managing money, etc.).
- Grade 3 Severe or medically significant but not immediately life-threatening; hospitalization or prolonged hospitalization indicated; disabling; limiting self-care activities of daily life (e.g. bathing, dressing and undressing, feeding self, using the toilet, and taking medications), but not bedridden.
- Grade 4 Life-threatening consequences; urgent intervention indicated.
- Grade 5 Death related to AE.

7.4 Correlation Between AEs and Investigational Drug

The relationship between the investigational drug and AEs can be determined using the followings:

Table 5. Correlation determination between AEs and investigational drug

Correlation	Criteria
Definitely Related	● The AE occurrence has a reasonable time relationship with administration time; ● The investigational drug can more reasonably explain the AE than the other causes (such as concurrent disease, environment, toxicity, or other treatment received); ● The AE resolves or is alleviated after treatment interruption or dose reduction; ● The event meets the recognized pharmacological AE type; ● The AE does not occur after re-administration.
Probably Related	● The AE occurrence has a reasonable time relationship with administration time; ● The investigational drug provide more reasonable explanations on the AE than the other causes (such as concurrent disease, environment, toxicity, or other treatment received); ● The AE resolves or is alleviated after treatment interruption or dose reduction (if applicable);
Probably Unrelated	● Other causes provide more reasonable explanations on the AE than the investigational drug (such as concurrent disease, environment, toxicity, or other treatment received); ● The AE does not resolve or be alleviated after treatment interruption or dose reduction (if applicable), or the situation is unclear; ● The AE does not occur after re-administration or the situation is unclear.
Definitely Unrelated	● The AE occurrence has no reasonable time relationship with administration time, or ● Other causes provide evident explanations (such as concurrent disease, environmental, toxicity, or other treatment received by the subject).

Correlation	Criteria
Unable to Determine	● The above information is unclear and the AE cannot be determined based on the available information. Further follow-up information is not accessible to the investigator.

7.5 Recording of AEs

The investigator shall document AEs and SAEs using medical terms and concepts. Avoid colloquialisms/abbreviations. All the AEs (including SAEs) shall be documented on the AE forms in the eCRFs.

7.5.1 Collection and time of AEs

The investigator shall use non-leading questions when asking the subjects about AEs.

All the AEs, including SAE, that occur after the signing of the ICF within 90 days since the last dose shall be collected, regardless of whether it is observed by the investigator or self-reported by the subject.

Within 90 days since the last dose, if the subjects receive other anti-tumor therapy, any AEs related to the study drugs shall be collected, and be followed-up until the adverse reactions return to grade 0-1 or baseline.

After 90 days since the last dose, the investigator should report any SAEs that are considered related to the study drugs.

7.5.2 AE Follow-Up

The AE shall be followed until the events return to the baseline values or grade 0–1, or until the investigator believes that no further follow-up is required for reasonable reasons (if the event cannot be resolved or has already been improved). If the event cannot be resolved, a reasonable explanation shall be documented in the eCRF. The outcome of an AE/SAE and date shall be documented in the eCRF and medical record, regardless of whether the event is related to the study drugs.

7.5.3 Contents of AE documentation

The investigator must document all the AEs, including the diagnosis (document signs and symptoms including the laboratory abnormalities if there is no diagnosis), time and date of occurrence (if applicable), CTCAE grade of severity and changes in severity (events $\geqslant$ grade 3), whether it is an SAE, whether it is an AE of special interest (AESI), measures taken for the study

drugs, treatment for the AE and outcome of the event, and relationship between the event and study drugs.

For an SAE, the investigator shall also provide the date when the AE meets the criteria for an SAE, the date when the investigator is informed of the SAE, the reason of being an SAE, date of hospitalization, date of hospital discharge, possible cause of death, date of death, whether an autopsy has been performed, causality assessment of the study procedures, causality assessment of other drugs, and other possible causes of the SAE. The investigator shall provide the rationales of the causality and a description of the SAE. In the SAE description, the followings shall also be included: the subject number, age, gender, height, and weight; indication for receiving the investigational drug, cancer staging, and overall condition; SAE occurrence, development, outcome, and result; laboratory results related to the SAE (the time of the examination, units, and normal ranges must be provided); medical history, onset and duration of concurrent diseases related to the SAE; medication history and initiation, duration, and dosage of concomitant medications related to the SAE; initiation, duration, and dosage of the investigational drug.

Descriptions of the AE are as follows:

Diagnosis, signs, and symptoms

Document the definite diagnosis, if there is one, rather than just listing the independent signs and symptoms (e.g. hepatic failure rather than jaundice, elevated transaminase, and asterixis). Signs and symptoms shall be reported as separate AEs/SAEs if cannot be attributed to the diagnosis. If it is determined that the signs and symptoms are caused by the diagnosis, then only the diagnosis shall be reported, included the signs and symptoms. The record of signs and symptoms shall then be deleted. A follow-up SAE report shall be submitted.

AEs secondary to other events

Generally, AEs secondary to other events (such as result of another event or clinical sequelae) shall be documented as the primary event, unless the event is severe or an SAE. However, clinically significant secondary events shall be recorded as independent adverse events in the eCRFs if they occur at different time than the primary event. If the relationship between events is unclear, document them as separate events in the eCRFs.

Ongoing or recurrent AEs

An ongoing AE refers to an event that does not resolve and is ongoing between two assessment time points. These AEs shall only be documented once in the eCRFs. The initial severity shall be documented, and the information shall be updated if the event exacerbates.

Recurring AEs refer to AEs that have resolved between the two time points of assessment but subsequently occur again. These events shall be independently documented in the eCRFs.

Laboratory abnormalities

Any clinically significant laboratory abnormalities shall be reported as AEs. The investigator is responsible for reviewing all the laboratory abnormalities, and determine whether the findings shall be reported as AEs.

Death

During the entire course of the study, all the deaths that occur within 90 days after the last dose shall be documented in the eCRFs and Mortality Report Form and reported to the sponsor timely, regardless of the causality with the study drugs.

If the cause of death is known, record the cause of death as an AE and the outcome of the event as a death and submit an SAE report; if the cause of death is unclear, the AE shall be recorded as Death of Unknown Cause in the AE form, and submit the SAE report as Death of Unknown Cause. The exact cause of the death shall be further investigated.

If the cause of death is confirmed to be PD, then the event shall not be documented and reported as an AE/SAE. However, the event shall be documented in the Mortality Report Form of the eCRF and reported to the sponsor timely.

Pre-existing medical conditions

Symptoms/signs present during the screening period will be recorded and reported as AEs only if their severity, frequency, or property becomes aggravated (except for worsening of the studied disease). The relative changes shall be documented, such as increased frequency of headaches.

Hospitalization and prolonged hospitalization, or surgery

Any AEs leading to hospitalization or prolonged hospitalization shall be recorded and reported as SAEs, with the following exceptions:

- Hospitalization or prolonged hospitalization as required by study protocol (such as for dose administration or efficacy evaluation).
- Hospitalization due to a pre-existing medical condition that remains stable, e.g. elective

surgery/therapy scheduled prior to the study.

However, elective surgery/therapy required because of the exacerbated condition during the study (e.g. surgery/therapy required earlier than scheduled) shall be considered as an AE.

PD

PD is defined as the worsening of subject condition caused by the primary tumor that the study drug is targeting, the appearance of new lesions, or the progression of the primary lesion. PD will not be reported as an AE. Any deaths, life-threatening events, hospitalization or prolonged hospitalization, permanent or significant disability/incapacity, congenital anomaly/birth defects, or other important medical events caused by PD will not be reported as an SAE.

Overdose

An overdose is the administration of a drug at more than the dose specified in the study protocol. All the occurrences of overdose must be documented in the eCRF.

7.6 Expedited Reporting of SAEs and Pregnancy

SAE reporting:

SAEs should be reported from the signing of informed consent to 90 days (inclusive)after the last doseof investigational drug administration. The investigator must fill out the "CFDA SAE Report Form", regardless of whether it is the initial report or a follow-up report, and sign and date the form. The investigator must report the SAE to the sponsor, CFDA, and ethics committee within 24 hours of noticing the event. Refer to the table below for contact details.

For SAEs occurring outside of the above-mentioned period, those considered related to the investigational drug shall also be reported to the sponsor.

The investigator must submit the completed SAE report form to the sponsor within 24 hours of noticing the event. The investigator shall urgently perform visit on missing information and provide a complete SAE report for events that result in death or are life-threatening.

The investigator shall also report the event to the CFDA, health administration departments, and EC in accordance with the regulations.

Table 6**. SAE report contacts**

Organization	Contact Person	Fax/Telephone/Address
Hospital Name	EC	Hospital Fax/Telephone

Innovent Biologics (Suzhou) Co., Ltd.	Clinical Study Department PV	Fax: 021-31652800 Email: drugsafety@innoventbio.com
Office of Drug Research and Supervision, Department of Drug and Cosmetics Registration, China Food and Drug Administration		Address: Building 2, No. 26, Xuanwumen West Street, Xicheng District, Beijing Postal Code: 100053 Telephone: 010-88330732 Fax: 010-88363228
Medical Administrative Department, Health Administration		Address: No. 38, Lishi Road, Xicheng District, Beijing Telephone: 010-68792001 Fax: 010-68792734
Province, Autonomous Region, Municipality Food and Drug Administration	Based on the requirements of the Food and Drug Administration Department of each province, autonomous region or municipality	

Pregnancy

The risk of embryotoxicity exists for the similar kind of drugs. All the subjects with childbearing potential must take effective contraceptive measures.

During the study, if a female subject becomes pregnant, she must be withdrawal from the study. The investigator must report to the sponsor within 24 hours of noticing the event and submit the Innovent Clinical Study Pregnancy Report/Follow-Up Form.

During the study, if a female partner of a male subject exposed to the study drugs becomes pregnant, the subject will continue in the study. The investigator must report to the sponsor within 24 hours of noticing the event and submit the Innovent Clinical Study Pregnancy Report/Follow-Up Form.

The investigator must continuously monitor and follow-upthe outcome of the pregnancy until 8 weeks after the subject gives birth. The outcome shall be reported to the sponsor.

If the outcome of the pregnancy is stillbirth, spontaneous abortion, fetal malformation (any congenital anomaly/birth defects), or medical abortion, it shall be considered a SAE and the event requires to be reported in accordance with SAE procedures and time limits.

If the subject also experiences a SAE during the pregnancy, the CFDA SAE Report Form shall also be filled out and reported according to SAE's procedures.

7.7 Abnormal Hepatic Function

It is considered as drug-induced liver injury if abnormal AST and/or ALT levels are accompanied with abnormal elevation of TBIL, and the following conditions are met without other possible causes. Such cases shall always be considered as important medical events and be expeditiously reported as per the procedures and time limits.

Table 7. Liver injuries required to be reported as SAEs

Baseline	Normal (AST/ALT and TBIL)	Abnormal (AST/ALT and TBIL)
Treatment	ALT or AST ≥ 3 × ULN with TBIL ≥ 2 ×ULN and ALP ≤ 2 ×ULN and no hemolysis	ALT or AST ≥ 8 ×ULN and TBIL increase ≥ 1× ULN or value ≥ 3× ULN

Once being notified with the abnormalities, the subject must return to the study site promptly (ideally within 48 hours) and receive an assessment. The assessment must include the laboratory tests, detailed medical history, and physical assessment, and the possibility of hepatic tumor (primary or secondary) shall be considered.

Other than repeated AST and ALT tests, albumin, creatine kinase, TBIL, direct and indirect bilirubin, γ-GT, PT/INR, and ALP shall also be tested. Detailed medical history include history of alcohol, acetaminophen, soft drugs, various supplements, traditional Chinese medicine, chemical drug exposure, family diseases, occupational exposure, sexual behavior, travel, contact with patients with jaundice, surgery, blood transfusion, hepatic diseases or allergies, cardiac diseases, and immune diseases. Further tests may include the detection of acute hepatitis A, B, C and E, hepatic imaging (such as biliary tract), autoantibodies, and echocardiography. If a retest showed consistency with the criteria outlined in Table 10 and there are no other possible causes, the possibility of drug-induced liver injury could be considered before all the results of etiological tests are accessible. These potentially drug-induced liver injury shall be reported as SAEs, and the Appendix 5: Abnormal Hepatic Function Monitoring and Follow-Up Report shall be submitted to the sponsor.

7.8 Managing of Drug-Related Toxicities

During the course of the trial, the sponsor will conduct regularly monitoring of safety. Detailed information regarding the frequency of review and type of data to be reviewed will be presented in a separate safety review plan.

7.8.1 irAEs

Since the mechanism of action of IBI308 involves T-cell activation and proliferation, irAEs are likely to be observed during this study. Refer to Section 5.4 for the definition of an irAE. Signs and symptoms of irAEs shall be monitored.

Refer to Sections 5.3 and 5.4 for administration adjustments and management of AEs of IBI308. Refer to Appendix 7 (Tables 1 and 2) for a detailed guide on irAE management.

7.8.2 AESIs

AESIs refer to events that require close monitoring in order to enhance the understanding of the safety of the investigational drug. AESIs can be non-serious events.

AESIs for this trial include the followings:

- Infusion reactions ≥ grade 3
- Diarrhea/colitis, uveitis, interstitial pneumonia ≥ grade 2
- Suspected immune-related AEs ≥ grade 3

8 Statistics

8.1 Statistical Analysis Plan

A detailed statistical analysis plan (SAP) will begin to be written after the first enrollment and will be finalized prior to database locking. The SAP will contain details of all analyses and the presentation of results.

8.2 Hypothesis Test

The primary efficacy endpoint is ORR evaluated using the 2014 Lugano Criteria. The hypotheses for the superiority test are as follows:

H0: ORR ≤ 30%

H1: ORR > 30%

The superiority is determined using confidence intervals (CIs). Superiority of IBI3088 monotherapy for the treatment of relapsed or refractory ENKTL-NT is established if the lower limit of the (1-α)% CI for ORR is greater than 30% (α may be adjusted according to interim analysis).

8.3 Analysis Population

Analysis population include the safety set (SS), full analysis set (FAS), and per-protocol set (PPS):

1) SS: subjects who received at least one dose of the investigational drug.

2) FAS: subjects with measurable lesion at baseline and received at least one dose of the investigational drug. Subjects who do not meet the criteria for ENKTL-NT by central pathological review are excluded in the FAS.

3) PPS: a subset of the FAS, includes subjects with good compliance and no serious protocol violations or prohibited medications.

8.4 Statistical Methods

8.4.1 General statistical analysis

Variable data will be summarized using the mean, standard deviation, median, maximum, and minimum. Attributes data will be described using frequency and percentage.

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

8.4.2 Analysis of primary efficacy endpoint

ORR is evaluated using the 2014 Lugano Criteria:

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

, superiority is tested using (1-α)% CI based on the binomial distribution.

8.4.3 Analysis of secondary efficacy endpoints

- TTR

TTR (CR or PR): time from the first dose to the first tumor response.

The median TTR and corresponding 95% CI will be estimated via the Kaplan-Meier method, and survival curves will be plotted.

- DoR

DoR (CR or PR): time from first date of response to PD or death. Subjects who neither progress nor die will be censored at the date of their last tumor imaging evaluation.

The median DoR and corresponding 95% CI will be estimated via the Kaplan-Meier method, and survival curves will be plotted.

- PFS

PFS: time from first dose to first PD (by imaging), or to death due to any causes. Subjects who neither progress nor die will be censored at the date of their last tumor imaging evaluation. Subjects who did not have any tumor imaging evaluation after baseline will be censored on the date of enrollment.

The median PFS (mPFS) and corresponding 95% CI will be estimated via the Kaplan-Meier method, and survival plots will be plotted.

- OS (investigator-evaluated)

OS: time from first dose to death.

The median OS and corresponding 95% CI will be estimated via the Kaplan-Meier method, and survival curves will be plotted.

- DCR

$$DCR = \frac{\text{Number of Subjects with } CR + PR + SD}{\text{Total Number of Subjects}} * 100\,\%$$

, superiority is tested using 95% CI based on the binomial distribution.

8.4.4 Biomarker evaluations

Descriptive summary statistics of PD-L1 expression levels and distribution will be presented, and the association with efficacy will be explored.

The potential association between number of TIL and treatment efficacy will be summarized using descriptive statistics.

Dynamic changes in EBV DNA copy number in peripheral blood will be summarized using descriptive statistics, and the potential association with efficacy will be explored.

Dynamic changes in immune cell phenotypes in peripheral blood will be summarized using descriptive statistics, and the potential association with efficacy will be explored.

The correlation between immune-related cytokines IL-6, IL-15, TNF-α and soluble PD-L1 and efficacy of anti-PD-1 treatment will be presented using descriptive statistics.

Post-hoc analyses may possibly be carried out. The analyses described in this section will be carried out based on the data collected.

8.4.5 Quality of life analysis

The EQ-5D-5L and EROTC QLQ-C30 scores at each evaluation time point will be calculated. The overall score and each dimension score at each time point, as well as relative changes from baseline, will be summarized using descriptive statistics.

8.4.6 Safety analysis

The safety analysis will use the SS. Safety parameters include AEs, laboratory examinations, vital signs, ECG, immunogenicity, etc.

8.4.6.1 Drug exposure

The amount of drug exposure and duration of treatment (number of treatment cycles) will be summarized.

8.4.6.2 AEs

All the AEs will be coded according to MedDRA.

The incidence (frequency) of AEs, TEAEs, ADRs, irAEs, AESIs, SAEs, and AEs resulting in study treatment discontinuation will be summarized. The severity distribution of TEAEs, ADRs, irAEs, AESIs, and AEs resulting in study treatment discontinuation will be summarized using NCI CTCAE v4.03 presented via SOC/PT.

Subjects who discontinue the treatment due to AEs, develop SAE, or die will be listed (include at least the followings: start and end date of the AEs, severity grades, relationship with study drugs, measures taken, and outcomes).

8.4.6.3 Laboratory tests

Measurements and changes after treatment in count of whole blood cells and blood biochemistry parameters will be described using mean ±SD, maximum, minimum, and median. Normal and abnormal changes after treatment will be described using the cross-classification table.

Routine urinalysis: A cross-classification table is used to describe changes between normalities and abnormalities before and after the treatment.

The proportion of subjects with "clinically significant abnormalities" will be presented. The clinical significance will be determined by the investigator.

Subjects with abnormal changes after treatment (whether clinically significant or not) will be listed.

8.4.6.4 ECG

Descriptive statistics are used for ECG and changes from baseline. A cross-classification table is used to describe ECG and changes from baseline before and after the treatment and data lists will be provided.

8.4.6.5 Vital signs, physical examination and other safety-related examinations

Descriptive statistics of vital signs and relative changes from baseline will be shown.

Abnormal changes from baseline in physical examination will be listed.

8.4.7 Immunogenicity

The rates of ADA and NAB development will be calculated. Subjects' antibody titer will be listed.

8.4.8 Compliance

The frequency and proportion of subjects who violate the treatment regimen will be presented.

The proportion of subjects administered study drug doses between 80–120% of the dose specified in the protocol,

who complete the study, and who complete different number of treatment cycles will also be summarized.

8.4.9 Subjects' baseline characteristics

Subjects' demographics (sex and age), tumor diagnosis information (pathological diagnosis, tumor staging, prior treatment), baseline tumor evaluation (target lesion, number of non-target lesions, sites, total diameter, etc.), and other baseline information (height and weight (BMI, BSA), vital signs, laboratory tests, past/concomitant medications) will be analyzed using descriptive statistics.

8.4.10 Interim analysis

One interim analysis is planned for this study:

Time point for the analysis: after the first 20 subjects have completed the treatment as per the study protocol for the safty evaluation.

8.4.11 Multiple comparisons and adjustments

One interim analysis is planned for this study. The interim analysis will analyze safety data of the first 20 subjects, and the α will not be adjusted.

8.4.12 Subgroup analysis

Treatment efficacy in PD-L1-positive subjects is analyzed.

Subgroup efficacy analyses will be performed based on age and previous treatment.

8.4.13 Eligible subject data lists

In addition to subjects' data list, tumor evaluation (date of evaluation, lesion status, evaluation results) and efficacy endpoints of subjects who have achieved CR and PR will be listed separately.

PFS data of all the subjects at the end of the study will be also be presented.

8.4.14 Exploratory analysis

The association between PD-L1 expression levels and treatment efficacy will be examined using descriptive statistics.

The association between number of TIL and treatment efficacy will be summarized using descriptive statistics.

The association between dynamic changes in EBV DNA copy number and treatment efficacy will be presented using descriptive statistics.

Dynamic changes in immune cell phenotypes in peripheral blood will be summarized using descriptive statistics, and the potential association with efficacy will be explored.

The correlation between immune-related cytokines IL-6, IL-15, TNF-α and soluble PD-L1 and efficacy of anti-PD-1 treatment will be presented using descriptive statistics.

8.5 Sample size estimation

This is a single-arm trial. The primary objective is to evaluate the efficacy of IBI308 monotherapy for the treatment of relapsed or refractory extranodal NK/T-Cell Lymphoma. 20-60 subjects will be enrolled. Assuming a null hypothesis of 30% ORR, α of 0.05 (two-sided), power of 80%, a 50% ORR after IBI308 treatment will be achieved and the minimum sample size will thus be 43.

The sponsor will evaluate the safety data from the first 20 subjects to determine whether the study shall be discontinued prematurely due to safety concerns.

8.6 Methods for Controlling Bias

8.6.1 Randomization and blinding

This is a single-arm, open-label study. There is no randomization or blinding.

8.6.2 Blinding maintenance evaluation

Not applicable.

8.6.3 Emergency unblinding

Not applicable.

9 Quality assurance and quality control

In accordance with GCP guidelines, the sponsor is responsible for the implementation and maintenance of quality assurance and quality control systems as per appropriate standard operating procedures to ensure the study is implemented and authentic data is collected, documented, and reported in accordance with the requirements of the protocol, GCP, and applicable regulations.

9.1 Clinical monitoring

The sponsor or its authorized contract research organization (CRO) will conduct clinical monitoring of this study. The clinical research associate (CRA) shall perform the monitoring in accordance with the standard operating procedures provided by the sponsor or CRO, and has the same rights and responsibilities as the sponsor's CRA. The CRA must maintain regular communication with the investigator, authorized research personnel, and sponsor.

Before the study begins, the CRA will assess the competency of each study site, and report issues related to facilities, technical equipment, and medical personnel to the sponsor. During the course of the study, the CRA is responsible for the monitoring of whether the written ICF from all subjects has been obtained and whether the data records are correct and complete. The CRA shall compare the data inputted in the eCRFs with the raw data, and inform the investigator of any errors or omissions. Besides, the CRA will also control the compliance of the protocol and study procedures for each study sites, arrange for the supply of investigational drug, and ensure that the drug is kept under proper conditions.

The monitoring visits shall be conducted in accordance with the requirements of relevant laws and regulations. From the time the subjects are enrolled, each center shall receive regular visits for the purpose of monitoring. After each visit to the investigator, the CRA shall submit a written report to the sponsor.

9.2 Data Management/Coding

This study will use an electronic data collection (EDC) system, and the research data will be recorded in the eCRFs by the investigators or its authorized personnel. Before the initial of the study site or data entry, the investigators and authorized personnel shall be properly trained and appropriate security measures shall be taken for the computer and other equipment.

Data entry into the eCRFs shall be completed as soon as possible during or after visiting. The eCRFs shall be updated at any time to ensure that they reflect the latest data of the subjects. To avoid the differences in outcome evaluations by different evaluators, it is recommended that the baseline and all the subsequent efficacy and safety evaluations of a given subject shall be performed by the same individual. The investigators are required to review the data to ensure the accuracy and correctness of all the data entered into the eCRFs. If no evaluations are conducted during the study, or some obtained information are not evaluable, not applicable, or unknown,

the investigators shall record the above information in the eCRFs. The investigator shall sign the verified data electronically.

The CRA will review the eCRFs, and evaluate the completeness and consistency by comparing with the source document to ensure consistency of key data. Data entry, corrections, and modifications shall be performed by the investigator or designee. The data in the eCRFs is submitted to the data server and any modifications in the data shall be recorded in the audit trail, including reasons, operator names, time, and dates of modification. The roles and permission levels of the personnel responsible for data entry in the study site will be determined in advance. The CRA or data management personnel may raise an inquiry in the EDC in the event of suspicious data. The study site personnel are responsible for dealing with such inquiry. The EDC system will record the audit trail of the inquiry, including the investigator name, time, and date.

Unless otherwise stated, the eCRFs shall only be used as forms to collect data, instead of source. The source documents are used by the investigators or hospital, including all records related to the subjects, which are able to demonstrate the presence, inclusion criteria, and participation of subjects (laboratory records, ECGs, pharmaceutical records, subject folders, etc.).

The investigator is responsible for the maintenance of all source documents and shall offer the documents to the CRA for review during each visit. In addition, the investigator must submit a complete eCRF for each enrolled subject, regardless of the duration of participation. The protocol number and subject numbers of all supporting documents (such as laboratory records or hospital records) submitted with the eCRFs shall be carefully verified. All the personal privacy information (including the subjects' names) shall be deleted or made illegible to protect the privacy of the subjects. The investigator verifies that the record has been reviewed using an electronic signature and ensures the accuracy of the recorded data. The electronic signature shall be completed using the investigator's user ID and password. The system will automatically attach the date and time of signing to the signature. The investigator must not share his/her user ID and password with others. If the data in the eCRFs are required to be changed, the change shall be performed according to the procedure outlined by the EDC system. All the changes and corresponding reasons shall be recorded in the audit trail.

AEs and concomitant diseases/history shall be coded. The dictionary for coding will be described in the Clinical Study Report (CSR).

9.3 Quality Assurance Audits

During the course of the study, the sponsor or designee may conduct quality assurance audits on the study sites, database and related research documents. At the same time, the corresponding regulatory authorities may also inspect the study sites, database and related research documents at their own discretion. The investigator shall notify the sponsor immediately after being notified of inspection from regulatory authorities.

The sponsor's quality assurance department will audit the clinical trial sites. The audits include the supply of drugs, required trial documents, records of informed consent process, as well as the consistency of medical report forms with the source documents. The content and scope of the audits can also be increased as the circumstance requires. After reasonable notice, the investigator shall allow auditors commissioned by the sponsor to conduct audits related to the trials and inspections conducted by the regulatory authorities. The primary purpose of an audit or an inspection is to verify that the rights or health of the trial subjects are protected, the signing of the informed consent form and the correct implementation of the trial process, and all data related to the evaluation of the investigational drug is processed, reported and pre-planned. In addition, the protocol, facility, ethical standard operating procedures, GCP and applicable regulatory requirements are consistent. The investigators shall have direct access to all trial files, source records, and source data.

10 Ethics

10.1 EC

The sponsor or designee will prepare the relevant documents including the trial protocol, ICF, Investigator’s Brochure, subject recruitment materials or advertising, and other documents required by regulations, which are to be submitted to the corresponding EC in of the study site for approval. Prior to the start of the trial, written approval from the EC must be obtained and submitted to the sponsor. The written approval from the EC shall specify the name, number, version number and version number of other documents (such as ICF) and date of approval. The investigator is required to notify the sponsor of the EC's written comments regarding delay, interruption, and re-approval of the study.

The study site must follow the requirements of the EC in the study site. Protocol modifications, ICF or recruitment materials shall be submitted to the EC for approval. Local safety reports shall be made and updated regularly in accordance with the regulations from the EC, and the final report

shall be submitted. All the above documents and EC approvals must be provided to the sponsor or designee.

10.2 Ethics

The process of study and informed consent are subject to the Declaration of Helsinki, relevant GCP requirements, as well as laws and regulations related to the protection of drug and data in China.

GCP provides ethical and scientific, global quality standards for the design, implementation, documentation, and reporting of clinical studies involving human subjects. This study will be conducted in accordance with the GCP and relevant national regulations and in accordance with the relevant ethical principles of the Declaration of Helsinki to protect the rights, safety, and health of the subjects.

The investigator is required to follow the procedures specified in this protocol and must not change the procedures without the permission from the sponsor. Any protocol violations must be reported to the EC, sponsor, or regulatory authorities.

10.3 Subject Information and Informed Consent

Before the start of any study process, the ICF is used to explain the risks and benefits of this study to potential participants, and the expression used in the ICF shall be straightforward. The ICF statement shall clarify that this ICF is voluntarily signed, and the risks and benefits of participating in this study shall be clearly outlined. The subject can withdraw from the study at any time. Subjects can only be enrolled if he/she fully understands the study in detail, has received satisfactory answers to his/her inquiries, and has sufficient time for consideration. Written consent must also be obtained from the subject or his/her legal representative. All the signed ICFs must be kept in the investigator's files or in the subject's folder.

The investigator is responsible for the interpretation of the ICF to the subject, obtaining informed and dated ICF from the subject or his/her legal representative prior to the start of the study. After signing, the investigator shall send the subject a copy of the signed ICF. The investigator is required to document the process of informed consent in the source study document.

10.4 Data Protection of Subjects

An ICF shall include (or in some cases, use separate files together) information on data and privacy protection.

Take precautions to ensure the confidentiality of the documents and prevent the disclosure of information that can determine the identity of the subject. However, under special circumstances, some personnel may be permitted to see the genetic data and personal identification number of a subject. For example, in the event of a medical emergency, the sponsor, designated physician, or investigator will have access to the subject identification code and the subject's genetic data. In addition, relevant regulatory authorities require access to relevant documents.

11 Study Management

11.1 Data Processing and Record Keeping

Records from the clinical trial (such as protocol and protocol revision, completed eCRFs, and signed ICFs) are to be kept and managed in accordance with the GCP. The study sites shall keep these documents for 5 years after the end of the study.

The study documents shall be reasonably kept for future interviews or data traceability. Security and environmental risks shall be considered when storing documents.

No study documents shall be destroyed without the written consent from the sponsor and investigator. The investigator/study site may transfer the study documents to other parties that comply with the record-keeping requirements or to another location that meet record-keeping requirements only after notifying the sponsor and obtaining the written consent.

11.2 Source Data/File Access

The investigator agrees that the sponsor, CRO, and relevant authorized regulatory agencies shall have direct access to all the study-related documents, including medical records of the subjects.

11.3 Protocol Amendments

Any possible amendments to the protocol during the course of the study will be communicated between and agreed by the sponsor and the investigator. The sponsor shall ensure that the protocol amendment is submitted to the regulatory authority in a timely manner.

All revisions to the protocol shall be kept as supplements to the protocol. Any changes to the protocol must be submitted to the EC for approval or filing in accordance with the ECs regulations. If necessary, it shall also be submitted to regulatory authorities for approval and only implemented after being approved by the EC and regulatory authorities (if applicable) (with the exception of changes to the protocol that eliminate direct hazards to the trial subjects).

11.4 Responsibilities of the Investigator

The investigator shall adhere to the protocol, ethical principles of the Declaration of Helsinki, Chinese GCP and requirements of the corresponding regulations for this study.

The detailed responsibilities of the relevant investigators are listed in Chapter 5 (Investigator's Responsibilities) of the Chinese GCP (Order No. 3).

11.5 Publishing Policy

All the data generated in this study is the confidential information owned by the sponsor. The sponsor has the right to publish study results. Information on the publishing policies of the sponsor and investigator will be described in the clinical trial agreement.

All the information on this trial (not limited to the protocol and Investigators Brochure) must be kept strictly confidential. The investigator must recognize that the scientific or medical information derived from this trial may be of commercial value to the sponsor. The investigator shall keep the information and data related to this study confidential. The sponsor must be consulted in advance and written consent must be obtained prior to publishing of any study-related information or conclusions. In order to protect the rights and interests, the sponsor may request the investigator not to publish information on this trial before the investigational product is approved for marketing.

The sponsor has the right to announce or publish information or data related to the trial or to report it to the drug administration. The sponsor must obtain the consent of the investigator if the name of the investigator is included in the content of the announcement, publication or advertising.

11.6 Financing and Insurance

The sponsor shall purchase insurance for participants in the study in accordance with local regulations and minimum requirements. Insurance related terms shall be saved in the study folder.

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13 Appendixes

Appendix 1: Signature Page for Investigator

Protocol Title: A Multicenter, Single Arm, Phase II Clinical Trial Evaluating the Efficacy and Safety of IBI308 Monotherapy for the Treatment of Relapsed or Refractory Extranodal NK/T-Cell Lymphoma, Nasal Type (ORIENT-4)

Protocol Number: CIBI308D201

This protocol is a trade secret owned by Innovent Biologics (Suzhou) Co., Ltd.. I have read and fully understood this protocol, and agree to conduct this study in accordance with the requirements found in this protocol and the Good Clinical Practice, and in compliance with relevant laws and regulations and the Declaration of Helsinki. Also, I promise not to reveal any confidential information to a third-party without the written consent from Innovent Biologics (Suzhou) Co., Ltd..

Instructions for investigators: please sign and date this page, print the name of the investigator, position, and study site, and return the signed form to Innovent Biologics (Suzhou) Co., Ltd..

I have read the entire contents of this study protocol and shall perform the study as required:

Signature of Investigator: _____ Date: _____

Name (Print): _____

Title of Investigator: _____

Study Site/Address: _____

_____

_____

APPENDIX 2: ECOG PERFORMANCE STATUS

ECOG PERFORMANCE STATUS

Grade	Description
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (e.g., light housework, office work).
2	In bed <50% of the time. 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	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours
4	100% bedridden. Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair.
5	Dead.

Oken M, Creech R, Tormey D, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol. 1982;5:649-655.

APPENDIX 3: Lugano 2014 Recommendations

Lugano 2014 will be used in this study for assessment of non-Hodgkin lymphoma. As published in the journal of clinical oncology.

Cheson, B. D., et al. (2014). "Recommendations for initial evaluation, staging, and response assessment of Hodgkin and non-Hodgkin lymphoma: the Lugano classification." J Clin Oncol 32(27): 3059-3068.

APPENDIX 4 IWG 2007 Recommendations

IWG 2007 will be used in this study for assessment of non-Hodgkin lymphoma. As published in the journal of clinical oncology.

Cheson, B. D., et al. (2007). "Revised response criteria for malignant lymphoma." J Clin Oncol 25(5): 579-586.

Appendix 5: Abnormal Hepatic Function Monitoring and Follow-Up Report

Please submit the report to Innovent PV:

Fax: 021-31652800 Email: drugsafety@innoventbio.com

Contact information of reporter (please provide the followings in order to receive a timely response):

Reporter's Email: Reporter's Telephone:

Reporter's Signature: Date of Report:

Abnormal Hepatic Function Follow-Up Information:

Trial Number: Subject Number:

1. Symptoms of abnormal hepatic function (check the followings if present):

   Decreased appetit e☐, tired of grease ☐, indigestion ☐, nausea ☐, emesis ☐, bloating ☐, abdominal pain ☐, diarrhea ☐, constipation ☐, clay stool ☐, fatigue ☐, weakness ☐, lethargy ☐, weight loss ☐, asterixis ☐, mental state changes ☐, hemorrhagic tendency ☐, fever ☐, others ☐

2. Signs of abnormal hepatic function (check the followings if present):

   Facial appearance of liver disease ☐, spider nevus ☐, liver palm ☐, ascites ☐, abdominal wall varicose veins ☐, jaundice ☐, yellow body fluid ☐, hepatomegaly ☐, splenomegaly ☐, liver area tenderness ☐, hepatic encephalopathy ☐, dyspnea ☐, crackles ☐, peripheral edema ☐, jugular varicose veins ☐, abnormal heart sounds ☐, others ☐

3. Disease history (check the followings if present):

   Viral hepatitis (HBV-A ☐; HBV-B ☐; HBV-C ☐; HBV-D ☐; HBV-E ☐), alcoholic hepatitis ☐, fatty liver ☐, hepatic cancer ☐, hepatic metastasis ☐, hepatic cirrhosis ☐, liver transplantation ☐, blood transfusion ☐, elevated liver enzymes prior to investigational drug administration ☐, autoimmune disease ☐, biliary tract disease ☐, cardiovascular disease ☐, hypotension ☐, diabetes ☐, surgery ☐, bone metastasis or bone damage ☐, HIV infection ☐, EB virus infection ☐, drug toxicity ☐, obesity ☐, others ☐

4. Family history (check the followings if present):

5. Concomitant medication and diet (check the followings if present):

Chemotherapy ☐, Chinese herbal medicine ☐, OTC ☐, dietary supplement ☐, alcohol consumption ☐, drug abuse ☐, history of chemical exposure ☐, anti-infectives ☐, paracetamol ☐, NSAIDS ☐, metronidazole ☐, others ☐

6. All the relevant laboratory test results (include those at the baseline, during treatment period, and after the treatment. If tested, please check and provide the **test results**, **units and reference ranges**):

   Count of whole blood cells ☐,

   Eosinophil count ☐,

   AST ☐, ALT ☐, ALP ☐, GGT ☐,

   Total bilirubin ☐/Direct bilirubin ☐,

   Total serum protein ☐/Albumin ☐/Immunoglobulin ☐,

   Total cholesterol ☐/cholesterol ester ☐,

   Coagulation function ☐, such as:

   Other ☐, such as:

7. Serologic tests (if performed, please check and provide the **test results)**:

   Epstein-Barr virus (EBV) ☐,

   Cytomegalovirus (CMV) ☐,

   Herpes simplex virus (HSV) ☐,

   Toxoplasmosis ☐,

   Hepatitis (A ☐, B ☐, C ☐, D ☐, E ☐),

   HIV ☐,

   Anti-nuclear antibodies ☐,

   Other antibodies ☐, such as:

   Others ☐, such as:

8. Auxiliary tests or procedures (if performed, please check and provide the **test results)**:

   Liver ultrasound ☐,

   Abdominal CT ☐,

   Liver biopsy ☐,

   Liver transplantation (planned or completed) ☐,

Others □, such as:

Appendix 6: List of Pre-Existed Autoimmune Diseases Prior to Enrollment

Ask whether the subject has acquired or congenital immunodeficiency or autoimmune diseases. These subjects are excluded from the study. Unless the subject has a history of allergic reactions and juvenile arthritis, the likelihood of suspected autoimmune disease is very low. In addition, subjects with transient autoimmune manifestations due to acute infections (such as Lyme arthritis) can enroll if have been treated with antibiotics. If an autoimmune disease cannot be confirmed, please contact the sponsor's medical manager.

Autoimmune diseases include but are not limited to:

Acute sporadic encephalomyelitis
IgA nephropathy
Addison's disease
Inflammatory bowel disease
Alopecia
Interstitial cystitis
Ankylosing spondylitis
Myasthenia gravis
Antiphospholipid antibody syndrome
Lupus
Aplastic anemia
Lyme disease (chronic)
Asthma
Meniere's syndrome
Autoimmune hemolytic anemia
Corneal ulcer
Autoimmune hepatitis
Localized autoimmune hypophysitis
Multiple sclerosis
Autoimmune hypoparathyroidism
Myasthenia gravis

Autoimmune myocarditis
Neuromuscular ankylosis
Autoimmune ovaritis
Myoclonus syndrome
Autoimmune orchitis
Optic neuritis
Autoimmune thrombocytopenia purpura
Ord's thyroiditis
Bechet disease
Pemphigus
Bullous pemphigoid
Pernicious anemia
Celiac disease
Multiple arteritis
Chronic fatigue syndrome
Polyarthritis
Chronic inflammation demyelinating Polyneuropathy
Autoimmune syndrome
Churg-Strauss syndrome
Primary biliary cirrhosis
Crohn's disease
Psoriasis
dermatomyositis

Rett syndrome
Type I diabetes
Rheumatoid arthritis
Autonomic dysfunction
Sarcoidosis
Eczema
Scleroderma
Sjogren syndrome
Bullous dermolysis
Stiff-person syndrome
Pemphigus during pregnancy
Takayasu arteritis
Giant cell arteritis
Ulcerative colitis
Pulmonary hemorrhage-glomerulonephritis syndrome
Vitiligo
Graves’ disease
Vogt-Kovanagi-Harada disease
Guillain-Barre syndrome
Vulvodynia
Hashimoto's disease

Wegener's granulomatosis
Kawasaki disease

Appendix 7: IBI308 Administration Adjustments and Toxicity Management

Table 1. IBI308 administration adjustments and toxicity management of major potential irAEs

<table>
<tr><th></th><th colspan="2">AE Grade/Administration Adjustments</th><th>Toxicity Management</th></tr>
<tr><td rowspan="4">General Principles</td><td colspan="2">AEs are graded according to NCI CTCAE v4.03. Refer to this guideline if the event is an irAE</td><td rowspan="4">It is recommended to manage irAEs according to the guideline in this table.
– Subjects shall be fully evaluated to rule out any alternative causes (e.g. PD, concomitant medication, infection, etc.)
– The event is an irAE if there are no clear alternative causes and treatment with corticosteroids is required
– Consider symptomatic and local treatment for low grade events (grade 1 or 2, unless otherwise stated)
– Consider systemic glucocorticoid therapy for persistent low grade events (grades 1–2) or severe events (grade ≥ 3)
– If the event re-occurs or worsens during tapering of glucocorticoids, the glucocorticoid dose shall be increased until symptoms resolve</td></tr>
<tr><td>Grade 1</td><td>No dose adjustments required</td></tr>
<tr><td>Grade 2</td><td>Interrupt
• If worsens, treat as a grade 3/4 event
• If reduces to grades 0–1 or baseline, continue the treatment at the next scheduled date</td></tr>
<tr><td>Grade 3</td><td>Interrupt or permanently discontinue</td></tr>
</table>

	AE Grade/Administration Adjustments		**Toxicity Management**
	Grade 4	Permanently discontinue	or improve, then taper with a lower rate - Once persistent clinical improvement is observed, subjects receiving glucocorticoids IV can start tapering the dose or switch to an equivalent dose of glucocorticoid PO at an earlier time (a lower bioavailability of oral administration should be considered) - For events that unresponsive to glucocorticoid treatment, consider a stronger immunosuppressants, e.g. TNF blockers (e.g. infliximab) or mycophenolate mofetil, after discussing with the physicians - For grade 3/4 local inflammation of lesions (such as local pain, irritation, and rash), IBI308 may be continued as determined by the investigator
Pneumonitis	Any grade		- Monitor signs and symptoms of pneumonitis or interstitial lung disease (e.g. new shortness of breath, cough, chest pain or exacerbation of existing symptoms and signs), evaluate subjects by imaging, pulmonary function, and other examinations - Initial examination may include clinical evaluation, arterial oxygen saturation, laboratory tests, and high-resolution CT scans
	Grade 1	No dose adjustments required However, consider interrupting the treatment based on clinical needs and during diagnostic tests for other causes	For grade 1 events: - Monitor signs and symptoms and arterial oxygen saturation for 2–4 days - Perform other laboratory tests if clinically indicated - Consider consulting a respirologist and infectious diseases specialist

	AE Grade/Administration Adjustments		**Toxicity Management**
	Grade 2	Interrupt • If worsens, treat as a grade 3/4 event • If reduces to grades 0–1 or baseline, continue the treatment at the next scheduled date	For grade 2 events: − Monitor signs and symptoms daily, consider hospitalization − Discuss with sponsor's medical manager, consider systemic glucocorticoid treatment − Repeat imaging if clinically indicated − If no improvement is seen within 3–5 days, consider other tests and increasing the glucocorticoid dose − If no improvement is seen within 3–5 days, consider a stronger immunosuppressant (e.g. infliximab) − Once improved, taper glucocorticoids within 4 weeks, and consider prophylactic antibiotic − Consider consulting a respirologist and infectious diseases specialist

	AE Grade/Administration Adjustments		**Toxicity Management**
	Grade 3 or grade 4	Permanently discontinue	For grade 3–4 events: - Discuss with sponsor's medical manager - Consider consulting a respirologist and infectious diseases specialist - Hospitalization - Supportive care (oxygen) - Begin systemic glucocorticoid treatment based on experience - If no improvement is seen within 3–5 days, consider other tests and stronger immunosuppressants (e.g. infliximab) - Once improved, taper glucocorticoids within 4 weeks, and consider prophylactic antibiotic
Diarrhea or Enterocolitis	Any grade		- Monitor possible signs and symptoms related to diarrhea/enterocolitis (abdominal pain, enterospasm, changes in bowel habits, melena, mucous stool, bloody stool, or muscle guarding) - Subjects shall be fully evaluated to rule out any alternative causes (e.g. PD, infection, etc.) - If alternative causes cannot be determined, consider glucocorticoid treatment for low grade events to prevent from escalating to high grade - Use analgesics with caution (may mask the symptoms of perforation and peritonitis)

	AE Grade/Administration Adjustments		**Toxicity Management**
	Grade 1	No dose adjustments required	For grade 1 events: - Closely monitor symptom exacerbation - Consider symptomatic treatment, including fluid replacement, electrolyte replacement, diet modifications, and loperamide administration
	Grade 2 or Grade 3	Interrupt • If worsens, treat as a grade 3/4 event • If reduces to grades 0–1 or baseline, continue the treatment at the next scheduled date	For grade 2–3 events: - Consider symptomatic treatment, including fluid replacement, electrolyte replacement, diet modifications, and loperamide and/or budesonide administration - If the event persists for > 3–5 days or worsens, consider systemic corticosteroid treatment - If no improvement is seen within 3–5 days, consider other tests and increasing the glucocorticoid dose - If no improvement is seen or exacerbation occurs within 3–5 days, consider other tests and stronger immunosuppressants (e.g. infliximab) - If not reduces to grade 0–1 within 3–4 days, discuss with sponsor's medical manager - Once improved, taper glucocorticoids within 4 weeks, and consider prophylactic antibiotic

	AE Grade/Administration Adjustments		**Toxicity Management**
	Grade 4	Permanently discontinue	For grade 4 events: - Monitor frequency and volume of bowel movement, maintain hydration - If applicable, perform emergency GI consultation and lower GI endoscopy and imaging to confirm the presence of intestinal perforation - Begin systemic glucocorticoid treatment based on experience - If no improvement is seen within 3–5 days, consider increasing the glucocorticoid dose - If no improvement is seen within 3–5 days, consider other immunosuppressants (e.g. infliximab, but not in subjects with perforations or sepsis) - Once improved, taper glucocorticoids within 4 weeks, and consider prophylactic antibiotic

	AE Grade/Administration Adjustments		**Toxicity Management**
Hepatitis (ALT, AST, or TBIL increased)	Any grade		– Monitor hepatitis-related signs and symptoms (e.g. jaundice, tea-colored urine, nausea, emesis, loss of appetite, hepatalgia, hemorrhagic tendency, etc.) – Monitor and evaluate hepatic function – Evaluate alternative causes (e.g. viral hepatitis, PD, concomitant medication) – The dose adjustments and toxicity management in this table is applicable only to subjects with normal ALT, AST, and TB at baseline; for subjects with ALT, AST, or TB > ULN at baseline, interrupt the drug if ALT, AST, or TB elevation of ≥ 50% for < 7 days and discontinue permanently if ALT, AST, or TB elevation of ≥ 50% for ≥ 7 days. Toxicities should be managed based on the investigator's clinical judgment.
	Grade 1	No dose adjustments required	For grade 1 events: – Continue monitoring hepatic function according to protocol

	AE Grade/Administration Adjustments		**Toxicity Management**
	Grade 2	Interrupt • If worsens, treat as a grade 3/4 event • If reduces to grades 0–1 or baseline, continue the treatment at the next scheduled date	For grade 2 events: – If not reduces to grade 0–1 within 3–4 days, discuss with sponsor's medical manager – For ALT, AST, or TBIL elevations, retest hepatic function within 3–4 days and increase monitoring frequency – If the event persists for > 3–5 days or worsens, consider systemic corticosteroid treatment – If no improvement is seen within 3–5 days, consider other tests and increasing the glucocorticoid dose – If no improvement is seen within 3–5 days, consider stronger immunosuppressants (e.g. mycophenolate mofetil) – Once improved, taper steroids within 4 weeks, and consider prophylactic antibiotic

	AE Grade/Administration Adjustments		**Toxicity Management**
	Grade 3 or grade 4	Permanently discontinue	For grade 3–4 events: - Discuss with sponsor's medical manager - Begin systemic glucocorticoid treatment based on experience - If no improvement is seen within 3–5 days, consider stronger immunosuppressants (e.g. mycophenolate mofetil) - If no improvement is seen within 3–5 days, consider other immunosuppressants based on local guidelines - If applicable, consult a gastroenterologist, perform abdominal examination and imaging - Once improved, taper glucocorticoids within 4 weeks, and consider prophylactic antibiotic
Dermatitis	Any grade		- Monitor signs and symptoms or dermatitis, e.g. rash, exudation, hypopigmentation, photaesthesia, and pruritus - If there is formation of bullae, contact the sponsor's medical manager - Consult a dermatologist - Perform skin biopsy when necessary
	Grade 1	No dose adjustments required	For grade 1 events: - Consider symptomatic treatment, including oral antipruritic agents (e.g. diphenhydramine or hydroxyzine) and local treatment (e.g. urea cream or topical glucocorticoids)

	AE Grade/Administration Adjustments		**Toxicity Management**
	Grade 2	No dose adjustments required • For a refractory (> 1–2 weeks) grade 2 event, interrupt until reduces to grades 0–1 or baseline, continue the treatment at the next scheduled date	For grade 2 events: − Consider symptomatic treatment including oral antipruritic agents and local treatment − Consider a medium-potency topical glucocorticoid − If no improvement is seen with 3–5 days, discuss with sponsor's medical manager and consider systemic glucocorticoid treatment − Consult a dermatologist − Consider skin biopsy if persists for > 1–2 weeks or relapses − Once improved, taper glucocorticoids within 4 weeks, and consider prophylactic antibiotic
	Grade 3	Interrupt • If worsens, treat as a grade 4 event • Permanently discontinue if a grade 3 rash does not reduce to grades 0–1 or baseline within 30 days	For grade 3–4 events: − Discuss with sponsor's medical manager − Consider hospitalization − Monitor affected area (rule of nine) − Consult a dermatologist − If clinically feasible, consider skin biopsy (preferably more than once) − Begin systemic glucocorticoid treatment based on experience − If no improvement is seen within 3–5 days, consider other tests and increasing the glucocorticoid dose − Once improved, taper glucocorticoids within 4 weeks, and consider prophylactic antibiotic
	Grade 4	Permanently discontinue	

	AE Grade/Administration Adjustments		**Toxicity Management**
Hypopituitarism	All grades		- Monitor signs and symptoms of endocrine disorders, including weakness, fatigue, drowsiness, nausea, emesis, chills, changes in bowel habits, behavioral changes, mental state changes, hypotension, hypoglycemia, dizziness, headache, impaired vision, low libido in males, irregular menstruation in females, etc. - Subjects shall be fully evaluated to rule out any alternative causes (e.g. PD, brain metastasis, infection, etc.) - Monitor and evaluate pituitary function: TSH, FT3, FT4, adrenocorticotropic hormone, cortisol, luteinizing hormone, follicle stimulating hormone, growth hormone, prolactin, Na^+, blood glucose, estradiol, testosterone, and other laboratory parameters related to endocrine disorders. Perform functional tests when necessary (including adrenocorticotropic hormone (ACTH) stimulation test and insulin-induced hypoglycemia test) - Consider pituitary MRI - Consider consulting an endocrinologist - Consider testing for autoantibodies
	Grade 1	No dose adjustments required	For grade 1 events: - Monitor pituitary function - Subjects shall be fully evaluated to rule out any alternative causes - Consider consulting an endocrinologist if clinically indicated

	AE Grade/Administration Adjustments		**Toxicity Management**
	Grade 2	Interrupt • If worsens to grades 3–4, permanently discontinue • If reduces to grades 0–1 or baseline, continue the treatment at the next scheduled date	For grade 2–4 events: – Discuss with sponsor's medical manager – Consult an endocrinologist – Hospitalization when necessary – Evaluate endocrine function, consider pituitary MRI if clinically indicated – Begin hormone replacement therapy when necessary (cortisone replacement therapy shall begin one week prior to levothyroxine treatment) – Begin immunosuppressive therapy based on experience, consider systemic glucocorticoid treatment – Once improved, taper glucocorticoids within 4 weeks (the dose of cortisone used for hormone replacement may be adjusted accordingly, but subjects whose endocrine function do not recover require long-term treatment); consider prophylactic antibiotic during taper to prevent infections
	Grade 3 or grade 4	Permanently discontinue	

	AE Grade/Administration Adjustments		**Toxicity Management**
Adrenocortical Insufficiency	Any grade		- Monitor signs and symptoms of endocrine disorders, including fatigue, pigmentation, loss of appetite, hypotension, and weakness - Subjects shall be fully evaluated to rule out any alternative causes - Monitor and evaluate adrenal function: cortisol, adrenocorticotropic hormone, blood sodium, blood potassium, blood glucose, and other endocrine laboratory parameters suspected to be related to adrenal function. The ACTH stimulation test shall be performed when necessary - Immunosuppressive therapy when necessary - Hormone replacement therapy (cortisone) when necessary - Consider consulting an endocrinologist - Consider testing for autoantibodies
	Grade 1	No dose adjustments required	For grade 1 events: – Monitor adrenal function – Consider consulting an endocrinologist if clinically indicated
	Grade 2	Interrupt • If worsens to grades 3–4, permanently discontinue • If reduces to grades 0–1 or baseline, continue the treatment at the next scheduled date	For grade 2 events: – Discuss with sponsor's medical manager – Evaluate adrenal function, begin hormone replacement therapy when necessary

	AE Grade/Administration Adjustments		**Toxicity Management**
	Grade 3 or grade 4	Permanently discontinue	For grade 3–4 events: – Discuss with sponsor's medical manager – Consult an endocrinologist – Consider systemic corticosteroid treatment – Begin corticosteroids with mineralocorticoid activity immediately for adrenal crisis, severe dehydration, hypotension, or shock – Once improved, taper glucocorticoids within 4 weeks (the dose of cortisone used for hormone replacement may be adjusted accordingly, but subjects whose endocrine function do not recover require long-term treatment); consider prophylactic antibiotic during taper to prevent infections
Hyperthyroidism/Hypothyroidism	Any grade		- Monitor signs and symptoms of thyroid dysfunction, e.g. hyperthyroidism (palpitations, sweating, increased appetite and bowel movement, and weight loss) and hypothyroidism (general weakness, fatigue, cold, memory loss, and constipation) - Subjects shall be fully evaluated to rule out any alternative causes - Monitor and evaluate thyroid function - Consider consulting an endocrinologist - Consider testing for thyroid autoantibodies (antithyroglobulin antibodies, anti-thyroid peroxidase antibodies, and thyroid-stimulating hormone receptor antibodies)

	AE Grade/Administration Adjustments		**Toxicity Management**
	Grade 1 or grade 2	No dose adjustments required	For grade 1–2 events: – Monitor thyroid function and thyroid autoantibodies regularly – L-thyroxine replacement therapy or anti-thyroid medications when necessary
	Grade 3 or grade 4	Hyperthyroidism • Permanently discontinue Hypothyroidism • No dose adjustments • required	For grade 3–4 events: – Discuss with sponsor's medical manager – Monitor thyroid function and thyroid autoantibodies – Consult an endocrinologist *Hyperthyroidism* – Anti-thyroid medications – Consider β-blockers for tachycardia *Hypothyroidism* – L-thyroxine replacement therapy
Type I Diabetes	Any grade		– Monitor signs and symptoms closely, e.g. polyuria, polydipsia, polyphagia, fatigue, weakness, and weight loss – Subjects shall be fully evaluated to rule out any alternative causes – Monitor and assess pancreas islet function: blood glucose, insulin, c-peptide, β-cell autoantibodies, blood ketones, and other endocrine laboratory parameters related to type I diabetes
	Grade 1 or grade 2	No dose adjustments required	For grade 1–2 events: – Monitor and assess pancreas islet function – Start insulin therapy when necessary

	AE Grade/Administration Adjustments		**Toxicity Management**
	Grade 3	Interrupt – Resume treatment after blood glucose is under control	For grade 3–4 events: – Consult with sponsor's medical manager – Monitor and assess pancreas islet function – Consider consulting an endocrinologist – Blood glucose control with insulin, adjust insulin dose accordingly – If ketoacidosis occurs, subjects shall be hospitalized to receive insulin, fluid replacement, and alkali therapy
	Grade 4	Permanently discontinue	
Renal Insufficiency (Creatinine Elevated)	Any grade		– Monitor signs and symptoms closely (e.g. oliguria, dark urine, anemia, fatigue, and weight loss) – Subjects shall be fully evaluated to rule out any alternative causes – Monitor and evaluate renal function – Consider consulting a nephrologist – Consider kidney biopsy when necessary to distinguish between inflammatory and non-inflammatory causes
	Grade 1	No dose adjustments required	For grade 1 events: - Monitor creatinine levels Q1W - If creatinine level returns to baseline level, resume routine creatinine monitoring according to the study protocol

	AE Grade/Administration Adjustments		**Toxicity Management**
	Grade 2 or grade 3	Interrupt • If reduces to grades 0–1 or baseline, continue the treatment at the next scheduled date • If persists for > 7 days or worsens, treat as a grade 4 event	For grade 2–3 events: − Discuss with sponsor's medical manager − Monitor creatinine levels every 2–3 days − Begin systemic glucocorticoid treatment based on experience − If reduces to grade 1, taper glucocorticoid for at least 1 month**,** consider prophylactic antibiotic to prevent infections − Consider kidney punch biopsy − Consult a nephrologist
	Grade 4	Permanently discontinue	For grade 4 events: − Discuss with sponsor's medical manager − Monitor creatinine levels once daily − Begin systemic glucocorticoid treatment based on experience − If reduces to grade 1, taper glucocorticoid for at least 1 month**,** consider prophylactic antibiotic to prevent infections − Consult a nephrologist − Consider kidney punch biopsy

	AE Grade/Administration Adjustments		**Toxicity Management**
Immune-related neurotoxicities (except for myasthenia gravis and Guillain-Barrésyndrome)	Any grade		- Monitor the subject's systemic symptoms (headache, nausea, dizziness, behavioral changes, or weakness) - Subjects shall be fully evaluated to rule out any alternative causes (e.g. PD, infection, metabolic syndrome, medications, etc.) - Consider appropriate diagnostic tests (e.g. electromyography and nerve conduction study) - If applicable, begin symptomatic treatment and consult a neurologist
	Grade 1	No dose adjustments required	- Closely monitor signs and symptoms
	Grade 2	Interrupt • If reduces to grades 0–1 or baseline, continue the treatment at the next scheduled date • If worsens, treat as a grade 3 event	For grade 2–4 events: - Discuss with sponsor's medical manager - Consider consulting a nephrologist - Hospitalization when necessary - Manage neuropathy and neuropathic pain with appropriate medications (e.g. gabapentin, duloxetine, etc) - Consider systemic corticosteroid treatment - If no improvement is seen within 3–5 days, consider other tests and immunosuppressants (e.g. intravenous immunoglobulin G, IVIgG) - Once stabilized, taper glucocorticoids within ⩾ 4 weeks
	Grade 3	Permanently discontinue	
	Grade 4		

	AE Grade/Administration Adjustments		**Toxicity Management**
Immune-related peripheral neuropathy, e.g. Guillain-Barré syndrome and myasthenia gravis	Any grade		- Monitor signs and symptoms closely (myasthenia gravis: eye or limb soreness and discomfort, blurred vision, fatigue, which worsens as the day goes on; Guillain-Barrésyndrome: sudden and severe nerve pain, paralysis of the limbs, and prickling or burning sensation in the limbs) - Timely diagnosis of immune-related peripheral neuropathy is very important, as subjects may suffer from unpredictable acute compensation, which may lead to severe disease or death.Pay special attention to signs and symptoms that may indicate serious consequences, e.g. significant dysphagia, rapidly progressive weakness, respiratory insufficiency, or autonomic dysfunction - Neuroelectrophysiological tests shall be performed to rule out any alternative causes (e.g. PD, infection, metabolic syndrome, medications, etc.) It is worth noting that cancer itself and cancer treatment can affect neural function. The diagnosis of immune-related peripheral neuropathies is thus difficult. Neurological consultation shall be actively carried out. - Plasmapheresis or IVIgG should be considered for subjects with Guillain-Barrésyndrome (glucocorticoids ar e generally ineffective)
	Grade 1	No dose adjustments required	For grade 1 events: - Discuss with a physician - Monitor signs and symptoms - Consider consulting a nephrologist

<table>
<tr><th></th><th colspan="2">AE Grade/Administration Adjustments</th><th>Toxicity Management</th></tr>
<tr><td rowspan="2"></td><td>Grade 2</td><td>Interrupt
• If reduces to grades 0–1 or baseline, continue the treatment at the next scheduled date
• If worsens, treat as a grade 3–4 event</td><td rowspan="2">For grade 2–4 events:
− Discuss with sponsor's medical manager
− Monitor signs and symptoms
− Consider consulting a nephrologist
− Hospitalization when necessary
− Manage neuropathy and neuropathic pain with appropriate medications (e.g. gabapentin, duloxetine, etc.)
Myasthenia Gravis
− Glucocorticoids may be used to treat myasthenia gravis (shall be used under the supervision of a neurologist since corticosteroids, especially high-dose, may result in initial exacerbation of symptoms)
− Subjects intolerant to glucocorticoids may be treated with plasmapheresis or IVIgG
− For myasthenia gravis-like neurotoxicities, consider acetylcholinesterase inhibitors in addition to glucocorticoids
Guillain-Barre Syndrome
− Plasmapheresis or IVIgG should be considered for subjects with Guillain-Barrésyndrome (glucocorticoids are generally ineffective)</td></tr>
<tr><td>Grade 3 or grade 4</td><td>Permanently discontinue</td></tr>
</table>

Table 2. IBI308 administration adjustments and toxicity management of other potential irAEs

	CTD Grade/Administration Adjustments	Toxicity Management
Any grade	Dose adjustments are not required for AEs unrelated to study treatment or laboratory abnormalities that are not clinically significant (events caused by underlying disease)	Manage based on local clinical practice
Grade 1	No dose adjustments required	
Grade 2	Consider interruption until reduces to grade 0–1 or baseline	
Grade 3	• First occurrence: interrupt until reduces to grade 0–1 or baseline • Second occurrence: permanently discontinue • For an AE that reduces to grades 0–2 within 7 days, or grades 0–1 or baseline within 14 days, interrupt and then resume the treatment at the next scheduled date Otherwise, permanently discontinue	
Grade 4	Permanently discontinue (Note: for grade 4 laboratory abnormalities, the event shall be determined based on clinical signsasymptoms and the clinical judgment of the investigator)	

Table 3. Dose adjustments and toxicity management for infusion reactions

CTD Grade	Administration Adjustments	Toxicity Management
Any grade		– Manage based on local clinical practice – Monitor infusion-related reactions (e.g. fever or chills, flushing and/or pruritus, changes in heart rate and blood pressure, dyspnea, chest discomfort, rash, etc.) and allergic reactions (e.g. systemic urticaria, angioedema, asthma, hypotension, tachycardia, etc.)
Grade 1	Reduce to 50% of the original infusion rate or interrupt the infusion until the infusion reaction resolves	For grade 1–2 events: – Administer acetaminophen and/or antihistamine according to local clinical practice based on the investigator' judgment – Consider prophylactic premedications for subsequent infusion according to local clinical practice
Grade 2	Reduce to 50% of the original infusion rate or interrupt the infusion until the infusion reaction resolves, then resume at 50% of the original infusion rate	
Grade 3/4	Permanently discontinue	For grade 3–4 events: – Manage severe infusion-related reactions according to local clinical practice (e.g. administration of epinephrine, diphenhydramine, ranitidine, and glucocorticoids)

Appendix 8: EQ-5D-5L Scale

By placing a tick (√) in one box in each group below, please indicate which statements best describe your own health state today.

Mobility

I have no problems in walking about. ☐

I have slight problems in walking about. ☐

I have moderate problems in walking about. ☐

I have severe problems in walking about. ☐

I am unable to walk about. ☐

Self-Care

I have no problems caring for myself. ☐

I have slight problems washing or dressing myself. ☐

I have moderate problems washing or dressing myself. ☐

I have severe problems washing or dressing myself. ☐

I am unable to wash or dress myself. ☐

Usual Activities (e.g. work, study, housework, family or leisure activities)

I have no problems with performing my usual activities. ☐

I have slight problems performing my usual activities. ☐

I have moderate problems performing my usual activities. ☐

I have severe problems performing my usual activities. ☐

I am unable to perform my usual activities. ☐

Pain/Discomfort

I have no pain or discomfort. ☐

I have slight pain or discomfort. ☐

I have moderate pain or discomfort. ☐

I have severe pain or discomfort. ☐

I have extreme pain or discomfort. ☐

Anxiety/Depression

I am not anxious or depressed. ☐

I am slightly anxious or depressed. ☐

I am moderately anxious or depressed ☐

I am severely anxious or depressed ☐

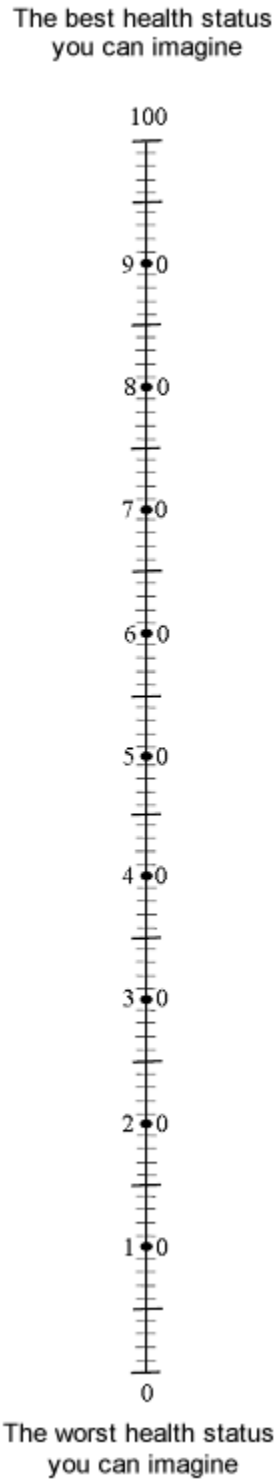
I am extremely anxious or depressed ☐

To help reflect your health status, we have drawn a scale (similar to a thermometer). On this scale, the best health status you can imagine is marked 100 and the worst health status you can imagine is marked 0.

Please mark your health status today on the scale on the right.

Please draw a line from the box to the point on the scale that indicates how good or bad your health status is today.

Your health status today



Appendix 9: EORTC-QLQ-C30 (v3) Quality of Life Scale

We would like to know about you and your health status. Please answer all the questions yourself by circling the number that best applies to you. There are no "right" or "wrong" answers. The information that you provide will be kept confidential.

Please fill in your initials:_____

Date of Birth: _____ YYYY_____MM_____DD

Today's date: _____ YYYY_____MM_____DD

	Not at All	A Little	Quite a Bit	Very Much
1. Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase?	1	2	3	4
2. Do you have any trouble taking a long walk?	1	2	3	4
3. Do you have any trouble taking a shortwalk outside of the house?	1	2	3	4
4. Do you need to stay in bed or a chair during the day?	1	2	3	4
5. Do you need help with eating, dressing, washing yourself or using the	1	2	3	4

During the past week:	Not at All	A Little	Quite a Bit	Very Much
6. Were you limited in doing either your work or other daily activities?	1	2	3	4
7. Were you limited in pursing your hobbies or other leisure time activities?	1	2	3	4
8. Were you short of breath?	1	2	3	4
9. Have you had pain?	1	2	3	4
10. Did you need to rest?	1	2	3	4
11. Have you had trouble sleeping?	1	2	3	4
12. Have you felt weak?	1	2	3	4
13. Have you lacked appetite?	1	2	3	4

14. Have you felt nauseated?	1	2	3	4
15. Have you vomited?	1	2	3	4
16. Have you been constipated?	1	2	3	4

During the past week:	**Not at All**	**A Little**	**Quite a Bit**	**Very Much**
17. Have you had diarrhea?	1	2	3	4
18. Were you tired?	1	2	3	4
19. Did pain interfere with your daily activities?	1	2	3	4
20. Have you had difficulty in concentrating on things, like reading a	1	2	3	4
21. Did you feel tense?	1	2	3	4
22. Did you worry?	1	2	3	4
23. Did you feel irritable?	1	2	3	4
24. Did you feel depressed?	1	2	3	4
25. Have you had difficulty remembering things?	1	2	3	4
26. Has your physical condition or medical treatment interfered with your	1	2	3	4
27. Has your physical condition or medical treatment interfered with your	1	2	3	4
28. Has your physical condition or medical treatment caused you financial	1	2	3	4

For the following questions, please circle the number between 1 and 7 that best applies to you

29. How would you rate your overall <u>health</u> during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

30. How would you rate your overall <u>quality of life</u> during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

Summary of Amendment

Alternative Version 2 to Version 1 (Version Date:May.11, 2017)

Main change	Description
1. Sample sizes changed from minimum of 60 patients to 20-60 patients	When 28 patients were enrolled, several early PD were observed, and the Lugano 2014 criteria made response evaluation difficult due to the lack of a definition for pseudo-progression. Therefore, enrollment was paused, but treatment was continued to confirm the true nature of the pseudo-progression according to investigator's discretion. After 3 months of observation and in-depth analysis of the 28 patients, sintilimab demonstrated 67.9% ORR when taking pseudo-progression into consideration. Planned total enrollment was not reached. When hypothesizing that the 15 yet-to-be-enrolled patients would be non-responders, there would be 19 responders out of 43 (28 actually enrolled + 15 fictive), providing a 95% CI by Wilson's method of 30.4%-58.9%, where the lower boundary is still greater than the pre-planned 30% threshold. There's no need to enroll a total of 60 patients.
2. Add RNA expression as a biomarker	Detection of RNA expression could help to capture potential biomarker for predicting response.
3. Modify the tratement duration up to 24 months	No clinical benefit evidence to support a long treatment duration for more than 2 years.
4. Modify the final injection volume (after preparation) from 250 ml to 100 ml	Based on the updated stability test of sintilimab, the recommended final concentration is 1.5~2 mg/ml.
5. Remove the second interim analysis	There no need to perform a second interim analysis.