Clinical Study Protocol

Title	Efficacy and Safety Evaluation of IBI308 in Treatment of Patients With Relapsed/Refractory Classical Hodgkin's Lymphoma: a Multicenter, Single Arm, Phase II Study (ORIENT-1)
Protocol No.	CIBI308B201
Version Date	05Feb2018/Version2.0
Investigational Product	IBI308
Study Phase	Phase II
Sponsor	Innovent Biologics. Ltd

Sponsor Signature Page

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Title	Name (Print)	Signature	Date
Medical Director	Hui Zhou	Hui Zhou	2018.2.5

Synopsis

Protocol No.	CIBI308B201
Sponsor	Innovent Biologics. Ltd
Investigational Product	IBI308
Active Ingredient	Recombinant humanized anti-programmed death receptor 1 (PD-1) monoclonal antibody
Title	Efficacy and Safety Evaluation of IBI308 in Treatment of Patients With Relapsed/Refractory Classical Hodgkin's Lymphoma: a Multicenter, Single Arm, Phase II Study (ORIENT-1)
Study Phase	Phase II
Estimated Duration of Study	36 months
Objectives	**Primary Objectives** • ORR of IBI308 monotherapy in relapsed or refractory cHL assessed by IRRC (Independent Radiological Review Committee). **Secondary Objectives** • ORR of IBI308 monotherapy in relapsed or refractory cHL assessed by investigator; • CR and PR of IBI308 monotherapy in relapsed or refractory cHL; • DCR of IBI308 monotherapy in relapsed or refractory cHL; • TTR of IBI308 monotherapy in relapsed or refractory cHL; • DOR of IBI308 monotherapy in relapsed or refractory cHL; • PFS and 6-month PFS rates of IBI308 monotherapy in relapsed or refractory cHL; • Evaluate the safety of IBI308 monotherapy in patients with relapsed or refractory cHL. • Evaluate PK/PD/immunogenicity of IBI308 monotherapy in patients with relapsed or refractory cHL. • Evaluate the quality of life of patients with relapsed or refractory cHL after IBI308 monotherapy (according to the EQ-5D-5L and EORTC QLQ-C30 scales). **Exploratory Objectives** Assess the relationship between PD-L1 expression, immune-related gene mRNA, and other potential biomarkers in relapsed or refractory cHL and IBI308 efficacy.
Study Design	This study is a multicenter, single-arm, phase II study to evaluate the efficacy and safety of IBI308 in relapsed or refractory classic Hodgkin's lymphoma. This study will enroll patients with relapsed or refractory cHL to receive intravenous (IV) IBI308 at 200 mg every three weeks (Q3W) for up to 24 months, or until disease progression, death, unacceptable adverse event(s), subject withdraws informed consent or other reasons specified in protocol. If the subject still has no disease progression after 24 months of

	IBI308 treatment and the investigator judges that the subject will still benefit from the study drug, the subject should sign additional informed consent to continue receiving free IBI308 treatment. For subjects with first disease progression, if the clinical condition is stable, the investigator may let the subject continue to receive treatment until the total treatment time reaches 24 months or until disease progression, death, unacceptable adverse event(s), subject withdraws informed consent, or other reasons specified in protocol. The primary endpoint of the study is overall response rate (ORR), defined as the percentage of subjects with optimal response to partial and complete response, evaluated according to the IWG 2007 criteria, and the Lugano 2014 criteria as an adjunct to the standard, both evaluated by IRRC. Analysis of primary endpoints will be performed after the last subject who meets the statistical and imaging assessment requirements and completes up to 24 weeks of follow-up. Subjects will have a safety follow-up 90 days after the last dose of IBI308.
Inclusion Criteria	1. Histopathological confirmed classical Hodgkin's lymphoma (cHL). 2. Relapsed/refractory cHL patients who have failed after at least two lines of therapy (including radiotherapy and autologous hematopoietic stem cell transplantation, ASCT); subject with no response to or with progression after ASCT is eligible for enrollment. 3. At least one measurable disease (long axis>15 mm or short axis>10 mm, with uptake on ^{18}FDG-PET) 4. Eastern Cooperative Oncology Group Performance Status (ECOG PS) 0-2. 5. Sign the informed consent form and be willing and able to comply with scheduled visits and other requirements of the study. 6. Age ≥ 18. 7. Life expectancy ≥ 12 weeks. 8. Subjects of reproductive potential must be willing to use adequate contraception during the whole course of the study and through 90 days after the last dose of study medication. 9. Adequate organ and bone marrow function: 1) Count of Blood Cells: absolute neutrophil count (ANC) ≥ 0.75 × 10^9 / L; platelet count (PLT) ≥ 50 × 10^9 / L; hemoglobin content (HGB) ≥ 8.0 g / dL; no granulocyte colony-stimulating factor, platelet or red blood cells infusion in the last 14 days. 2) Liver function: total bilirubin (TBIL) ≤ 1.5 × normal upper limit (ULN); alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ≤ 2.5 × ULN. 3) Renal function: serum creatinine (Cr) ≤ 1.5 × ULN 4) Thyroid function: thyroid stimulating hormone (TSH) in normal range (TSH abnormalities due to non-autoimmune causes can be enrolled).

Exclusion Criteria	1. Known nodular lymphocyte predominant Hodgkin lymphoma. 2. Known central nervous system lymphoma. 3. Received ASCT within 90 days before the first dose of study medication. 4. Prior exposure to any anti-PD-1, anti-PD-L1 or anti-CTLA-4 antibody. 5. Currently participating in another interventional clinical study, unless participating in an observational study or during follow-up period of another interventional study. 6. Received any investigational agent within 4 weeks before the first dose of study medication. 7. Received last dose of radiotherapy or anti-tumor therapy (chemotherapy, targeted therapy, tumor immunotherapy or arterial embolization) within 3 weeks before the first dose of study medication; received last dose of nitrosourea or mitomycin C within 6 weeks before the first dose of study medication. 8. Received systemic treatment with corticosteroids (> 10 mg daily prednisone equivalent) or other immunosuppressive medications within 4 weeks before first dose. Inhaled, nasal spray or topical steroids and adrenal replacement steroid doses are permitted in the absence of active autoimmune disease. 9. Received a live vaccine within 4 weeks of the first dose of study medication or plan to receive live vaccine during study period. 10. Underwent major operation (craniotomy, thoracotomy or laparotomy) within 4 weeks of the first dose of study medication or with open wound, ulcer or fracture. 11. Activite, known or suspected autoimmune diseases or history of the disease with two years before enrollment. Vitiligo, psoriasis, hair loss, or Graves disease which do not need systemic treatment in 2 years, or hypothyroidism which only need thyroid hormone replacement therapy, or type-1 diabetes which only need insulin replacement therapy is eligible for enrollment. 12. Known primary immunodeficiency disorders. 13. Active tuberculosis. 14. Known history of allogeneic organ or allogeneic hemopoietic stem cell transplantation. 15. Known allergy or hypersensitivity to any monoclonal antibodies or any components used in their preparation. 16. Uncontrolled concomitant disease, including but not limited to : 1) Human Immunodeficiency Virus (HIV) infection (HIV antibody positive) 2) Active or poorly controlled severe infection 3) Symptomatic congestive heart failure (New York Heart Association grade Ⅲ-IV) or symptomatic, poorly controlled arrhythmia

	4) Poorly controlled arterial hypertension (SBP ≥ 160mmHg or DBP ≥ 100mmHg) with standard treatment 5) Prior arterial thromboembolism event, including myocardial infarction, unstable angina, stroke or transient ischemic attack, within 6 months before enrollment 6) Prior life-threatening blood loss or grade 3/4 gastrointestinal/varicosity bleeding requiring blood infusion, endoscopic or surgical intervention within 3 months of enrollment 7) Prior deep vein thrombosis, pulmonary embolism or any other severe thromboembolism events (implanted port or catheter caused thrombosis, or superficial vein thrombosis are not considered as severe thromboembolism events) within 3 months before enrollment 8) History of uncontrolled metabolic disorder, non-malignant organ or systemic disease or secondary carcinomatous reaction, with high medical risk and/or uncertainty of survival evaluation 9) With hepatic encephalopathy, hepato-renal syndrome or hepatic cirrhosis of Child-Pugh grade B or higher. 10) History of intestinal obstruction or the following diseases: inflammatory bowel disease or extensive bowel resection (partial colonic resection or extensive small bowel resection, concomitant with chronic diarrhea), Crohn's disease, ulcerative colitis or chronic diarrhea 11) Other acute or chronic diseases, mental illness, or abnormal laboratory test results that may lead to the following outcomes: increase the risk of participating in study or study drug administration, or interfere with the interpretation of the study results and considered by investigator as "NOT" eligible to participate in this study 17. Known acute or chronic active hepatitis B infection (chronic HBV carrier or non-active HBsAg positive subject is eligible) or acute or chronic active hepatitis C (HCV antibody negative subject is eligible; HCV RNA examination is required for HCV antibody positive subject, subject is eligible for enrollment if result was negative) 18. History of gastrointestinal perforation and /or fistula within 6 months before enrollment 19. Subjects with interstitial lung disease 20. Uncontrolled third space effusion, e.g. ascites or pleural effusion cannot be drained or controlled 21. Other primary malignancy, with the exception of: 1) Curable malignancy (e.g. papillary thyroid carcinoma) 2) Without active disease in the last 5 years and with very low recurrence risk

	3) Non-melanoma skin cancer or malignant freckle-like nevus with adequate treatment and no evidence of recurrence ; 4) Adequately treated in-situ carcinoma 22. Women who are pregnant or in lactation period.
Drug Administration	IBI308 100mg/10ml 200 mg i.v. Q3W
Evaluations	**Efficacy** ● Efficacy is evaluated according to IWG 2007 and Lugano 2014 by IRRC and the investigator, including ORR, DCR, TTR, DOR, PFS and PFS rate at 6 months. **Safety** ● Incidence, causality and severity of adverse events (AE), treatment emergent AEs, AEs of special interest, and serious AEs ● Vital sign, physical examinations, and laboratory examination, before, during and after treatment **Immunogenicity** ● Anti-drug antibody (ADA) and neutralizing antibody (NAB) **PK/PD** 12 subjects from selected research sites are included in PK/PD analysis ● To describe PK profiles of single and multiple dose of IBI308. PK parameters include area under curve (AUC), C_{max}, CL, V and $t_{1/2}$ ● PD analysis includes but not limited to PD-1 receptor occupancy **Biomarker** ● Samples will be collected for biomarker analysis, which includes but not limited to PD-L1 expression and other tumor related genes (IDO1, CXCL9, CXCL10, HLA-DRA, STAT1, IFNG massager RNA) **Quality of life** ● EQ 5D-5L and EORTC QLQ-C30
Statistical Analysis	**Sample size estimated** The study was a single arm study. The planned sample size of 80 patients provided 80% power to reject the null hypothesis that the proportion of patients achieving an objective response is 40% or fewer, assuming an objective response of 56% and given a two-sided alpha of 5%. Considering the possible drop-off of patients, 90 patients will be recruited to ensure at least 80 evaluable patients. **Hypothesis** H_0: ORR≤40% H_1: ORR>40% α =0.05 (two-sided) and superiority test is based on confidence interval (CI). **Interim analysis** In this study, an interim analysis is planned to conduct at the time point when all the enrolled subjects finished two tumor assessments by IRRC. The purpose of the interim analysis is for conditional BLA submission at the early

	stage, and the endpoint is the primary efficacy endpoint ORR according to IWG2007. **Primary efficacy endpoint** Binomial distribution will be applied to estimate ORR and 95% CI for superiority test. **Secondary efficacy endpoint** TTR, DOR, PFS: Kaplan-Meier will be used to estimate median values and 95% CR, PR, DCR: Binomial distribution will be applied to estimate ORR and 95% CI. **Safety endpoint** The safety analysis will be conducted by description of incidence rates and grades of AEs. **Immunogenicity** The positive rates of ADA antibody and NAB will be calculated, and the antibody levels of positive subjects will be described with listings. **PK/PD** Describe PK/PD parameters, such as AUC, Cmax, CL, V, t1/2 and PD-1 receptor occupancy. **Quality of life** Describe results on EQ-5D-5L and EORTC QLQ-C30. **Biomarker** Describe PD-L1 expression, and other tumor related gene expression, and their potential relations with treatment efficacy.

Table 1 Schedule of Activities

Protocol Activity	**Screen**	**Treatment Period**						**Treatment Disconinuation[1]**	**Safety Visit**
		Cycle 1	Cycle 2	Cycle 3	Cycle 4	Cycle 5	Cycle 6 and after		
	1	2	3	4	5	6	7 ~ N	Early Termination/Treatment Discontinuation Visit	
	-28~-1 D	Day 2	Day 22 （±3 days）	Day 43 （±3 days）	Day 64 （±3 days）	Day 85 （±3 days）	Every 3 Weeks （±3 days）		90 Days（±7）after last dosing
Regular Activities									
Informed consent [1]	X								
Review inclusion/ exclusion criteria	X								
Demographics/Medical History/Prior treatment[2]	X								
Vital sign[3]	X	X	X	X	X	X	X	X	X
Height/weight[4]	X							X	
Physical examination	X		X	X	X	X	X	X	
ECOG PS	X	X	X	X	X	X	X	X	
12 lead ECG[5]	X			X		X	X	X	
Clinical safety laboratory test[6]	X		X	X	X	X	X	X	X
Pregnancy test [7]	X							X	
Thyroid function [8]	X		X	X	X	X	X	X	X
PK[9]		X	X		X		X		

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PD[10]		X	X				X		
Immunogenicity [11]		X	X		X				X
HIV, HBV and HCV[12]	X								
Adverse Event [13]	X	X	X	X	X	X	X	X	X
Concomitant Treatment	X	X	X	X	X	X	X	X	
Efficacy evaluation									
Bone marrow biopsy [14]	X								
Tumor radiological evaluation [15]	X			X			X		
Disease related symptom evaluation [16]		X	X	X	X	X	X	X	
Treatment administration									
IBI308[17]		X	X	X	X	X	X		
Quality of life evaluation									
EQ-5D-5L/ EORTC QLQ-C30 [18]		X		X			X	X	
Biomarker									
Archived or fresh tumor	X								

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		Cycle 1	Cycle 2	Cycle 3	Cycle 4	Cycle 5	Cycle 6 and after		
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	-28~-1 D	Day 2	Day 22 （±3 days）	Day 43 （±3 days）	Day 64 （±3 days）	Day 85 （±3 days）	Every 3 Weeks （±3 days）		90 Days（±7）after last dosing
sample collection [19]									
Blood sample [20]		X		X			X		

Note：

1. informed consent forms (ICF）is signed before any study procedure is taken.
2. Prior treatment includes：treatments based on initial diagnosis, including chemotherapy, radiotherapy and surgery
3. Vital sign includes body temperature, pulse rate, breathing, and blood pressure.
4. Height and weight are measured at screening; weight is measured at treatment discontinuation visit.
5. 12 lead ECG is schedule at screening, every 2 cycle before dosing, and treatment discontinuation visit.
6. CBC：red blood cell, HGB, white blood cell, PLT, lymphocyte count, ANC. Blood chemistry: liver function [TBIL, ALT, AST, γ-glutamyltransferase, alkaline phosphatase, albumin, total protein, lactic dehydrogenase]，renal function [blood urea nitrogen, Cr]，Na, K, Cl, Mg, Ca, P, lipase，fasting blood glucose, FBG. Urine routine： PH, urinary albumin, urine protein, urine red blood cell, urine glucose. The screening period, 7 days before the first study drug administration and the second cycle start every 3 days before the study drug administration and at the safety follow-up. Safety laboratory examination will be conducted at each research center.
7. Women with fertility potential will have a urine or serum pregnancy check within 3 days prior to the first dose and at the end of the treatment visit. If the urine pregnancy test result cannot be confirmed as negative, a serum pregnancy test will be performed, which is based on the serum pregnancy result. Test will be conducted at each research center.

8. During the screening period, starting at the beginning of the second cycle, within 3 days before the study drug administration and at the safety follow-up. Screening period to check for triiodothyronine (T3), thyroxine (T4), free thiiodothronine (FT3), free tetraiodothyronine (free thiiodothronine) , FT4) and TSH, only check TSH at the beginning of the second cycle, if other abnormalities, consider checking other thyroid function indicators. Inspections will be conducted at each research center.
9. PK: PK testing was performed in 12 subjects at designated research centers. The total number of PK blood collection points set in the first cycle is 8: 1 hour before the start of IBI308 infusion, immediately after the end of infusion (+5min), 1h±5min after the end of infusion, 6h±15min, 24h±1h after the start of infusion. 48h±2h, 168h±8h (day 8), 336h±12h (day 15); if the administration is delayed on the first day of the second cycle due to AE or other reasons, the first cycle needs to be increased by 504h±24h (Day 22) Sampling. From the second cycle, PK sample collection is performed every two cycles (the second, fourth, and sixth phase cycles, and so on). Except for the fourth cycle, the sampling time is: within 1 hour before the start of the infusion and the end of the infusion. Immediately (+5min). The fourth cycle (intensive sampling) blood collection time: within 1 hour before the start of the infusion, immediately after the end of the infusion (+5min), 1h ± 5min after the end of the infusion, 6h ± 15min, 24h ± 1h, 48h ± after the infusion 2h, 168h ± 8h (day 8), 336h ± 12h (day 15), 504h ± 24h (day 22, ie, within 1 hour before the fifth cycle of administration).
10. PD: PD testing was performed in 12 subjects in the designated study center. The total number of PD blood collection points set in the first cycle was 3: 1 h before the start of the IBI308 infusion, 24 h ± 1 h after the start of the infusion, and 168 h ± 8 h (Day 8). At the beginning of the second cycle, sample collection is performed every four cycles (the second, sixth, tenth, fourteenth, etc., and so on). Blood collection point: within 1 hour before the start of the infusion.
11. The immunogenicity test will be performed during the first cycle, the second cycle, the fourth cycle, and every 4 cycles (the 8th, 12th, and 16th cycles, etc.) within 1 hour before the IBI308 infusion and during the safety follow-up. The inspection will take place at the central laboratory.
12. Five hepatitis B (HBsAg, HBsAb, HBcAb, HBeAg, HBeAb) tests, HBV DNA, HCV antibodies and HIV antibody tests are performed during the screening period. If HCV antibodies are positive, HCV RNA will be further examined. For hepatitis B virus carriers, it is recommended to monitor viral activity regularly during the study period. Inspections will be conducted at each research center.
13. AE and laboratory safety assessments will be evaluated according to NCI CTCAE version 4.03. The definition, record, correlation judgment, severity judgment, reporting time limit and processing of AE and SAE are described in Section 7 of the scheme.
14. For subjects with a positive baseline bone marrow biopsy, a bone marrow biopsy (completed within 2 weeks of imaging assessment) is required if there is a complete imaging remission during treatment; if the bone marrow biopsy biopsy cannot determine the nature, the immunization group is required. Confirmation; immunohistochemistry to determine no malignant components can be judged as complete remission, otherwise the efficacy is evaluated as partial remission.

15. Tumor imaging using enhanced CT (subject to hypersensitivity to CT contrast agents, MRI) and PET. Enhanced CT examination time is baseline (baseline assessment will be performed within 28 days prior to enrollment), 6/15/24 weeks (±7 days), every 12 weeks after 24 weeks (±14 days), and every 16 weeks after 48 weeks Week (±14 days), the examination site includes the neck, chest, abdomen, basin and other required anatomical sites until the start of new anti-tumor treatment, disease progression, withdrawal of ICF or death of the subject; The tester needs to confirm after 4~6 weeks; for patients who stop treatment except for the progress of imaging disease, it is still necessary to carry out imaging evaluation according to the program after stopping the drug until the start of new anti-tumor therapy, disease progression, subject withdrawal of ICF or death. PET examinations were performed at baseline, week 15 (±7 days), or early termination of study drug treatment. The requirements for PET examinations are detailed in the Image Acquisition Guide.
16. Assessment of disease-related symptoms (including fever, night sweats, weight loss) before each cycle of medication, and complete elimination of disease-related symptoms is one of the conditions for evaluating CR
17. IBI308 200 mg, administered intravenously, once every 3 weeks for up to 24 months, or until disease progression, death, intolerance, withdrawal of informed consent or other reasons as specified in the protocol. For the first time in which the disease progresses, if the clinical situation is stable, the investigator can continue to receive treatment until the total treatment time reaches 24 months or recurrence of disease progression, death, toxicity intolerance, withdrawal of informed consent. Or other reasons specified by the program.
18. The quality of life assessment was assessed using the EQ-5D-5L and EORTC QLQ-C30 scales on the day of the first dose, each imaging assessment, and the end of treatment visit.
19. Subjects who meet the inclusion criteria are required to provide archived tumor tissue at baseline or 4 unstained 4-5 micron sections prepared freshly during the screening period for PD-L1 testing. For the detection of mRNA expression of immune-related genes, subjects should provide as much as possible of the archived tumor tissue at baseline or 4 unstained 4~5 micron sections prepared freshly during the screening period.
20. Subjects are required to provide 10 ml whole blood samples at the following time points: before the first dose, during the treatment period, and before the next treatment.
21. Treatment termination: Treatment termination includes early termination (in addition to disease progression leading to discontinuation of the drug) and study treatment (end of disease leading to discontinuation of the drug), and treatment termination at the end of treatment. For patients who discontinued treatment for reasons other than imaging disease progression, an imaging evaluation was performed every 12 weeks (±7 days) after discontinuation of the drug until one of the following events occurred: initiation of new anti-tumor therapy, disease progression, subject withdrawal of ICF and death.

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List of Abbreviations

Abbreviation	Definition
%CV	percent coefficient of variation
%RE	percent relative error
abs	absolute
AE	adverse event
ALT	alanine aminotransferase
ANOVA	analysis of variance
AST	aspartate aminotransferase
AUC	area under the concentration-time profile
AUC_{extrap}%	percent of AUC_{inf} due to extrapolation
AUC_{inf}	area under the plasma concentration-time profile from time zero extrapolated to infinite time
AUC_{last}	AUC from time 0 to last quantifiable concentration
BMI	body mass index
BP	blood pressure
CDK	cyclin-dependent kinase
CI	confidence interval
C_{last}	last quantifiable concentration
CL_{cr}	creatinine clearance
CL/F	apparent clearance
CL_u/F	unbound CL/F
C_{max}	maximum plasma concentration
CO_2	carbon dioxide
CRF	case report form
CRO	contract research organization
CRU	Clinical Research Unit
CYP3A4	cytochrome P450 3A4
DCT	data collection tool
DNA	deoxyribonucleic acid
ECG	electrocardiogram
eGFR	estimated glomerular filtration rate
eNCA	electronic non-compartmental analysis
FDA	Federal Drug Administration
FL	Florida
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
GGT	gamma-glutamyl transferase
HGB	hemoglobin
hr	hour(s)
ICD	Informed Consent Document

Abbreviation	Definition
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
INR	international normalized ratio
IRB	Institutional Review Board
K_2EDTA	dipotassium etheylendiaminetetraacetic acid
LLN	lower limit of normal
LLOQ	lower limit of quantification
MCH	mean corpuscular hemoglobin
MCHC	mean corpuscular hemoglobin concentration
MCV	mean corpuscular volume
MDRD	Modification of Diet in Renal Disease
MedDRA	Medical Dictionary for Regulatory Activities
msec	millisecond(s)
PD	pharmacodynamics
PK	pharmacokinetics
PT	prothrombin time
QC	quality control
QT interval	time from electrocardiogram Q-wave to the end of the T-wave corresponding to electrical systole
QTc	QT interval corrected for heart rate
QTcF	QTc using Fridericia's formula
RBC	red blood cell
SAE	serious adverse event
$S_{cr, std}$	serum creatinine measured with a standardized assay for serum creatinine
SOP	standard operating procedure
SOC	system organ class
$t_{½}$	terminal half-life
TEAE	treatment-emergent AE
T_{last}	time of C_{last}
T_{max}	time for C_{max}
US	United States
V_z/F	apparent volume of distribution
WBC	white blood cell

1 Background

1.1 Disease Background

As a malignancy originating from the lymphatic hematopoietic system, lymphoma can be classified into two categories, namely Hodgkin lymphoma and non-Hodgkin lymphoma according to pathologic character. In 2015, 88000 estimated new cases of lymphoma were diagnosed in China [1]. Based on morphology and immunophenotype, Hodgkin lymphoma is divided into two categories: nodular lymphocyte predominant Hodgkin lymphoma and classical Hodgkin lymphoma (cHL). The latter is further divided into four types, i.e. lymphocyte rich, mixed cellularity, nodular sclerosing and lymphocyte depleted [4]. According to a pathological analysis of 10002 Chinese lymphoma patients, the proportion of Hodgkin lymphoma was 8.54%, of which cHL accounted for 93.56% [3]. The cure rate after first-line treatment of Hodgkin lymphoma is approximately 85% [4], and the rest 15% are considered refractory or have a tendency to relapse. For relapsed or refractory cHL, the second-line standard treatment in Europe and the United States is high-dose chemotherapy combined with autologous hematopoietic stem cell transplantation [5]. Due to the low acceptance of transplant therapy and limited medical resources in China, the second-line treatment for relapsed or refractory cHL patients is chemotherapy in general. According to historical data, the rate of non-treatment failure three years after second-line chemotherapy is 34%, and this rate three years after second-line high-dose chemotherapy in combination with autologous hematopoietic stem cell transplantation was 55% [6, 7]. High quality evidence is still lacking for third-line therapy or above [5]. Currently, monotherapy includes Brentuximab Vedotin [8], bendamustine [9], lenalidomide [10] and everolimus [11]. Brentuximab Vedotin showed an ORR of 75% and a PFS of 5.6 months in 102 patients who failed high-dose chemotherapy combined with autologous hematopoietic stem cell transplantation [8]. It has not been approved in China yet. Bendamustine had an ORR of 56% and a DOR of 5 months in 36 patients who had failed an average of four lines of therapy [9]. Lenalidomide demonstrated 19% of ORR and 4 months of PFS in 38 patients who had failed an average of four lines of therapy [10]. Of the 19 patients who failed an average of six line treatment, everolimus showed an ORR of 47%, and time to progression of 7.2 months [11]. The ORR of the above single regimen was between 19-56%, however, the disease control duration was short. Therefore, there is a significantly unmet clinical need for relapsed or refractory cHL which progress beyond second-line therapy in China.

The PD-1/PD-L1 pathway may play an important role in the onset and progression of cHL. The rate of PD-L1 expression in Reed Sternberg cell (RS cell) of cHL was 65% in nodular sclerosing type (87/134), 81% in mixed cellularity type (60/74), 90% in lymphocyte rich type (9/10) and 67% in lymphocyte depleted type (4/6) [12]. High expression of PD-L1 in RS cells in cHL is usually caused by a copy number abnormality at the 9p24.1 site, which contains the PD-L1, PD-L2 and JAK2 genes. In a study of 108 patients with cHL, FISH was used to detect PD-L1 and its copy number. Polyploid, copy number increase and copy number amplification were 5% (5/108), 61% (56/108) and 39% (36/108) respectively [13]. JAK2 activates downstream transcription factor STAT and further increases PD-L1 expression [14]. In addition, EB virus infection can also cause an increase in PD-L1 expression [15]. Since the expression of PD-L1 can cause immune escape of RS cells, blocking the signal pathway of PD-L1/PD1 may relieve immune suppression and promote the clearance of RS cells by immune system.

Anti-PD-1 monoclonal antibodies Nivolumab and Pembrolizumab have shown significant efficacy in cHL [16, 17]. In patients who failed high-dose chemotherapy in combination with autologous hematopoietic stem cell transplantation and Brentuximab Vedotin, the ORR of Pembrolizumab was 72.5% (50/69). In patients who are not suitable for high dose chemotherapy or autologous hematopietic stem cell transplantation, the ORR of Pembrolizumab was 65.4% (53/81) after failure of Brentuximab Vedotin [18]. The ORR of Nivolumab in patients who failed high-dose chemotherapy in combination with autologous hematopoietic stem cell transplantation and Brentuximab Vedotin was 66.3% (53/80) [17]. Currently, Nivolumab has been approved by the US FDA for cHL patients who have failed high-dose chemotherapy combined with autologous hematopoietic stem cell transplantation and Brentuximab Vedotin.

Nivolumab and Pembrolizumab have shown significant efficacy in cHL patients who have failed multi-line therapy, demonstrating the effectiveness of blocking PD-1/PD-L1 pathway in relapsed and refractory cHL. To this end, this clinical trial is designed to evaluate the efficacy and safety of IBI308 in relapsed and refractory cHL.

1.2 Tested Drug (IBI308)

1.2.1 Mechanism of IBI308

Immune checkpoints are a group of immunosuppressive molecules with the physiological function of regulating the intensity and breadth of immune response, thereby avoiding damage of normal tissues. Tumor cells can express these immune checkpoint molecules to escape immune attacks. Currently validated immune checkpoints include CTLA-4 and PD1/PD-L1. With its safety profile and broad indications, monoclonal antibody targeting PD1/PD-L1 pathway has shown promising prospect.

PD-1 is mainly expressed on activated T cells, with two ligands being PD-L1 and PD-L2. PD-L1 is its main ligand, which is expressed on activated T cells, antigen presenting cells and tumor cells as well [19]. The binding of PD-1/PD-L1 plays an important role

in regulation of T cell activation and peripheral immune tolerance. When not expressing PD-1, T cells interact with antigen-presenting cells, proliferate and secrete activating cytokines, and exert tumoricidal effect. After activation, T cells will express PD-1. When binding with PD-L1 on tumor cells, the inhibitory signal will prevent T cell from further activation and secretion of activating cytokines, causing immune escape and cancer progression. By blocking the interaction between PD-1 and PD-L1, the tumoricidal capability of T cell will be restored [20].

So far, the US FDA has approved the listing of three PD-1/PD-L1 products, namely Bristol-Myers Squibb (BMS) anti-PD-1 monoclonal antibody Nivolumab (trade name: OPDIVO), Merck Anti-PD-1 mAb Pembrolizumab (trade name: KEYTRUDA), and Genetech anti-PD-L1 monoclonal antibody Atezolizumab (trade name: Tecentriq). The indications include advanced melanoma, advanced NSCLC, advanced cHL, advanced renal cell renal cell carcinoma and urothelial carcinoma, advanced head and neck cancer. In addition, several other indications are currently under Phase III clinical trials or application. The listing of the above drugs has established the important position of PD-1/PD-L1 immune checkpoint inhibitors in tumor immunotherapy. At present, there is no PD-1/PD-L1 immune checkpoint inhibitor listed in China. It is of great significance to develop such monoclonal antibodies to improve the outcome of advanced cancer patients in China.

Recombinant human-derived anti-PD-1 monoclonal antibody injection (R&D code: IBI308) is a recombinant human-derived IgG4 monoclonal antibody, which has shown in vitro and in murine preclinical model to effectively block the PD-1/PD-L1 pathway and exhibit anti-tumor activity (for detailed results, please refer to the investigator's manual).

1.2.2 Results from IBI308 Clinical Studies

The Phase Ia dose escalation trial of IBI308 was initiated in September 2016, which was planned to enroll approximately 12-24 subjects with advanced solid tumors who had failed standard treatment. The dose escalation would follow the classic “3+3” design and 4 dose levels (1 mg/kg, 3 mg/kg, 200 mg and 10 mg/kg) would be evaluated. After completion of evaluation of the 1 mg/kg dose level, subjects would be randomized to either 3 mg/kg or 200 mg for independent evaluation. The dose-limiting toxicity (DLT) observation period was 28 days after the first dose in each dose level. After completion of DLT observation, the subjects are allowed to continue the subsequent IBI308 treatment (1 mg/kg, 3 mg/kg, and 10 mg/kg every 2 weeks or 200mg every 3 weeks) until disease progression, intolerance, withdrawal of informed consent, or other reasons for discontinuation of the study (whichever occurs first).

Pharmacokinetic evaluation of 1 mg/kg IBI308 was carried out in a multi-tumor subject (n=3). Preliminary results of single-dose administration showed that 1 mg/kg IBI308 reached the maximum exposure of a single dose at the end of the infusion. After reaching the peak, the distribution was rapidly completed and elimination was slow (t1/2 was approximately 17.3d). It is a typical two compartment model of monoclonal

antibody, with a half-life similar to the physiological half-life of IgG4.

Preliminary results of pharmacodynamic studies showed that IBI308 could rapidly (in 24h) saturate the peripheral PD-1 receptor (95.8±2.3%) at a dose level of 1 mg/kg, and could maintain the occupancy of PD-1 receptor during the study phase of decreasing concentration (28d, C28d: 3.70 ± 0.15 μg/mL). Steady status is expected to be reached on Day 84 with continuous dose of 1 mg/kg Q2W (6 doses total). Provided no significant variation in drug clearance characteristics, the steady-state trough concentration is approximately 13μg/mL, which will sustainably maintain peripheral PD-1 receptor occupancy.

Until February 8, 2017, three subjects each of the following dose levels, 1 mg/kg, 3 mg/kg, and 200 mg, have completed DLT observation, with no DLT observed.

1.3 Benefit/risk assessment

Based on the mechanism of IBI308 and clinical safety profile of similar products, it is predicted that the major adverse events during clinical trial may be inflammations caused by activation of the immune system, including pneumonitis, colitis, hepatitis, renal dysfunction and inflammation of the endocrine system. According to the clinical data of the existing anti-PD-1 monoclonal antibodies, it is tolerated well despite of a relatively high incidence of adverse events, most of which will be alleviated after treatment. Only a small percentage of subjects have discontinued treatment due to severe adverse events. Since symptoms of immune related adverse events is atypical at early phase, researchers should pay close attention to early symptoms and signs, make timely judgments, adjust dose and give proper treatment per protocol section 5.4. Meanwhile, cautiously screen and exclude subjects with autoimmune diseases.

In conclusion, the clinical pharmacology and safety data of IBI308 from Phase Ia clinical trial have demonstrated its pharmacological activity and safety in patients with advanced cancer. The efficacy of similar anti-PD-1 monoclonal antibody in cHL, supports the clinical trial of IBI308 in patients with relapsed or refractory cHL in China.

2 Trial Objectives

2.1 Primary Objectives

- ORR of IBI308 monotherapy in relapsed or refractory cHL assessed by IRRC.

2.2 Secondary Objectives

- ORR of IBI308 monotherapy in relapsed or refractory cHL assessed by investigator;
- CR and PR of IBI308 monotherapy in relapsed or refractory cHL;
- DCR of IBI308 monotherapy in relapsed or refractory cHL;
- TTR of IBI308 monotherapy in relapsed or refractory cHL;
- DOR of IBI308 monotherapy in relapsed or refractory cHL;

- PFS and 6-month PFS rates of IBI308 monotherapy in relapsed or refractory cHL;
- Evaluate the safety of IBI308 monotherapy in patients with relapsed or refractory cHL.
- Evaluate PK/PD/immunogenicity of IBI308 monotherapy in patients with relapsed or refractory cHL.
- Evaluate the quality of life of patients with relapsed or refractory cHL after IBI308 monotherapy (according to the EQ-5D-5L and EORTC QLQ-C30 scales).

2.3 Exploratory Objectives

Assess the relationship between PD-L1 expression, immune-related gene mRNA, and other potential biomarkers in relapsed or refractory cHL and IBI308 efficacy.

3 Study Design

3.1 Study Plan

This study is a multicenter, one-arm, phase II study to evaluate the efficacy and safety of IBI308 in relapsed or refractory classic Hodgkin's lymphoma. This study will enroll patients with relapsed or refractory cHL to receive intravenous (IV) IBI308 at 200 mg every three weeks (Q3W) for up to 24 months, or until disease progression, death, unacceptable adverse event(s), subject withdraws informed consent or other reasons specified in protocol. If the subject still has no disease progression after 24 months of IBI308 treatment and the investigator judges that the subject will still benefit from the study drug, the subject should sign additional informed consent to continue receiving free IBI308 treatment. . For subjects with first disease progression, if the clinical condition is stable, the investigator may let the subject continue to receive treatment until the total treatment time reaches 24 months or if disease progression, death, unacceptable adverse event(s), subject withdraws informed consent, or other reasons specified in protocol.

The primary endpoint of the study is overall response rate (ORR), defined as the percentage of subjects with optimal response to partial and complete remission, evaluated according to the IWG 2007 criteria, and the Lugano 2014 criteria as an adjunct to the standard, both evaluated by IRRC. Analysis of primary endpoints will be performed after the last subject who meets the statistical and imaging assessment requirements and completes up to 24 weeks of follow-up. Subjects will have a safety follow-up 90 days after the last dose of IBI308.

If the enrollment progressed slowly within the first 6 months after the start of the study (the number of subjects enrolled in the group within 6 months is less than 30), the sponsor may terminate the enrollment of the study early.

3.2 Study Rationales

3.2.1 Rationales of Single Arm Study Design

There is no high-quality evidence in three or more prior lines of systemic therapy to treat replaced/refactory cHL, and most evidence is monotherapy [5], including Brentuximab Vedotin [8], bendamustine [9], lenalidomide [10] and Vimos [11]. Brentuximab Vedotin has not yet been listed in China. Bendamustine had an ORR of 56% and a DOR of 5 months in 36 patients who had failed an average of four-line treatment [9]. The lenalidomide in the 38 patients who failed the average 4-line treatment had an ORR of 19% and a PFS of 4 months [10]. Of the 19 patients who failed the average 6-line treatment with everolimus, the ORR was 47% and the disease progression time was 7.2 months [11]. The sample size of the above studies is small and is not a recognized standard treatment. The ORR of Pembrolizumab and Nivolumab in patients with relapsed or refractory cHL who failed high-dose chemotherapy combined with autologous hematopoietic stem cell transplantation and Brentuximab Vedotin was 72.5% (50/69) [18] and 66.3% (53/80) respectively[17]. The ORR of Pembrolizumab in patients who were not suitable to receive high-dose chemotherapy combined with autologous hematopoietic stem cell transplantation or Brentuximab Vedotin failed was 65.4% (53/81) [18]. The above data indicate that anti-PD-1 monoclonal antibody alone has obvious curative effect on relapse or refractory cHL failure of multi-line treatment. Because of the lack of standard treatment in domestic third-line and above, this study chose a single-arm design.

3.2.2 Rationales of Choosing 200 mg/kg Q3W

This study is intended to be administered with 200 mg IBI308 Q3W. The choice of this mode of administration is based primarily on the ongoing Phase I (CIBI308A101) study of safety and exposure (concentration)-response (PD-1 receptor occupancy) relationship data, combined with preclinical in vitro/in vivo efficacy and other similar drugs' data.

The in vivo pharmacodynamic study of the SCID-Winn murine model and The MC38 murine colon carcinoma model showed that the tumor suppressor ability of IBI308 increased with dose escalation, and the 10 mg/kg IBI308 dose group significantly inhibited tumor growth. The equivalent dose in mankind was 0.8 Mg/kg. IBI308 can rapidly (24 hours) saturate the peripheral PD-1 receptor (95.8±2.3%) at a dose of 1mg/kg, and maintain peripheral PD-1 occupancy level during the period of IBI308

concentration continuously to decrease (28d, C28d: 3.70±0.15). The distribution of IBI308 in cynomolgus monkey's different tissue showed that the IBI308 exposure of organs such as lung, liver, colon, small intestine, and lymph nodes was about 3.5-1/10 of its in serum. Under the premise that the subject did not significantly change the drug clearance characteristics, IBI308 200 mg Q3W was expected to be administered to the steady state for 84 days (4 times), and the steady-state trough concentration was expected to be about 26 μg/mL. Under which IBI308 could continue to maintain peripheral and target organ PD-1 receptor occupancy. The above evidence supports the selection of IBI308 200 mg Q3W as a dosing regimen.

3.2.3 Rationales of Primary Endpoint Analysis at Week 24

One Study of the evaluations of Nivolumab monotherapy in a relapsed or refractory cHL patient study (Checkmate 205), of which one cohort enrolled patients failure from a high-dose chemotherapy combination with autologous stem cell transplantation and Brentuximab Vedotin. The results were published and the primary end point was ORR assessed by independent image review committee. The primary endpoint was analyzed at the time when all the 80 subjects were followed up for an average of 6 months. The ORR of the cohort was 65.3% (53/80), and the median time to first objective response was 2.1 months (IQR, 1.9-3.0 months). 31 cases had first objective response (58%, 31/53) at 9.33 weeks (the first scheduled tumor evaluation time for the study was week 9) [17]. In this study, the final analysis was performed at the time when the subject was followed up till maximum 24 weeks of treatment and at which the majority of objective mitigation events were expected to be observed. Because patients with response often have long-lasting duration of remission, and the reported median duration of response is 7.8 months in Checkmate205, subsequent assessments every 12 weeks can reduce unnecessary examinations for patients with remission [17].

3.2.4 Rationales of Choosing ORR as the Primary Endpoint

In a study of 756 patients with relapsed/refractory cHL after failure of second-line standard therapy, the median progression-free survival was 1.3 years, with a median overall survival of 2.4 years [6].So for relapsed/refractory cHL, The Objective response rate is a common primary study end point in one-arm phase II study, as referring to the research design of the similar study (Brentuximab Vedotin [8], Nivolumab [17], Pembrolizumab [18]). We chose ORR as our study primary endpoint.

3.2.5 Rationales of Continuation of Treatment after Disease Progression

Clinical data from listed products indicate that a small number of patients continue to receive immunotherapy may still receive clinical benefit despite prior evidence of disease progression (according to routine response criteria) before clinical objective response and/or disease stabilization [17, 21]. This phenomenon is currently explained with two reasons. First, increased inflammatory cells within the tumor may result in an increase in tumor volume, manifested as measurable lesion enlargement and the appearance of new, visible, immeasurable lesions. Over time, the malignant and inflammatory portions of the mass may shrink, resulting in significant imaging and clinical signs of improvement. Second, in some patients, the anti-tumor immune response is initiated slowly, and its early inhibition of tumors is less than tumor growth speed over time, anti-tumor activity will predominate and be manifested as an improvement in imaging response and clinical signs. In Checkmate 205, nine patients of the cHL who were re-administered after disease progressions, 6 of them were observed a further reduction in tumor burden [17]. Therefore, subjects treated with IBI308 will be allowed to continue to receive IBI308 if they are initially evaluated by IWG 2007 to have progressed disease, as the investigator confirm they will have clinical benefit and are tolerant to the study drug (see section 5.1.2). But they discontinue the study treatment after evidence of further progress.

4 Patient Eligibility Criteria

4.1 Inclusion Criteria

10. Histopathological confirmed classical Hodgkin's lymphoma (cHL).
11. Relapsed/refractory cHL, which failed second line and above therapy (including radiotherapy and autologous hematopoietic stem cell transplantation, ASCT); subject with no response to or with progression after ASCT is eligible.
12. At least one measurable disease (long axis>15 mm or short axis>10 mm, with uptake on 18FDG-PET)
13. Eastern Cooperative Oncology Group Performance Status (ECOG PS) 0-2.
14. Signed written informed consent form and willing and able to comply with scheduled visits and other requirements of the study.
15. Age ≥ 18.
16. Life expectancy ≥ 12 weeks.

17. Subjects of reproductive potential must be willing to use adequate contraception during the course of the study and through 90 days after the last dose of study medication.

18. Adequate organ and bone marrow function:

    5) Count of Blood Cells: absolute neutrophil count (ANC) ≥ 0.75 × 10^9 / L; platelet count (PLT) ≥ 50 × 10^9 / L; hemoglobin content (HGB) ≥ 8.0 g / dL; no granulocyte colony-stimulating factor, platelet or red blood cells infusion in the last 14 days.

    6) Liver function: total bilirubin (TBIL) ≤ 1.5 × normal upper limit (ULN); alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ≤ 2.5 × ULN.

    7) Renal function: serum creatinine (Cr) ≤ 1.5 × ULN

    8) Thyroid function: thyroid stimulating hormone (TSH) in normal range (TSH abnormalities due to non-autoimmune causes can be enrolled).

4.2 Exclusion Criteria

23. Known nodular lymphocyte predominant Hodgkin lymphoma.

24. Known central nervous system lymphoma.

25. Received ASCT within 90 days of the first dose of study medication.

26. Prior exposure to any anti-PD-1, anti-PD-L1 or anti-CTLA-4 antibody.

27. Currently participating in an interventional clinical study, unless participating in observational study or during follow-up period of an interventional study.

28. Received any investigational agent within 4 weeks of the first dose of study medication.

29. Received last dose of radiotherapy or anti-tumor therapy (chemotherapy, targeted therapy, tumor immunotherapy or arterial embolization) within 3 weeks of the first dose of study medication; received last dose of nitrosourea or mitomycin C within 6 weeks of the first dose of study medication.

30. Received systemic treatment with corticosteroids (> 10 mg daily prednisone equivalent) or other immunosuppressive medications within 4 weeks of first dose.

Inhaled or topical steroids and adrenal replacement steroid doses are permitted in the absence of active autoimmune disease.

31. Received a live vaccine within 4 weeks of the first dose of study medication or plan to receive live vaccine during study period.
32. Underwent major operation (craniotomy, thoracotomy or laparotomy) within 4 weeks of the first dose of study medication or with open wound, ulcer or fracture.
33. Unrecovered toxicity (grade >1, according to NCI CTCAE 4.03) due to prior anti-tumor therapy before the first dose of study medication.
34. Known primary immunodeficiency.
35. Active tuberculosis.
36. Known history of allogeneic organ or allogeneic hemopoietic stem cell transplantation.
37. Known allergy or hypersensitivity to any monoclonal antibodies or any components used in their preparation.
38. Uncontrolled concomitant disease, including but not limited to :
    12) Human Immunodeficiency Virus (HIV) infection (HIV antibody positive)
    13) Active or poorly controlled severe infection
    14) Symptomatic congestive heart failure (New York Heart Association grade II-IV) or symptomatic, poorly controlled arrhythmia
    15) Poorly controlled arterial hypertension (SBP ≥ 160mmHg or DBP ≥ 100mmHg) with standard treatment
    16) Prior arterial thromboembolism event, including myocardial infarction, unstable angina, stroke and transient ischemic attack, within 6 months of enrollment
    17) Prior life-threatening blood loss or grade 3/4 gastrointestinal/varicosity bleeding requiring blood infusion, endoscopic or surgical intervention within 3 months of enrollment
    18) Prior deep vein thrombosis, pulmonary embolism or any other severe thromboembolism events (implanted port or catheter caused thrombosis, or

superficial vein thrombosis are not considered as severe thromboembolism) within 3 months before enrollment

19) History of uncontrolled metabolic disorder, non-malignant organ or systemic disease or secondary carcinomatous reaction, with high medical risk and/or uncertainty of life expectancy evaluation

20) With hepatic encephalopathy, hepatorenal syndrome or hepatic cirrhosis of Child-Pugh grade B or higher.

21) History of intestinal obstruction or the following diseases: inflammatory bowel disease or extensive bowel resection (partial colonic resection or extensive small bowel resection, concomitant with chronic diarrhea), Crohn's disease, ulcerative colitis or chronic diarrhea

22) Other acute or chronic diseases, mental illness, or abnormal laboratory test results that may lead to the following outcomes: increase the risk of participating in study or study drug administration, or interfere with the interpretation of the study results and considered by investigator as "NOT" eligible to participate in this study

39. Known acute or chronic active hepatitis B infection (chronic HBV carrier or non-active HBsAg positive subject is eligible) or acute or chronic active hepatitis C (HCV antibody negative subject is eligible; HCV RNA examination is required for HCV antibody positive subject, subject is eligible if result was negative)

40. History of gastrointestinal perforation and /or fistula within 6 months before enrollment

41. Subjects with interstitial lung disease

42. Uncontrolled third space effusion, e.g. ascites or pleural effusion cannot be drained or controlled

43. Other primary malignancy, with the exception of:

5) Curative malignancy (e.g. papillary thyroid carcinoma)

6) Without active disease in the last 5 years and with very low recurrence risk

7) Non-melanoma skin cancer or malignant freckle-like nevus with adequate treatment and no evidence of recurrence ;

8) Adequately treated in-situ carcinoma

44. Women who are pregnant or nursing.

4.3 Limitations During the Study Period

Women with fertility potential were defined as women who had not undergone sterilization (ie, bilateral tubal ligation, bilateral salpingectomy, or total hysterectomy) or non-menopausal (menopausal defined as 12 months of amenorrhea without alternative medical reasons).

Women who are menopausal for 12 months without alternative medical reasons are considered menopausal. Requirements are as below:

Women <50 years of age can be considered menopausal women if they stop menstruating for 12 months or more after stopping exogenous hormone therapy and their lutein hormone and follicle stimulating hormone levels are within the recognized postmenopausal range.

Woman ≥ 50 years of age can be considered menopausal if one of the following criteria is met: no menstruation for 12 months or more after stopping of all exogenous hormone therapy; underwent radiotherapy induced oophorectomy and the time from last menstruation >1 year; underwent chemotherapy induced menstruation and the time from last menstruation >1 year, underwent surgical sterilization (bilateral oophorectomy or hysterectomy).

Table 2. Effective contraception methods (required to use at least 2 methods)

Barrier	Intrauterine device	Hormone therapy
Male condom with spermicide	Copper T-ring	Implant
Uterine cap with spermicide	Progesterone-releasing T-ring[a]	Hormone injectables or injections
Barrier with spermicide	levonorgestrel-releasing intrauterine device (eg.Mirena®)[a]	Contraceptive compounds Low-dose oral contraceptive pills Contraceptive patchs

[a] This is also considered as a hormonal method

4.4 Discontinue of Treatment/Withdrawal from Study

Subjects should terminate/exit the study in any of the following situations:

1. Subjects who do not meet the inclusion/exclusion criteria, and the sponsor and

the investigator discuss and decide that they are not eligible to continue participating in the study;

2. Subjects severely violated the study protocol, and the sponsor and the investigator discuss and decide that they are not eligible to continue participating in the study

3. Subjects are enrolled in any other type of drug research which is considered to be incompatible with the scientific or medical science of the study.

4. Subjects are lost to follow-up (the research center staff should contact the lost participant to determine the cause of the dropout and try to reschedule the visit. This contact date and the contact information used should be recorded in the research document).

5. The researcher decides

1) Based on the risk and benefit of the subject, the investigator believes that the subject should discontinue treatment or withdraw from the study.

2) If the subject needs to receive another medication for any reason and it has demonstrated that the medication is effective in treating the indications for this study, the subject should withdraw from the study before using the new medication.

3) Progress of the disease or what the investigator believes is not suitable to continue the treatment.

4) Any treatment-related adverse events that are considered life-threatening, regardless of the severity.

5) The toxicity of study drug meets the withdrawal criteria (see 5.4).

6. The subject or his trustee (such as a parent or legal guardian) requests to withdraw from the study or discontinue the study drug (if the subject withdraws informed consent for treatment but does not withdraw informed consent for follow-up, he or she remains in long-term follow-up).

7. The sponsor may terminate the study or discontinue the subject's participation in the study due to medical, safety or regulatory reason, or other reason related to laws, regulations, and good clinical practice (GCP).

The reason and the date of the termination will be collected for all subjects. For subjects

who discontinue treatment, the relevant study procedures and study visits in the schedule of events should also be performed as much as possible.

5 Investigational Products

5.1 Treatment Plan

5.1.1 Treatment Administration

The study drug, IBI308, will be administrated intravenously at 200 mg Q3W until maximum of 24 months, or until disease progression, death, intolerable toxicity, withdrawal of informed consent, or other reasons per the protocol. Other drugs in the study were non-study drugs.

5.1.2 Continuation of Treatment after Disease Progression

Subjects can continue to receive IBI308 after first disease progression, by IWG 2007, if they met all the following criteria:

1. Patients may receive clinical benefits and their conditions will not worsen rapidly, if continue to receive the study treatment, as assessed by the investigator;

2. Able to tolerate study drugs;

3. The ECOG PS is stable;

4. Does not delay the treatment of serious complications requiring urgent intervention (such as central nervous system metastasis);

5. Subjects need to be fully informed before continuing to receive treatment with IBI308, and the investigator needs to clarify all foreseeable risks or discomforts and alternative treatment options.

Subject to the above criteria, the decision to continue treatment after progression requires the investigator to discuss the decision with the sponsor's medical manager and record it in the study record.

Subject data those who continue to receive IBI308 after initial disease progression are to be collected and data variables are to be collected as described in Table 1.

If the patient continues to receive the study drug after confirmation, the radiographic evaluation will continue at the frequency per protocol. Treatment can be continued until the total treatment time reaches 24 months or recurrence of disease progression, death,

toxicity intolerance, withdrawal of informed consent or other reasons per protocol.

Subjects who continue treatment with IBI308 after initial disease progression are to be recorded as “clinical deterioration” if they discontinue the treatment due to worsening of clinical symptoms without radiographic confirmed recurrence of disease progression.

5.2 Study Treatment (IBI308)

5.2.1 Description of Study Treatment

The study drug was recombinant human-derived anti-programmed death receptor 1 monoclonal antibody injection, referred as IBI308.

The main active ingredient is a recombinant whole human anti-programmed death receptor 1 monoclonal antibody with a finished product size of 10 mL: 100 mg. IBI308 does not contain any preservatives at a concentration of 10 mg/mL, excipients include 140 mmol/L mannitol, 25 mmol/L histidine, 20 mmol/L sodium dihydrate, 50 mmol/L sodium chloride, 0.02 mmol/L disodium edetate (disodium edetate), 0.2 mg/mL polysorbate 80, pH 6.0.

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

Manufacturer: Innovent Biologics (Suzhou) Co., Ltd.

5.2.2 Label and Package

The IBI308 minimum packaging unit is a box containing 1 IBI308 injection packed in a vial. The IBI308 box is printed with the drug name, drug number, dosage form, specifications, drug code, production batch number, expiration date, storage conditions, usage and dosage, precautions, and information about the sponsor. The same information is printed on the label of the vial and the box, but there is no information on the dosage form and precautions on the vial label. All boxes and vials are labeled "for clinical trial use only".

5.2.3 Storage

Stored in the dark at 2~8 °C, the effective period is 24 months. If there are quality problems such as turbidity and sedimentation in the injection, it should be sealed immediately and the sponsor will be notified immediately.

5.2.4 Preparation and Administration

The preparation and infusion process of IBI308 is as follows:

1. Two bottles of IBI308 injection are to be completely withdrawn and added to 100 ml of 0.9% (w/v) sodium chloride sterile saline intravenous infusion bag, and the preparation start time is to be recorded.

2. Gently invert the infusion bag to ensure uniformity of the drug in the infusion bag.

3. Administration is to be done by an intravenous infusion tube containing a 0.2 to 1.2 μm in-line filter (recommended infusion time was controlled for 30 to 60 minutes), and the administration start time and end time are to be recorded.

Note: Before the configuration, make sure that IBI308 injection is transparent, no turbidity, sedimentation and other quality problems; ensure that the first bottle of IBI308 injection acupuncture extraction time to the end of the drug does not exceed 24 hours (prepared infusion to be stored in refrigerator at 2~8°C); avoid mixing other drugs; avoid intravenous bolus.

5.3 Treatment Adjustment

5.3.1 General Rules

Before the study drug is administered, the subject's hematology, liver and kidney function must meet all treatment requirements, and all toxic reactions must have been alleviated to CTCAE v4.03 grade 0-1 or baseline severity (except hair loss and fatigue).

All treatment adjustment reasons and treatment should be recorded in the original medical record and electronic case report form (eCRF).

5.3.2 Adjustment of IBI308

The dose of IBI308 was not allowed to be adjusted throughout the study. The IBI308 medication adjustment protocol (only for AEs judged by the investigator to be associated with IBI308) is shown in the table below.

Table 1. IBI308 Adjustment Plan

Adverse Event	Severity	Adjustment
Pneumonitis	Grade 2	Suspend [a]
	Grade 3 or 4	Terminate

Adverse Event	Severity	Adjustment
Diarrhea/enterocolitis	Grade 2 or 3	Suspend [a]
	Grade 4	Terminate
Dermatitis	Grade 3	Suspend [a]
	Grade 4	Terminate
Hepatitis	Grade 2 AST、ALT or TBIL increased	Suspend [a]
	Grade 3 or 4 AST、ALT or TBIL increased	Terminate
Pituitary inflammation	Grade 2	Suspend [a]
	Grade 3 or 4	Terminate
Adrenal insufficiency	Grade 2	Suspend [a]
	Grade 3 or 4	Terminate
Hyperthyroidism	Grade 3 or 4	Terminate
Type 1 diabetes	Grade 3 hyperglycemia	Suspend [a]
	Grade 4 hyperglycemia	Terminate
Renal insufficiency	Grade 2 or 3 Cr increased	Suspend [a]
	Grade 4 Cr increased	Terminate
Neurotoxicity	Grade 2	Suspend [a]
	Grade 3 or 4	Terminate
Infusion reaction	Grade 3 or 4	Terminate
Other AE	Other Grade 3 AE on first appearance	Suspend [a]
	Same Grade 3 AE on second appearance	Terminate
	Grade 3 AEs that cannot solve to Grade 0-2/ baseline in 7 days or to Grade 0-1/baseline in 14 days	Terminate
	Other Grade 4 AE	Terminate [c]

a：can resume treatment after AEs solve to grade 0-1 or baseline severity

b：Pituitary inflammation, adrenal insufficiency, and type 1 diabetes can be re-administered with adequate control and only physiological hormone replacement therapy.

c：For the abnormality of the results of the level 4 laboratory test, whether to terminate the drug should be decided according to the clinical symptoms/signs and according to the clinical judgment of the investigator.

The maximum interval between drug pauses is 6 weeks. If the status of IBI308 can be re-used within 6 weeks, the subject permanently discontinues IBI308 and enters the follow-up phase. Except for the following two situations:

Due to the use of glucocorticoids in the treatment of immune related adverse events (irAE), the glucocorticoid reduction process caused IBI308 to be suspended for more than 6 weeks. In this case, you need to discuss with the sponsor's medical manager to decide if you can continue IBI308 treatment. The imaging examination to evaluate the efficacy is planned as planned and is not affected by the suspension of medication.

IBI308 has been suspended for more than 6 weeks due to treatment of AEs that may or may not be related to IBI308. In this case, you need to discuss with the sponsor's medical manager to decide if you can continue IBI308 treatment. The imaging examination to evaluate the efficacy is planned as planned and is not affected by the suspension of medication.

5.4 Principles of Handling Immune Checkpoints Inhibitor Toxicity

IBI308 works through activating T cells, which can cause autoimmune hyperfunction, leading to multiple systemic autoimmune diseases. In the clinical application of other immune checkpoint inhibitors, e.g. ipilimumab, nivolumab, pembrolizumab and atezolizumab, autoimmune-related AEs, such as pneumonia, diarrhea/colitis, renal insufficiency, rash, hepatitis, endocrine diseases and peripheral or central neuritis were observed. Once any of the above mentioned AEs is observed in this study, investigators are to monitor patients' symptoms and signs, conduct necessary exams to judge the causality of the AE.

If no alternative causes (such as disease progression, concomitant medications and infections) are found and treatment with glucocorticoids and/or other immunosuppressive agents is required (except for endocrine events such as hyperthyroidism/hypertropy, pituitary inflammation, type 1 diabetes, and adrenal insufficiency, immunosuppressive therapy may not be used, but it is still thought to be related to autoimmune hyperactivity caused by IBI308) , the above AE should be considered to be related to immune system hyperactivity caused by IBI308, diagnosed as irAE.

5.5 Concomitant Treatment

5.5.1 Prohibited Treatment

- Other radiotherapy for the treatment of tumors (except palliative radiotherapy), chemotherapy, immunotherapy, targeted therapy and hormone therapy.
- Immunosuppressive agents and high-dose glucocorticoids (i.e., more than 10 mg/day of prednisone or equivalent doses of other glucocorticoids, except for the treatment of AE).
- Immunoglobulin.
- Live attenuated vaccines.

- ASCT.

5.5.2 Allowed Treatment

- Medications that allowed by the protocol, as judged by the investigators (e.g., for the treatment of disease-related symptoms and treatment-related AEs).
- Local surgery or radiotherapy (radiation field does not include lungs) for isolated lesions (excluding target lesions) during study.
- Subjects who need long-term medication for underlying diseases such as high blood pressure and diabetes can continue to take the drug.
- Supportive treatment to relieve tumor-related symptoms.
- Allow local glucocorticoids to be used, such as external skin, eye drops, nasal spray, inhalation, etc.

5.5.3 Drug-drug interaction

IBI308: There is no data on interaction with IBI308 drugs.

5.6 Treatment Compliance

Study treatment was performed at the research site, and medication compliance was monitored with drug delivery records, patient dairy, and eCRF.

5.7 Drug Retrieve and Destroy

In this study, containers, vials, infusion bags, and syringes of used and partially used research drugs can be destroyed at the research site, according to the guidance of the research site and local regulatory authorities, once confirmed by the clinical monitor.

Any unused drug will be retrieved after the study is completed or terminated, or the drug expires, and destroyed by the sponsor. Designated clinical monitors will be in charge of drug retrieve and destroy.

5.8 Drug Record

The designated personnel of the research center shall promptly make relevant records of the receipt, distribution, use, inventory, destruction, recovery, damage, etc. of the research drug in accordance with the relevant regulations and guidelines and the requirements of the operational procedures of this test.

5.9 Complaint

To ensure the safety and quality of the study participants and to assist with process and drug improvements, the sponsor will collect product complaints related to the study drug used in the clinical trial.

Complaints related to the combined drug will be reported directly to the manufacturer based on the product description.

The investigator or his designee is responsible for completing the following product complaint process in accordance with the relevant provisions of this study:

- Use a research-specific complaint form to record the product complaints and related full descriptions.
- Fax the completed product complaint form to the sponsor or its designated person within 24 hours.

If the investigator is required to return the product for investigation, the investigator should return a copy of the product complaint form along with the product.

6 Procedure

6.1 Patient Recruitment

6.1.1 Patient Recruitment

The investigator will enroll the subjects as follows:

1. Obtain informed consent with the subject's signature prior to any research-related procedures.

2. The principle investigator or the designated trained personnel to review the inclusion/exclusion criteria to formally determine the eligibility of the subject.

Patients who did not meet the relevant criteria for this study (screening failure) could be rescreened. If a rescreening of the patient is considered, the investigator must contact the sponsor's medical manager. When rescreening, the patient must re-sign the ICF and will be reassigned a subject number.

6.1.2 Handling of Wrong Patient Enrolled

The inclusion criteria must be strictly adhered to. If a participant who does not meet the entry criteria is found, the sponsor's medical manager and investigator will discuss

whether to allow the subject to continue participating in the study, with or without the study drug. If the investigator believes that allowing the subject to continue participating in the study is appropriate for the subject from a medical perspective, and the sponsor's medical manager agrees with the investigator's decision, the subject may continue to participate in the study and accept study drug. If the investigator believes that the participant's continued participation in the study is medically appropriate, but the sponsor's medical manager disagrees with the investigator's decision, the subject may not continue to participate in the study (with or without study medication). The investigator was able to allow subjects who were accidentally enrolled in the study to continue to participate in the study only after receiving written approval from the sponsor.

6.2 Study Plan and Schedule

6.2.1 Screening

The following research procedures must be completed during the screening period (Days -28~-1) to ensure that the subjects are eligible for this study:

- Signing informed consent
- Check the inclusion/exclusion criteria
- Record demographics, medical history and prior medications
- Record vital signs, height and weight
- Physical examination
- ECOG PS
- 12-lead ECG
- CBC/ blood biochemistry / urine routine (within 7 days before the first dose)
- Pregnancy test (within 3 days before the first dose)
- Thyroid function
- HIV antibody, hepatitis B two-and-a-half and HBV DNA, HCV antibodies (HCV antibody-positive patients need to detect HCV RNA)
- Adverse event assessment
- Concomitant medication

- Bone marrow biopsy
- Tumor radiological assessment
- Archived or fresh tumor tissue samples
- Pathological diagnosis

See Table 1 for the study screening period.

See Sections 6.3, 6.4, and 6.5 for a detailed description of pathological diagnosis, tumor imaging assessment, and safety assessment.

6.2.2 Baseline (Prior to Day 1 of Cycle 1)

- Record vital signs
- ECOG PS
- PK
- PD
- Immunogenicity
- Adverse event assessment
- Concomitant medication
- Disease related symptoms assessment
- EQ-5D-5L and EORTC QLQ-C30 scale
- Biomarker blood sample collection

6.2.3 Treatment Visits

- Record vital signs
- Physical examination
- ECOG PS
- 12-lead ECG
- CBC / blood biochemistry / urine routine
- Thyroid function

- PK
- PD
- Immunogenicity
- Adverse event assessment
- Concomitant medication
- Tumor radiological assessment
- Bone marrow biopsy: if the imaging is completely relieved, the bone marrow biopsy needs to be reviewed.
- Disease related symptoms assessment
- Study drug administration
- Biomarker blood sample collection
- EQ-5D-5L and EORTC QLQ-C30

See Table 1 for study visits during the treatment period.

Detailed descriptions of tumor radiological assessment, safety assessment, PK, PD, and immunogenic blood collection are provided in Sections 6.4, 6.5, 6.6, 6.7, and 6.8.

6.2.4 Study Treatment Discontinuation Visit

Study treatment discontinuation visit at the end of study treatment

- Record vital signs and weight
- Physical examination
- ECOG PS
- 12-lead ECG
- CBC / blood biochemistry / urine routine
- Thyroid function
- Pregnancy test
- Adverse event assessment
- Concomitant medication

- EQ-5D-5L and EORTC QLQ-C30 scale

6.2.5 Safety Follow-up

- Vital signs
- CBC/ blood biochemistry / urine routine
- Thyroid function
- Adverse event assessment
- Immunogenicity

6.3 Pathological Diagnosis

The pathological slides used for pathological diagnosis in the research site during screening should be provided to the central pathological laboratory for pathological diagnosis confirmation. If the central pathological laboratory requires further pathological slides (white films) or wax blocks, the research site needs to provide. The patients with central pathological laboratory confirmed diagnosis can continue the treatment. Patients without central pathological laboratory confirmed diagnosis will be discontinued from the study if agreed by the research site. Diagnosis confirmation from central pathological laboratory will not affect the patient recruitment.

6.4 Radiographic Assessment

The baseline assessment should be performed within 28 days prior to the first study. The investigator can collect radiographic results from the 28 days prior to enrollment for evaluation.

Tumor radiography uses enhanced CT (MRI, for subjects who are allergic to CT contrast agents) and PET. Enhanced CT examination will be done at baseline (baseline assessment will be performed within 28 days prior to enrollment), weeks 6/15/24 (±7 days), every 12 weeks after 24 weeks (±14 days), and every 16 weeks after 48 weeks Week (±14 days). The examination site includes the neck, chest, abdomen, basin and other required anatomical sites until the start of new therapy, disease progression, withdrawal of ICF or death. The first disease progression needs to confirm after 4~6 weeks. For patients who discontinue treatment for other reasons than disease progression confirmed by radiology, it is still necessary to carry out radiological evaluation according to the protocol, after treatment discontinuation, until the start of new therapy, disease progression, subject withdrawal of ICF or death. PET

examinations were performed at baseline, week 15 (±7 days), or early termination of study treatment.

The tumor assessment was based on the IWG 2007 and the Lugano 2014 as an auxiliary evaluation criterion. IRRC is to be set in the study. Specific radiological assessment and sampling requirements can be found in the Radiology Sampling Guide.

6.5 safety evaluation

6.5.1 Laboratory Evaluation

Table 2. Laboratory Evaluation

CBC	RBC、HGB、WBC、PLT、LYM、ANC
Blood Chemistry	TBIL、ALT、AST、γ-GT 、ALP、ALB、TP、LDH、BUN、Cr、Na、K、Cl、 Mg、Ca、P、Lipase、Amylase and FBG
Urine routine	PH、UALB、UPRO、URBC and UGLU

6.5.2 Physical examination

Complete physical examinations include: general condition, respiratory tract, cardiovascular, abdomen, skin, head and neck (including ears, eyes, nose, throat), lymph nodes, thyroid, musculoskeletal (including spine and limbs), genitals/anus, and nerves System evaluation.

Refer to Table 1 for examination schedule.

6.5.3 12-lead ECG

The 12-lead ECG will be analyzed at the local laboratory according to Table 1.

A 12-lead ECG examination will be performed after the subject rests 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 examinations will be performed when there is a clinical need, for example, in the event of a cardiac related adverse event. The examiner completes the ECG assessment on the same day and records the results on the ECG. The same assessment method should be used throughout the study.

The investigator should evaluate all ECGs based on clinically significant abnormalities/no clinically significant abnormalities. If it is an abnormal result of clinical significance, the investigator should record the result as an AE in eCRF.

6.5.4 Vital signs

Vital signs examinations will be performed as described in Table 1. Vital signs include body temperature, pulse rate, respiratory rate, and blood pressure.

Investigators may perform additional vital sign assessment based on standard clinical practice or on a clinical basis.

Additional vital sign record values (if applicable) can be collected on the eCRF when AE/SAE occurs. The date and time of acquisition and measurement will be recorded in the appropriate section of the eCRF.

6.5.4.1 Pulse and blood pressure

After the subject rests for at least 5 minutes, the subject's supine posture blood pressure and pulse are to be measured. Two or more readings should be taken, with an interval of 2 minutes between measurements, taking the mean. If the first two systolic pressure readings differ by more than 5 mmHg, they should be measured again and averaged. The date and time of acquisition and measurement will be recorded in the appropriate section of the eCRF.

It is necessary to measure pulse and blood pressure before the study drug is administered.

6.5.4.2 Body Temperature and Breathing

On the planned dosing day, body temperature and breathing should be taken prior to drug administration.

6.5.5 Weight and height

Height was measured only during the screening period, and body weight was measured during the screening period and at the end of treatment.

6.5.6 Pregnancy test

Women with fertility potential (as defined in 4.3) are tested for pregnancy in urine or serum human chorionic gonadotropin (β-HCG) samples within 3 days prior to the first dose of study drug. If the urine β-HCG is positive or cannot be determined to be negative, a serum β-HCG sample pregnancy test is performed. If the result is positive, the subject is not eligible for admission/must stop participating in the study. A pregnancy is suspected during the study and should be reviewed.

6.5.7 Other Safety Assessment:

- Hepatitis B (HBsAg, HBsAb, HBcAb, HBeAg, HBeAb) and HBV DNA.
- HIV antibody, HCV antibody (if HCV antibody is positive, HCV RNA will be checked)
- Thyroid function: T3, T4, TSH, FT3 and FT4.

6.6 Pharmacokinetics

Twelve subjects in selected research sites will be chosen for PK analysis. The total number of PK blood collection in the first cycle is 8: within 1 hour before the start of IBI308 infusion, immediately after infusion (+5min), 1h±5min after infusion, 6h±15min after the start of infusion, 24h±1h. 48h±2h, 168h±8h (day 8), 336h±12h (day 15); if the administration is delayed on the first day of the second cycle due to AE or other reasons, the first cycle needs to include an 504h±24h (Day 22) sampling. From the second cycle, PK sample collection is performed every two cycles (the second, fourth, and sixth phase cycles, and so on). Except for the fourth cycle, the sampling time is: within 1 hour before the start of the infusion and immediately (+5min) after infusion, 1h ± 5min after infusion, 6h ± 15min, 24h ± 1h, 48h ± after the infusion, 168h ± 8h (day 8), 336h ± 12h (day 15), 504h ± 24h (day 22, ie, within 1 hour before the fifth cycle of administration).

2 ml of blood is to be collected using a procoagulant vacuum blood collection tube, serum is separated, and frozen for storage for PK analysis. Sampling methods, sample storage, transportation and analysis are detailed in the Laboratory Manual provided by the sponsor's designated central laboratory.

The concentration of IBI308 in the serum is analyzed by ELISA and tested by the sponsor's designated central laboratory. All subjects are required to measure plasma concentrations at the blood collection points per the protocol.

6.7 Pharmacodynamics

Twelve subjects in selected research sites will be chosen for PD analysis. The total number of PD blood collection in the first cycle is 3: within 1 hour before the start of the IBI308 infusion, 24 h ± 1 h after the start of the infusion, and 168 h ± 8 h (Day 8). At the beginning of the second cycle, sample collection is performed every four cycles (the second, sixth, tenth, fourteenth, etc., and so on).

An anticoagulated vacuum blood collection tube will be used to collect 1 ml of blood for PD-1 receptor occupancy analysis. Sampling methods, sample storage, transportation and analysis are detailed in the Laboratory Manual provided by the sponsor's designated central laboratory.

6.8 Immunogenicity

The immunogenicity test will be performed during the first cycle, the second cycle, the fourth cycle, and every 4 cycles (the 8th, 12th, and 16th cycles, etc.) within 1 hour before the IBI308 infusion and during the safety follow-up. The analysis will be done at the central laboratory.

Anti-drug antibody (ADA) titers will be tested in each subject, and ADA-positive serum samples will continue to be tested for neutralizing antibodies (NAb).

4 ml of whole blood will be collected using a coagulation vacuum blood collection tube, serum is separated, and frozen for storage for ADA and NAb analysis.

Sampling methods, sample storage, transportation and analysis are detailed in the Laboratory Manual provided by the sponsor's designated central laboratory.

6.9 Quality of life assessment

The quality of life assessment is conducted using the EQ-5D-5L and EORTC QLQ-C30 scales, on the first day of dosing, each radiographic assessment, and the end of treatment follow-up.

The EQ-5D-5L is a standardized tool for self-reporting health status indicators. Subjects will fill out 5 levels (no problem, mild, moderate, severe, and extreme) about their current health status, 5 dimensions (mobility, self-care, daily activities, pain/discomfort, and anxiety/depression) questionnaire. After synthesizing the levels of the five dimensions, the unique EQ-5D health status is defined. In addition, patients will be marked with a visual analog scale (VAS) ranging from 100 (the best imaginable health condition) to 0 (the worst health condition imaginable) to illustrate their current health status.

EORTC's QLQ-C30 is a core scale for all cancer patients. It has 30 entries and can be divided into 15 dimensions, with 5 functional dimensions (body, role, cognition, mood and social function), 3 symptoms dimensions (fatigue, pain, nausea and vomiting), 1 overall health/quality of life dimension, and 6 single items.

6.10 Biomarker analysis

Subject to the ethics committee, all subjects who meet the inclusion criteria are required to provide archived tumor tissue at baseline or 4 unstained 4-5 micron sections prepared freshly during the screening period for PD-L1 testing.

For the detection of mRNA expression levels of immune-related genes, subjects are required to provide archived tumor tissue at baseline or 4 unstained 4-5 micron sections prepared freshly during the screening period.

Subjects are required to provide 10 ml blood samples at the following time points: the screening period, the treatment period, and the efficacy evaluation before the next treatment. The following tests may be performed: dynamic analysis of peripheral blood mononuclear cells in the enrolled patients by analysis of surface markers of different subtypes of lymphocytes and circulating tumor cells (e.g., PD-L1, Tim-3, CSF1R, TIGIT, LAG-3) , OX40, 4-1BB, GITR, CTLA-4, FOXP3, PD-1, PD-L2, CD4, CD3, TAM-related markers, MDSC-related markers, B2M, B7-H3, B7-H4, VISTA, etc.), predict the efficacy and prognosis of patients with anti-PD-1 immunotherapy.

For a detailed description of sample handling, disposal, and shipping, refer to the Laboratory Manual.

6.11 Storage and destruction of biological samples

The sample will be disposed or destroyed and merged and anonymized. Additional analysis of the anonymized, combined samples may be performed to further evaluate and validate the analytical method. Any results obtained from these analyses may be reported separately from the CSR.

The sample reproducibility analysis (if performed) will be performed in parallel with the bioanalysis of the test sample. These findings will not be reported in the clinical study report, but will be given separately in a bioanalytical report.

7 Safety Reporting and Adverse Event Management

7.1 Definition of adverse events

An adverse event (AE) is defined as any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment. All adverse events should be reported since the consent form is signed until 90th day after last

administration of investigation products. AE includes but is not limited to the following situations:

- Exacerbation of preexisting (before entering the clinical trial) medical condition/disease (including symptoms, signs, and abnormalities in laboratory tests) ;
- Any new adverse medical conditions (including symptoms, signs, newly diagnosed diseases);
- Abnormal laboratory test values or results which have clinical significance.

7.2 Definition of serious adverse events

A serious adverse event is any adverse event occurring at any dose or during any use of Sponsor's product that:

- Results in death, except for deaths caused by the progression of clinical indications;
- Is life-threatening (The definition of “life-threatening” is the subject is at risk of death when AE occurs, but does not include AEs that may cause death if the event is aggravated);
- Requires inpatient hospitalization or prolongation of existing hospitalization, excluding the following:
  - ✓ Rehabilitation institution
  - ✓ Sanitarium
  - ✓ Routine treatment in emergency room
  - ✓ Day surgery (e.g. outpatient / day / ambulatory surgery)
  - ✓ Hospitalization or prolongation of existing hospitalization that is not associated with AE aggravation. For example: The patient was hospitalized for clinical indication or preexisting indication, no new adverse events or no aggravation of preexisting indication (such as retest laboratory abnormalities that persisted); hospitalization for management reasons (such as annual routine Physical examination); hospitalization which specified in the protocol (e.g. as required by the protocol); elective hospitalization not associated with AE aggravation (e.g. elective surgery); scheduled treatment or surgery should be performed during clinical trial which recorded as baseline data; hospitalized for blood product use only.
- Results in persistent or significant disability/incapacity;
- Is a congenital anomaly/birth defect;
- Is another important medical event. The definition of important medical events is AE that may not be immediately life-threatening or result in death or

hospitalization but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the definition above.

7.3 AE severity assessment

Investigator will evaluate the severity for all adverse events according to the NCI Common Terminology for Adverse Events (CTCAE), version 4.03.

For adverse event terms not included in NCI CTCAE version 4.03, the severity will be evaluated according to the general guideline of NCI CTCAE:

- Grade 1 Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
- Grade 2 Moderate; minimal, local or noninvasive intervention indicated; limiting ageappropriate instrumental ADL (Instrumental ADL refer to preparing meals,shopping for groceries or clothes, using the telephone, managing money, etc).
- Grade 3 Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self care ADL (Self care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridde)
- Grade 4 Life-threatening consequences; urgent intervention indicated.
- Grade 5 Death related to AE.

7.4 Causality assessment

The relationship between Investigation products and AE can be judged by the following classifications and criteria:

Table 3. Causality assessment

Causality	Criteria for Causality assessment
definitely related	The onset date of AE and administration of Investigation product is reasonable; The administration of Investigation products can explains the adverse event more reasonably than other causes (e.g. the subject's preexisting disease, environmental or toxic factors, or other treatments received by the subject); AE disappeared or reduction after drug withdrawal or dosage reducing; AE type is known for the suspected drug or its similar drugs AE reappear after re-medication.
Possible related	The onset date of AE and administration of Investigation product is reasonable; The administration of Investigation product can also reasonably explains the adverse event than other causes (e.g. the subject's preexisting disease, environmental or toxic factors, or other treatments received by the subject); AE disappeared or reduction after drug withdrawal or dosage reducing;

Causality	Criteria for Causality assessment
Possible unrelated	Another cause (e.g. the subject's preexisting disease, environmental or toxic factors, or other treatments received by the subject) can explains the adverse event more reasonably than Investigation products; AE still existed or no reduction after drug withdrawal or dosage reducing; AE dos not appear after re-medication..
Unrelated	The onset date of AE and administration of Investigation product is unreasonable; or The adverse event has other apparent causes (eg, the subject's original disease, environmental or toxic factors, or other treatments the subject receives).
Unable to judge	The above information is not available, The Investigtor can't assessment the causality according to the existing information and cannot get follow-up information.

7.5 AE record

Investigators should record AE or SAE using medical terminology/concept. Spoken and abbreviations should be avoided. All AEs (including SAE) should be recorded on the eCRF.

7.5.1 AE collection period

The investigator will collect AE via asking subject with non-inductive questions.

All adverse events, including serious adverse events, will be collected since the consent form is signed until 90th day after last administration of investigation products, either observed by investigator or by the spontaneous reported by subjects.

90 days after the last dose, the investigator should report serious adverse event associated with the study drug or procedure.

7.5.2 Follow-up of AE

Adverse events should be followed up until to baseline or grade 0~1 or the investigator believes that no further follow-up is required for reasonable reasons (if it cannot be recovered or has improved). If the adverse event cannot be recovered, a reasonable explanation should be recorded in the eCRF. Regardless of whether it is related to the study drug, the recovery condition and date of AE or SAE should be recorded in the subject's eCRF and medical records.

7.5.3 Contents of AE records

Investigator should record adverse events completely, including diagnosis (if no diagnosis, record symptoms, signs including laboratory abnormalities), start date and end dates (if applicable), CTCAE severity grade and changes (level 3 or above), serious

adverse event or not, adverse event of special interest or not, action taken for investigation products, the treatments for AE and the result of AE, and the relationship between adverse events and investigation product.

For serious adverse events, the investigator should also record the date on which the AE meets the SAE criteria, the date the investigator was informed of the SAE, the criteria for the AE meets SAE, the date of hospitalization, the date of discharge, the cause of death, the date of death, autopsy or not, and causal assessment with clinical procedure, causal assessment with other drugs, and other possible causes of SAE. The investigator should also provide a basis of causality assessment and the narrative of SAE. In the SAE narrative, the subject's number, age, gender, height, weight; the indications for study drug and disease staging, and related general conditions; SAE occurrence, development, outcome and clinical course; laboratory findings related to SAE (the time, unit and normal range must be provided); previous history of SAE, combined disease and its occurrence and duration; SAE-related medication history, combined drug and the start date, duration, and dosage of the treatment; the start date, duration, and dosage of investigation products.

The items related to the AE recording are described as follows:

Diagnosis, symptoms and signs

If a diagnosis has been made, the diagnosis should be recorded on the eCRF rather than individual symptoms and signs (e.g. recording liver failure, not jaundice, elevated transaminase, and flapping tremor). If the symptoms and signs are not sure be caused by the diagnosis at the time of reporting, they should recorded as separate AE/SAE. If it is sure that the symptoms and signs are caused by the diagnosis, only the diagnosis is reported separately, and the symptoms and signs are included in the diagnosis. The AE recording needs to delete symptoms and signs, and the SAE needs to send a follow-up update report.

Adverse events secondary to other events

Often, adverse events secondary to other events (e.g, caused by other events or clinical sequelae) should record their primary events unless the secondary event is severe or a serious adverse event. However, secondary events with significant clinical significance, if different from the time of occurrence of the primary event, should be recorded as independent adverse events in the eCRF. If the association between the events is not clear, it should be recorded separately in the eCRF.

Persistent or recurrent adverse events

A persistent adverse event is an adverse event that persists without a remission between the two evaluation time points. This adverse event should only be recorded once on the eCRF. The initial severity of the AE should be recorded and updated the severity when AE worsen.

The AE of recurrence refers to an AE that has been alleviated between the two evaluation time points, but then occurred again. The reoccurred AE should be recorded separately in the eCRF.

Abnormal laboratory test

Clinically significant laboratory findings should be reported as AE. It is the responsibility of the investigator to review all laboratory abnormalities and to make medical judgments as to whether each laboratory should report an abnormality as an AE.

Death

All deaths that occurred during the entire trial period, including deaths occur during 90 days after last administration of investigation products, whether or not related to the study drug, should be recorded in the death report form of the eCRF and reported to the sponsor timely.

When a death event is recorded, the cause of death is recorded as an adverse event, and the result of the adverse event is death, and the death is reported as SAE; if the cause of death at the time of reporting is unknown, it should be recorded as “Death NOS” in eCRF and reported as a SAE. The exact cause of death should be further investigated.

If death is clearly caused by tumor progression, it is not recorded and reported as an AE/SAE, but the investigator should record the death in the eCRF death report form and inform the sponsor timely.

Preexisting Medical status

Subjects' symptoms/signs during the screening period, only if there is a severity, frequency, or exacerbation of the disease (except for the worsening of the disease condition under study) should be recorded and reported as adverse events. Changes of preexisting medical status should be reflected in the record, such as "increased frequency of headache."

Hospitalization, prolongation of existing hospitalization or surgery

Any adverse events that result in hospitalization or prolongation of existing hospitalization should be recorded and reported as SAE, except following e:
Prolonged hospitalization or hospitalization according to the trial design requirements (e.g. for drug delivery, efficacy evaluation, etc.)

The subject was hospitalized for medical conditions that existed before participating clinical trial. For example, elective surgery/treatment scheduled before participating in the study.

However, if the preexisting disease aggravated, the aggravated preexisting disease should be recorded as AE/SAE.

Disease progression

Disease progression is defined the subject's condition worsen caused by the primary tumor which as the indication of investigation product. A new lesion relative to the primary tumor or progression of the original lesion is considered to be disease progression. Disease progression is not reported as an AE, The symptoms and signs Disease progression which result death, life-threatening, requiring hospitalization or prolonged hospital stay, leading to permanent or severe disability/capacity loss, leading to congenital anomalies/birth defects and other important medical events are not reported as SAE.

Overdose

The dosage over the dose specified in the protocol is the drug overdose. Overdose will be recorded in the eCRF.

7.6 SAE and pregnancy reporting process

SAE report:

SAE will be reported since the consent form is signed until 90th day after last administration of investigation products. If SAE occurs, whether it is initial report or follow-up report, the investigator must immediately completed SAE form with signature. The SAE should be reported sponsor, regulatory authority and the ethics committee within 24 hours of the investigator awareness. The contact details are shown in the table below.

If a SAE occurred outside the above-mentioned period, the SAE should also be reported

to sponsor when there is a reasonable relationship between this SAE and investigation product.

For SAEs that are life-threatening or death, the investigator should urgently follow up missing information and provide a complete SAE report to Sponsor, regulatory authority and ethics committees.

Table 4. SAE Reporting contact form

Organization	**Contact**	**Fax/telephone/address**
Hospitals name	Ethics committee	Fax/telephone of hospitals
Innovent	Innovent PV	fax：021-31652800 mail：drugsafety@innoventbio.com
China National Drug Administration		address：Building 2, No. 26, Xuanwumen West Street, Xicheng District, Beijing zip code：100053 phone：010-88330732 fax：010-88363228
National Health Commission of the People's Republic of China		address：No. 38, Lishi Road, Xicheng District, Beijing phone：010-68792001 fax：010-68792734
Provincial, autonomous region, municipal drug regulatory authority	Refer to the reporting requirements of the regulatory authorities of provinces, autonomous regions, and municipalities directly under the Central Government.	

Pregnancy

Similar drugs have a safety risk for embryotoxicity, and all subjects with fertility in clinical trials must take effective contraceptive measures.

When a female subject is pregnant during a clinical trial, the subject is should be excluded, Investigator should report to sponsor within 24 hours of awareness of pregnancy, and complete Innovent Clinical Trial Pregnancy Report/Follow-up Form.

When the male subject's partner is pregnant during the clinical trial, and the subject can still participate the clinical trial. Investigator should report to sponsor within 24 hours of awareness of pregnancy, and complete Innovent Clinical Trial Pregnancy Report/Follow-up Form.

The investigator should monitor the pregnancy and follow up the pregnancy results, until to 8 weeks after the mother delivers, and report the results to sponsor.

If the pregnancy results is stillbirth, spontaneous abortion, fetal malformation (any

congenital anomaly / birth defects), and abortion with medical reason, this condition should be considered as SAE, need to report as SAE and timeline.

If the subject has SAE at the same time during pregnancy, the Serious Adverse Event Report Form will be completed and reported in accordance with the SAE reporting procedure.

7.7 Events with abnormal liver function

If the AST and / or ALT levels are abnormal and the total bilirubin level is abnormally, the abnormal test can met following conditions and no other reason cause liver damage, this will be considered as drug-induced liver damage. Such conditions should always be considered an important medical event.

Table 7. Liver function damage as required by SAE

baseline	Normal (AST/ALT and total bilirubin)	abNormal (AST/ALT and total bilirubin)
Treatment period	ALT or AST≥ 3× ULN With Total bilirubin≥ 2× ULN And Alkaline phosphatase≤ 2× ULN And without hemolyse	AST or ALT≥ 8× ULN With Total bilirubin≥ 1× ULN or ≥ 3× ULN

Subjects should return to site for evaluation as soon as possible after receiving an abnormal result (preferably within 48 hours). The assessment should include laboratory tests, detailed medical history and physical assessment, and should consider the possibility of liver tumors (primary or secondary).

In addition to repeated testing for AST and ALT, laboratory tests should be performed including albumin, creatine kinase, total bilirubin, direct and indirect bilirubin, gamma-glutamyltransferase, prothrombin time/international Standardized ratio, alkaline phosphatase. Detailed medical history collection should include: history of drinking, acetaminophen, soft drugs, various supplements, Chinese medicine, history of exposure to chemical drugs, family history, occupational exposure, history of sexual behavior, travel history, and history of contact with patients with jaundice, surgery, blood transfusion, history of liver disease or allergic disease, history of heart disease, history of immune disease, etc. Further examination may include detection of acute hepatitis A, B, C and E, liver imaging (eg, biliary tract), autoantibodies, and cardiac ultrasound. If repeated testing met the criteria in Table 7, the potential of drug-induced liver damage should be considered without any other reason explaining abnormal liver function

testing, no need to wait all liver nosetiology results. Such potential cases of drug-induced liver damage should be reported as SAE.

7.8 Management of drug-related toxicity

Sponsor will conduct regular safety review during study. Detailed information, including the frequency of review and the type of data to be reviewed, will be recorded in a separate safety review plan for this trial.

7.8.1 Immune-related adverse events

As the mechanism of IBI308 is T cell activation and proliferation, immune-related adverse events (irAEs) may be observed during this study. For a detailed definition of irAE, see Section 5.4. The signs and symptoms of irAE should be monitored.

The dose adjustment of IBI308 and adverse event management principles are detailed in Sections 5.3 and 5.4. The disposal guidelines for irAE are detailed in attachment 7 (Tables 1 to 2).

7.8.2 Adverse Event of Special Interest

Adverse Event of Special Interest (AESI) is the event needs special close monitoring for the better understanding of the safety for the IP. AESI may be non-serious event.

Adverse Event of Special Interest (AESI) of the trial included:

- Infusion reaction which the grade is greater than or equal to 3
- Diarrhea colitis, uveitis, interstitial pneumonia which the grade is greater than or equal to 2
- Suspected immune-related adverse events which the grade is greater than or equal to 3

8 Statistical considerations

8.1 Statistical analysis plan

Detailed statistical analysis plan (SAP) will be prepared after first patient enrolled and will be finalized before data base lock.

8.2 Hypothesis testing

The primary efficacy endpoint of this study is ORR from IRRC according to IWG2007 criteria. The hypothesis of one sample superiority test is:

H_0：ORR≤40%

H_1：ORR>40%

Superiority test is based on confidence interval (CI). If the lower limit of the (1-α) % CI (α will be adjusted for interim analysis） is larger than 40%, it is statistically confirmed that IBI308 monotherapy is efficacious in patients with relapsed or refractory cHL.

8.3 Analysis populations

The following analysis populations will be defined:

Safety set (SS): patients who received at least one dose of study drug.

Full analysis set (FAS): patients who received at least one dose of study drug and with measurable disease at baseline. Patients that are not confirmed by IRRC as cHL will not be included in FAS population.

Per protocol set (PPS): subset of FAS, with no major protocol deviation that affects efficacy evaluation, no prohibited concomitant medication defined by protocol, and good compliance.

8.4 Statistical Method

8.4.1 General Statistical Method

Descriptive summary statistics are provided to summarize continuous data. Frequency and percentage are provided to summarize categorical data.

SAS 9.2 (or higher version) will be used for all the statistical analysis.

8.4.2 Analysis of Primary Endpoints

Per IWG 2007 criteria, ORR assessed by IRRC:

$ORR = \frac{CR + PR}{\text{Total Number of Subjects}} * 100\%$, and the (1-α) % CI will be calculated using binomial distribution for confirmation of superiority.

8.4.3 Analysis of Secondary Endpoints

Per IWG 2007 criteria, assessed by IRRC and investigators:

- ORR (Assessed by Investigators)

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

- TTR (Assessed by IRRC and Investigators)

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

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

- DOR (Assessed by IRRC and Investigators)

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

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

- PFS (Assessed by IRRC and investigators)

PFS: the time from the date of the first dose to the date of first disease progression (imaging), if subjects died due to any reason prior to the disease progression, PFS is the time from the date of first dose to the date of death. If subjects who did not die or had no disease progression, the censoring dates are the dates of the last imaging assessment dates. Subjects with no post-baseline imaging assessments will be censored on the date of enrollment.

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

- DCR (Assessed by IRRC and investigators)

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

using binomial distribution.

8.4.4 Biomarker assessment

Descriptive statistics will be summarized for different PD-L1 expression levels and explore its potential relations with treatment effect.

Descriptive analyses will also be provided for tumor immune related genes and its distribution and explore its potential relations with treatment effect.

The analysis not specified in this document may need to be done post hoc wisely. The analysis specified in this section may need to be done at discretion of the data availability.

8.4.5 Quality of life assessment

The score of EQ-5D-5L and EORTC QLQ-C30 at each assessment will be computed. The descriptive statistics for baseline value, values at each post-baseline assessment and the change from baseline will be summarized for each individual question score as well as the composite score.

8.4.6 Safety analysis

The safety analysis will be conducted on domains of Adverse Event, Clinical Laboratory Evaluation, Vital Sign Measurement, Electrocardiograms and Immunogenicity base on SS population.

8.4.6.1 Treatment Exposure

The study treatment exposure in doses and the treatment duration in days and cycles will be summarized for subjects.

8.4.6.2 Adverse Event

All AEs will be coded using MedDRA.

The overall incidence rates of AEs, TEAEs, drug related AE, Immune-related AEs (irAE), AEs of Special Interest (AESI), SAEs, important AEs and AEs leading to early study termination will be summarized. and by SOC and PT according to MedDRA, and further by severity grade according to NCI CTCAE 4.03.

A listing will be provided for subjects who discontinued the study drug due to AE, experienced at least one SAE, or died with information at least including AE’s start and

end date, severity grade, relation with study drug, action taken and outcomes.

8.4.6.3 Clinical Laboratory Evaluation

Hematology and Chemistry test results will be summarized with descriptive statistics for values of baseline, post-baseline and change from baseline. Shift tables will be provided for normality status of laboratory values changing from baseline to each post-baseline assessment.

Urinalysis will be analyzed by using shift tables with normality status changing from baseline to each post-baseline assessment.

For subjects with abnormal laboratory values, the status of "Abnormal, clinically Significant" will be determined by investigator and the category will be summarized in frequencies and percentages.

Subjects with abnormal post-baseline laboratory values with or without clinical significance will be provided in a listing.

8.4.6.4 Electrocardiograms

The ECG measurements at baseline, post-baseline and change form baseline will be summarized. The normality status changing from baseline to each post-baseline assessment will be also summarized in a shift table. Listings of ECG measurements will be provided as well.

8.4.6.5 Vital Sign, Physical Examination and Other relevant assessments

Vital sign will be summarized with descriptive statistics for baseline, post-baseline and change from baseline values. A listing will be provided for subjects who have post-baseline abnormal assessment in physical examination.

8.4.7 Immunogenic Endpoint

The positive rates of ADA antibody and NAB will be calculated, and the antibody levels of positive subjects will be listed.

8.4.8 Compliance Analysis

Summarize the percentage and frequency of subjects who violate the expected drug regimen.

The percentage of subjects who take the drug between 80% and 120% of the prescribed

dose in the study.

The percentage of subjects who complete the entire study and that who completed different treatment cycles.

8.4.9 Baseline characteristics of subjects

Descriptive statistics will be used for the endpoints below:

Demographic characteristics (gender and age), information about diagnosis and treatment of tumor (pathological diagnosis, clinical stage and previous treatment), baseline examination of tumor (target lesion, number of non-target lesion, location, total diameter, etc.); other baseline information (height, weight, body mass index, body surface area, vital signs, laboratory examinations, previous/concomitant/newly added medications, etc.).

8.4.10 Interim Analysis

In this study, an interim analysis is planned to conduct at the time point when all the enrolled subjects finished two tumor assessments as planned. The purpose of the interim analysis is for conditional BLA submission at the early stage, and the endpoint is the primary efficacy endpoint ORR according to IWG2007.

Given a two-sided alpha of 0.03 at interim analysis, if the lower limit of 97% CI of ORR is greater than 40%, it can be considered as superiority confirmed. Regardless of results at interim analysis, the study will continue till the last subject finish at 24 weeks tumor assessment at which time final analysis will be conducted. An alpha level of two-sided 0.05 is to be used in the final analysis if the study demonstrates superiority at the interim analysis, otherwise two-sided 0.036 level will be applied.

8.4.11 Multiple comparison and multiplicity adjustment

In this study, interim analysis is planned to be conducted once with an alpha level of two-sided 0.03. An alpha level of two-sided 0.05 is to be applied in the final analysis if the study demonstrated superiority at the interim analysis, otherwise two-sided 0.036 level will be applied.

8.4.12 Subgroup Analysis

Efficacy analysis in PD-L1 positive subjects.

Subgroup analysis of efficacy will also be conducted according to age and previous

treatment.

8.4.13 Listing of evaluable subjects

In addition to the overall listings of subjects, tumor evaluation of CR and PR (evaluation date, lesion status and evaluation results) and efficacy endpoints will be listed separately.

PFS data of all subjects at the end of study.

8.4.14 Exploratory Analysis

Correlation between different expression levels of PD-L1 and treatment effect.

8.5 Determination of sample size

This is a phase II single-arm study. Assuming the null hypothesis of ORR is ≤ 40%, two-sided alpha as 0.05, a total sample size of 80 will provide 80% power to detect a 16% difference for IBI308 monotherapy, that is, the ORR for IBI308 monotherapy reaches 56%. Considering a dropout rate as approximately 10%, the planned sample size is 90, to ensure at least 80 patients with available efficacy assessment (the EAS population).

The null hypothesis of ORR 40% is based on clinical research results of relevant drug monotherapy on relapsed or refractory cHL [9-11]. It also takes into consideration of study designs of similar drugs in clinical research of cHL.

8.6 Bias control

8.6.1 Randomization and blinding

This is a single arm, open label study, which does not involve randomization and blinding process.

8.6.2 Evaluation of blinding maintenance

Not applicable.

8.6.3 Unblinding and emergency unblinding

Not applicable.

9 Quality Assurance and Quality Control

In accordance with the guidelines of the GCP, it is the responsibility of the sponsor to

implement and maintain a quality assurance and quality control system in accordance with the appropriate standard operating procedures to ensure the implementation of clinical trials and the truthfulness of the data, and to collect, record and report compliance with the program, GCP and corresponding regulatory requirements.

9.1 Clinical Audit

The CRO authorized by the sponsor or sponsor will conduct a clinical audit of the study. The clinical monitor should conduct the audit according to the standard operating procedures of the sponsor or CRO and have the same rights and responsibilities as the sponsor's monitor. The auditor shall maintain regular communication with the investigator, the trial authorised personnel and the sponsor.

Before the study begins, the auditor will assess the competency of each research center and report issues related to facilities, technical equipment, or medical staff to the sponsor. During the course of the study, the monitor will be responsible for monitoring whether the investigator has obtained written informed consent from all subjects and whether the data records are correct and complete. At the same time, the monitor will also compare the data input to the eCRF with the original data and inform the researcher of errors or omissions. The monitor will also control the compliance of the research center's program and test procedures, arrange for the supply of research drugs, and ensure that the drugs are kept in the proper conditions.

The audit visit will be conducted in accordance with the requirements of relevant laws and regulations. From the time the subjects are enrolled, each center will receive regular monitoring visits. After each visit to the investigator, the auditor should 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 entered into the eCRF by the investigator or authorized researcher. Researchers and authorized researchers will be properly trained and appropriate security measures will be taken for the equipment used, etc., prior to the start of the research center or data entry.

Data entry for eCRF should be completed as soon as possible during or after the visit and updated at any time to ensure that it reflects the latest developments of the participants in the study. To avoid differences in outcome assessment by different evaluators, it is recommended that the same subject's baseline and all subsequent

efficacy and safety assessments be performed by the same individual. Researchers are required to review the data to ensure the accuracy and correctness of all data entered into the eCRF. If some assessments are not made during the study, or if certain information is unavailable, not applicable, or unknown, the investigator should record it in the eCRF. The investigator should electronically sign the verified data.

The CRA will review the eCRF and assess its completeness and consistency, and the CRA will compare the eCRF with the original documents to ensure consistency of key data. All data entry, corrections and modifications will be the responsibility of the investigator or his designee. The data in the eCRF is submitted to the data server and any changes to the data are recorded in the audit trail, ie the reason for the change, the name of the operator, the time and date of the modification will be recorded. The roles and authorities of the staff responsible for data entry in the research center will be predetermined. If there is any data challenge, the CRA or data management staff will issue a challenge in the EDC and the research center staff will be responsible for the Q&A. The EDC system will record the audit trail of the challenge, including the name, time and date of the investigator.

Unless otherwise stated, eCRF will only be used as a form to collect data, not as a source. The original document is used by the investigator or hospital, relevant to the subject, and demonstrates the presence, inclusion criteria, and all records of participation in the study, including laboratory records, ECG results, and pharmacy drug delivery records. , subject folder, etc.

The investigator is responsible for maintaining all original documents and for CRA to monitor them at each visit. In addition, regardless of the length of time the enrolled subjects participated in the study, the investigator must submit a complete eCRF for each enrolled subject. The program number and subject number of all supporting documents (such as laboratory records or hospital records) submitted with eCRF should be carefully verified, and all personal privacy information (including the subject's name) should be deleted or made illegible. To protect the privacy of the subject. The researcher verifies that the record has been reviewed by an electronic signature record and that the data of the record is accurate. The electronic signature will be completed using the researcher's user ID and password. The system will automatically attach the date and time of the signature. The researcher must not share the user ID and password with other people. If you need to change the data in the eCRF, you should follow the workflow defined by the EDC system. All changes and reasons for the changes will be

recorded in the audit trail.

Adverse events, concomitant diseases/history will be coded. The dictionary for coding will be described in the Clinical Research Summary Report (CSR).

9.3 Quality Assurance Audit

During the course of the study, the sponsor or the representative authorized by the sponsor may conduct quality assurance audits of the research center, research database and related research documents. At the same time, the corresponding regulatory agency may also inspect the research center, research database and related research documents at its own discretion. When the researcher receives the inspection notice from the regulatory body, he or she must immediately inform the sponsor.

The quality assurance department of the sponsor conducts an audit of the clinical trial institution. The audit includes: the supply of the drug, the required test documents, the record of the informed consent process, and the consistency of the medical report form with the original documents. The content and scope of the audit can also be increased depending on the situation. After reasonable notice, the investigator shall allow the auditors commissioned by the sponsor to conduct inspections related to the trials and inspections conducted by the regulatory authorities. The primary purpose of an audit or inspection is to verify that the rights or health of the participants in the trial are protected, that the signing of the informed consent and the implementation of the trial process are carried out correctly, and that all data related to the study drug evaluation are processed and reported and pre-planned, The program, facility, ethical standard operating procedures, GCP and applicable regulatory requirements are consistent. Researchers should have direct access to all test files, original records, and raw data.

10 Ethics

10.1 Ethics Committee

The sponsor or the representative authorized by the sponsor will prepare the relevant documents to be submitted to the Research Center's Ethics Committee (EC), including the trial protocol, informed consent, investigator's manual, subject recruitment materials or advertising and other regulatory requirements. Documents must be submitted to the appropriate EC for approval. Prior to the start of the study, written approval from the Research Center EC must be obtained and provided to the sponsor. The EC's approval must specify the name, serial number, version number and version number of the other study (e.g. informed consent) and the date of approval. The

investigator is required to notify the sponsor of the EC's written comments regarding delays, suspensions, and re-approval.

The research center must follow the requirements of the Center's EC. It may include revision of the program, revision of the informed consent form, revision of the subject's recruitment materials, submission of the EC for approval, local safety report requirements, regular reporting and update in accordance with EC regulations, and submission of the final report. All the above documents and EC approvals must be provided to the sponsor or its designee.

10.2 Ethics of the study

Access to the research process and informed consent is subject to the Helsinki Declaration, relevant GCP requirements, and laws and regulations related to drug and data protection in China.

GCP provides ethical, 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 Helsinki Declaration to protect the rights, safety and health of the subjects.

The researcher is required to follow the procedures specified in this protocol and may not change it without the permission of the sponsor. Any program violation will be reported to the EC, the sponsor, or the regulatory body.

10.3 Subject Information and Informed Consent

Before the start of any research process, informed consent (ICF) is used to explain the risks and benefits of this study to potential participants, and the language of informed consent should be straightforward. The ICF statement should make it clear that informed consent is voluntary and clearly identifies the risks and benefits of participating in the study, and the subject may withdraw from the study at any time. The investigator can only enroll the subject if he or she fully explains the details of the study, the subject's question is satisfactorily answered, and sufficient time is given for consideration and the written consent of the subject or his legal representative is obtained. All signed informed consent must be in the investigator's document or in the subject's folder.

The investigator is responsible for interpreting the informed consent of the subject and

obtaining informed and dated informed consent from the subject or his or her legal representative prior to the start of the study. After signing, the investigator should send the subject a copy of the signed informed consent form. The investigator is required to document the process of informed consent in the original test document.

10.4 Subject Data Protection

ICF will contain (or in some cases, together with separate files) information about data protection and privacy protection.

Take precautions to ensure the confidentiality of the documents and prevent the identification of the subject. However, under special circumstances, some people may see the genetic data and personal identification number of a subject. For example, in the event of a medical emergency, the sponsor, his representative doctor, or the researcher knows the subject identification code and has access to the subject's genetic data. In addition, relevant regulatory agencies require access to relevant documents.

11 Research Management

11.1 Data Processing and Record Saving

The documents in the clinical trial (plan and program revision, completed eCRF, signed ICF, etc.) are to be preserved and managed as required by the GCP. The research center should keep these documents for 5 years after the end of the study.

Study documents should be reasonably preserved for future visits or data traceability. Security and environmental risks should be considered when saving files.

No research documents may be destroyed without the written permission of the sponsor and the researcher. The investigator/research center may transfer the research documents to other parties who comply with the document retention requirements or transfer to other locations that meet the requirements only after notifying the sponsor and obtaining their written consent.

11.2 Raw Data / File Access Rights

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

11.3 Program revision

Any possible revisions to the program during the course of the study will be

communicated and agreed by the sponsor and the investigator. The sponsor should ensure that the program revision is submitted to the regulatory body in a timely manner.

All revisions to the programme should be maintained as a supplement to the programme. Any changes to the program must be submitted to the Ethics Committee for approval or filing in accordance with the ethics committee's rules. If necessary, it should also be submitted to the regulatory authority for approval and approved by the EC and regulatory authorities (if required) (except for changes to the program to eliminate direct hazards to the test subjects).

11.4 Researcher Responsibilities

The researcher will follow the program, the ethical principles of the Helsinki Declaration, the Chinese GCP and the corresponding regulatory requirements for this study.

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

11.5 Publication Policy

All data generated in this study are confidential information of the sponsor. The sponsor has the right to publish the research results. Information about sponsor and researcher publication policies will be described in the clinical trial protocol.

All information about this trial (not limited to the following documents: program, researcher's manual) must be kept strictly confidential. Researchers must recognize that the scientific or medical information derived from this trial may be of commercial value to the sponsor. The researcher should keep the information and data related to this test confidential. If you want to publicly publish the information related to this test or the conclusions obtained from the test, you must consult with the sponsor in advance and obtain the written consent of the sponsor. In order to protect their rights and interests, the sponsor may require the researcher not to publish information about the trial before the trial product is approved for marketing.

The sponsor has the right to publish or publish information or data related to the trial or to report it to the drug administration. If the sponsor needs to have the name of the researcher in the publication, publication or advertising content, the researcher's consent should be obtained.

11.6 Finance and Insurance

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

12 References

1. Chen W, Zheng R, Baade PD, Zhang S, Zeng H, Bray F, et al. Cancer statistics in China, 2015. CA Cancer J Clin 2016,66:115-132.

2. Jaffe ES. WHO Classification of lymphomas: implications for clinical practice and translational research. Hematology 2008,2009:523-531.

3. <Distribution of sub-categories of lymphoma in China- Multi-Center Case Report of 10002 Cases.pdf>.

4. <Standard and Increased-Dose BEACOPP Chemotherapy Compared with COPP-ABVD for Advanced Hodgkin's Disease.pdf>.

5. NCCN guidelines. Hodgkin Lymphoma, 2016 v3.

6. Arai S, Fanale M, DeVos S, Engert A, Illidge T, Borchmann P, et al. Defining a Hodgkin lymphoma population for novel therapeutics after relapse from autologous hematopoietic cell transplant. Leuk Lymphoma 2013,54:2531-2533.

7. Schmitz N, Pfistner B, Sextro M, Sieber M, Carella AM, Haenel M, et al. Aggressive conventional chemotherapy compared with high-dose chemotherapy with autologous haemopoietic stem-cell transplantation for relapsed chemosensitive Hodgkin's disease: a randomised trial. The Lancet 2002,359:2065-2071.

8. Younes A, Gopal AK, Smith SE, Ansell SM, Rosenblatt JD, Savage KJ, et al. Results of a pivotal phase II study of brentuximab vedotin for patients with relapsed or refractory Hodgkin's lymphoma. J Clin Oncol 2012,30:2183-2189.

9. Moskowitz AJ, Hamlin PA, Jr., Perales MA, Gerecitano J, Horwitz SM, Matasar MJ, et al. Phase II study of bendamustine in relapsed and refractory Hodgkin lymphoma. J Clin Oncol 2013,31:456-460.

10. Fehniger TA, Larson S, Trinkaus K, Siegel MJ, Cashen AF, Blum KA, et al. A phase 2 multicenter study of lenalidomide in relapsed or refractory classical Hodgkin lymphoma. Blood 2011,118:5119-5125.

11. Johnston PB, Inwards DJ, Colgan JP, Laplant BR, Kabat BF, Habermann TM, et al. A Phase II trial of the oral mTOR inhibitor everolimus in relapsed Hodgkin lymphoma. Am J Hematol 2010,85:320-324.

12. Menter T, Bodmer-Haecki A, Dirnhofer S, Tzankov A. Evaluation of the diagnostic and prognostic value of PDL1 expression in Hodgkin and B-cell lymphomas. Hum Pathol 2016,54:17-24.

13. Roemer MG, Advani RH, Ligon AH, Natkunam Y, Redd RA, Homer H, et al. PD-L1 and PD-L2 Genetic Alterations Define Classical Hodgkin Lymphoma and Predict Outcome. J Clin Oncol 2016,34:2690-2697.

14. Green MR, Monti S, Rodig SJ, Juszczynski P, Currie T, O'Donnell E, et al. Integrative analysis reveals selective 9p24.1 amplification, increased PD-1 ligand

expression, and further induction via JAK2 in nodular sclerosing Hodgkin lymphoma and primary mediastinal large B-cell lymphoma. Blood 2010,116:3268-3277.

15. Green MR, Rodig S, Juszczynski P, Ouyang J, Sinha P, O'Donnell E, et al. Constitutive AP-1 activity and EBV infection induce PD-L1 in Hodgkin lymphomas and posttransplant lymphoproliferative disorders: implications for targeted therapy. Clin Cancer Res 2012,18:1611-1618.

16. Pembrolizumab for relapsed/refractory classical Hodgkin lymphoma (R/R cHL): phase 2 KEYNOTE-087 study. J Clin Oncol 34, 2016 (suppl; abstr 7555).

17. Younes A, Santoro A, Shipp M, Zinzani PL, Timmerman JM, Ansell S, et al. Nivolumab for classical Hodgkin's lymphoma after failure of both autologous stem-cell transplantation and brentuximab vedotin: a multicentre, multicohort, single-arm phase 2 trial. The Lancet Oncology 2016,17:1283-1294.

18. Pembrolizumab in Relapsed/Refractory Classical Hodgkin Lymphoma: Primary End Point Analysis of the Phase 2 Keynote-087 Study. .

19. Zou W, Chen L. Inhibitory B7-family molecules in the tumour microenvironment. Nat Rev Immunol 2008,8:467-477.

20. Chen L, Han X. Anti-PD-1/PD-L1 therapy of human cancer: past, present, and future. Journal of Clinical Investigation 2015,125:3384-3391.

21. Wolchok JD, Hoos A, O'Day S, Weber JS, Hamid O, Lebbe C, et al. Guidelines for the evaluation of immune therapy activity in solid tumors: immune-related response criteria. Clin Cancer Res 2009,15:7412-7420.