CLINICAL STUDY PROTOCOL

Study Title:	A Randomized, Open-Label, Multicenter, Parallel, and Phase III Clinical Trial Comparing the Efficacy and Safety of IBI308 to Docetaxel in the Treatment of Subjects with Advanced or Metastatic Squamous Non-Small Cell Lung Cancer Who Have Failed Platinum-Based First-Line Chemotherapies(ORIENT-3)
Protocol No.:	CIBI308C301
Version and Date:	Jan. 14, 2020/Version 3.2
Product Name:	IBI308
Study Phase:	Phase III
Sponsor:	Innovent Biologics (Suzhou) Co., Ltd. No. 168 Dongping Street, Suzhou Industrial Park, Jiangsu, China
Sponsor Contact:	Zhou Hui Vice President of Medical Science and Strategic Oncology Department Tel.: (+86) 21-31652896 hui.zhou@innoventbio.com

Sponsor's Signature Page

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Project No.: CIBI308C301

Title	Name (Regular Script)	Signature	Date
Vice President of Medical Science and Strategic Oncology Department	Zhou Hui		
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Protocol Synopsis

Protocol no.	CIBI308C301
Sponsor	Innovent Biologics (Suzhou) Co., Ltd.
Investigational drug	Sintilimab (R&D code: IBI308)
Active ingredient	Recombinant fully human anti-PD-1 monoclonal antibody
Study title	A Randomized, Open-Label, Multicenter, Parallel, and Phase III Clinical Trial Comparing the Efficacy and Safety of IBI308 to Docetaxel in the Treatment of Subjects with Advanced or Metastatic Squamous Non-Small Cell Lung Cancer Who Have Failed First-Line Platinum-Based Chemotherapies(ORIENT-3)
Phase	Phase III
Study duration	Estimated 25 months
Study objectives	**Primary objective:** (1) To evaluate the overall survival (OS) of subjects with advanced/metastatic squamous non-small cell lung cancer (sqNSCLC) who have failed first-line platinum-based chemotherapy treated with IBI308 versus docetaxel. **Secondary objectives:** (1) To evaluate the objective response rate (ORR), disease control rate (DCR), duration of response (DoR), and progression free survival (PFS) of subjects with advanced/metastatic sqNSCLC who have failed first-line platinum-based chemotherapy treated with IBI308 versus docetaxel; (2) To evaluate the safety in subjects with advanced/metastatic sqNSCLC who have failed first-line platinum-based chemotherapy treated with IBI308 versus docetaxel; (3) To evaluate the influence on the quality of life in subjects with advanced/metastatic sqNSCLC who have failed first-line platinum-based chemotherapy treated with IBI308 versus docetaxel. **Exploratory objectives:** (1) To evaluate causalities of PD-L1 expression, immunity-related gene mRNA, and tumor mutation burden (TMB) with efficacy in subjects with advanced/metastatic sqNSCLC; (2) To evaluate causality of dynamic PD-L1 expression on circulating tumor cell (CTC) surface with efficacy in the IBI308 group; (3) To explore the application of Immune Response Evaluation Criteria in Solid Tumors (iRECIST) in the evaluations of PFS, ORR, DCR, and DoR of the IBI308 group.

Study design	This is a randomized, open-label, multicenter, parallel, and phase III clinical trial comparing the efficacy and safety of IBI308 to docetaxel in the treatment of subjects with advanced or metastatic sqNSCLC who have failed platinum-based first-line chemotherapies(ORIENT-3). This trial intends to enroll 290 subjects with advanced or metastatic sqNSCLC who have failed first-line platinum-based chemotherapies. The central randomization is adopted in this trial and the subjects will be stratified according to ECOG PS (0 or 1). After the subjects with advanced or metastatic sqNSCLC who have failed prior first-line platinum-based chemotherapies sign the informed consent form (ICF) and are screened based on the inclusion/exclusion criteria, the eligible subjectswill be randomized (1:1) to receive IBI308 (200 mg, IV, Q3W) or docetaxel (75 mg/m^2 IV, Q3W) until progressive disease (PD), death, intolerable toxicity, withdrawal of ICF, initiation of a new anti-tumor therapy, or treatment discontinuation due to any other reason specified in the protocol. This study will adopt RECIST v1.1 to carry out clinical tumor imaging evaluation. The tumor imaging evaluation, based on clinical situations of the subjects,will be conducted once every 6 weeks (± 7 days) ; or once every 9 weeks (±7 days) after 24 weeks of administration until PD, initiation of a new anti-tumor therapy, withdrawal of ICF by the subjects, or death. For IBI308 treatment arm, subjects who develop PD for the first time and are clinically stable, can continue treatment with IBI308 based on the investigator's judgment (see details in Section 5.1.2). Subjects who discontinue the treatment due to causes other than PD still need to receive imaging evaluation as stipulated in the protocol until the occurrence of next event (initiation of a new anti-tumor therapy, PD, withdrawal of ICF by the subjects, or death). After the study treatment is discontinued, 3 months of safety follow-up (30 ± 3 days and 90 ± 7 days after the last dosing) and survival follow-up (every 60 ± 7 days) will be carried out for the subjects. Primary efficacy endpoint in this study is OS, which is defined as the time from randomization to death (subjects who do not die will be censored on the date of the last known survival). An independent data monitoring committee (iDMC) is set up in this study to conduct an interim safety analysis for the trial.
Inclusion criteria	**Subjects shall meet the following inclusion criteria:** 1. Cytologically or histologically diagnosed with sqNSCLC; 2. Locally advanced, metastatic, or recurrent (i.e., ineligible for radical

	radiochemotherapy phase IIIB, IIIC, or IV) NSCLC (as per UICC/AJCC staging system, version 8), including the following four situations: 1) PD (RECIST v1.1) is observed during or after first-line platinum-based chemotherapy (including maintenance chemotherapy), and discontinuation, dose reduction, or replacement with any analogous drug for one of the medications is permitted in the first-line therapy; 2) Alternative systemic treatment regimen is required due to intolerable toxicity of first-line platinum-based chemotherapy regimen (at least one complete cycle of treatment is given); 3) Recurrent disease or metastasis is observed within 6 months after completion of platinum-based neoadjuvant/adjuvant chemotherapy (before or after radical surgery) or sequential/concurrent radical radiochemotherapy (platinum-based regimen); 4) Recurrent disease or metastasis is observed over 6 months after completion of platinum-based neoadjuvant/adjuvant chemotherapy (before or after radical surgery) or sequential/concurrent radical radiochemotherapy (platinum-based regimen), and PD is observed after or during platinum-based chemotherapy for the recurrent disease or metastasis; 3. With at least one measurable lesion (RECIST v1.1); 4. Males or females ≥ 18 and ≤ 75 years old; 5. ECOG PS score is 0 or 1; 6. Life expectancy ≥ 12 weeks; 7. Important organ and bone marrow functions meet the following requirements (excluding subjects who have received any cell therapy or growth factor therapy within 2 weeks prior to randomization): 1) Routine blood test: absolute neutrophil count (ANC) ≥ 1.5×10^9/L, platelet count (PLT) ≥ 100×10^9/L, and hemoglobin (HGB) ≥ 90 g/L (component blood transfusion shall not be carried out within 1 week prior to randomization); 2) Liver function: total bilirubin (TBIL) ≤ 1.5 × upper limit of normal (ULN), alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST) ≤ 2.5 × ULN, and serum albumin (ALB) ≥ 2.8 g/dL; 3) Renal function: serum creatinine (Cr) ≤ 1.5 × ULN, or creatinine clearance rate (CrCl) ≥ 40 mL/min (using standard Cockcroft-Gault equation): Female: $CrCl = \frac{(140 - Age) \times Weight\ (kg) \times 0.85}{72 \times Cr\ (mg/dL)}$

	Male: $CrCl = \frac{(140 - Age) \times Weight\ (kg) \times 1.00}{72 \times Cr\ (mg/dL)}$ 8. The subjects and their sex partners should take a medically accepted contraceptive measure (intrauterine device (IUD), contraceptive agent or condom, etc.) during study treatment and within 6 months after completion of study treatment; 9. Subjects who have signed written ICFs, and are able to comply with the follow-up visits and relevant procedures required in the protocol.
Exclusion criteria	**Subjects should be excluded if any of the following exclusion criteria is met:** 1. With known EGFR-sensitive mutation or ALK rearrangement; 2. Adenosquamous Carcinoma of Lung; 3. Have received anti-PD-1, anti-PD-L1, anti-CTLA-4 antibody or docetaxel therapy (not including docetaxel used in systemic treatment to cure any other malignant cancer and with potential dose-accumulating toxicity being eliminated); 4. Have received the following therapies: - Systemic anti-tumor therapy, such as chemotherapy, targeted therapy, and immunotherapy (including treatments with Chinese herbal medicine indicated for cancer), within 3 weeks prior to randomization; - Any investigational drugs within 4 weeks prior to randomization; - A high dose of immunosuppressant (systemic glucocorticoid therapy using prednisone at a dose of over 10 mg/day or the equivalent dose, excluding a single dose of prednisone over 10 mg/day or the quivalent does and glucocorticoids used as prophylactics for hypersensitivity, such as medications prior to CT) within 4 weeks prior to randomization; - Live attenuated vaccine within 4 weeks prior to randomization (or live attenuated vaccine that is planned during the study); - Major surgery (e.g., open cavity, open chest, or open abdomen operation), or current non-healing surgical wounds, ulcers, or fractures, within 4 weeks prior to randomization. 5. Have received any prior anti-tumor therapy and developed adverse reaction, which has not recovered to CTCAE grade ≤ 1 yet (not including hair loss or laboratory tests of no clinical significance); 6. With active autoimmune disease (inherited or acquired), such as interstitial pneumonia, uveitis, enteritis, hepatitis, hypophysitis, vasculitis, nephritis, and

	thyroiditis (subjects with vitiligo or childhood asthma that has completely resolved and does not require any intervention after adulthood can be enrolled; subjects with hypothyroidism necessitating hormone replacement therapy only or type I diabete subjects with well-controlled insulin level can also be enrolled); 7. With known history of allotransplantation (except corneal transplantation) or allogeneic hematopoietic stem cell transplantation; 8. Allergic to monoclonal antibodies or any ingredient of docetaxel preparations; 9. Received chest radiotherapy over 30 Gy within 6 months prior to randomization or palliative radiotherapy at a dose of ≤ 30 Gy within 7 days prior to randomization (palliative radiotherapy for osteopathy or intracranial lesions is accepted); 10. Symptomatic central nervous metastasis and/or carcinomatous meningitis. Subjects with asymptomatic brain metastases or with stable symptoms after treatment of brain metastases are allowed to participate in this study as long as meeting all the following criteria: presence of measurable lesions outside the central nervous system (CNS); absence of metastases in midbrain, pons, cerebellum, medulla oblongata, or spinal cord; no history of intracranial hemorrhage; and no glucocorticoid therapy is currently required; 11. Afflicted with interstitial lung disease; 12. With superior vena cava syndrome that is contraindicated for infusion; 13. Clinically uncontrollable third space effusion, such as pleural effusion or ascites that cannot be controlled by drainage or other methods prior to enrollment; 14. Afflicted with other uncontrolled severe diseases, including but not limited to: − Active or poorly controlled severe infections; − HIV infected subjects (with positive anti-HIV antibody); − Afflicted with acute or chronic active hepatitis B (HBV DNA > 1×10^3 copies/mL or > 200 IU/mL), or acute or chronic active hepatitis C (with positive HCV antibody); − With active pulmonary tuberculosis, etc.; − With class III–IV congestive heart failure (based on New York Heart Association Classification) or poorly controlled and clinically significant arrhythmia; − Uncontrolled arterial hypertension (systolic blood pressure ≥ 160 mmHg or diastolic blood pressure ≥ 100 mmHg); − With any arterial thrombosis, embolism, or ischemia within 6 months prior to enrollment, such as myocardial infarction, unstable angina, cerebrovascular

	accident, or transient cerebral ischemic attack, etc.; – Tumor compresses peripheral important organs (such as esophagus) with associated symptoms; – Uncontrolled hypercalcemia, or symptomatic hypercalcemia requiring further bisphosphonate therapy; – With other concurrent malignant cancers (except cured cancers, such as cervical carcinoma in situ and non-melanoma skin cancer). 15. Acute or chronic diseases, psychiatric disorders, or laboratory abnormalities that may lead to the following consequences: increased study drug-related risks, or interference with interpreting study results, and considered ineligible for participating in the study by the investigators; 16. Pregnant or lactatingfemale subjects.
Study drug, strength, and administration	• **IBI308** – Specification: 10 mL:100 mg – Administration: 200 mg, intravenous infusion (IV), Q3W, until PD, death, intolerable toxicity, withdrawal of consent, initiation of a new anti-tumor therapy, or treatment discontinuation due to any other protocol-specified reasons. • **Docetaxel** – Specifications: 20 mg/0.5 mL, 40 mg/1 mL, or 80 mg/2 mL – Administration: 75 mg/m^2, IV, Q3W, until PD, death, intolerable toxicity, withdrawal of consent, initiation of a new anti-tumor therapy, or treatment discontinuation due to any other protocol-specified reasons.
Evaluation criteria	**Efficacy evaluation:** • To evaluate OS, PFS, ORR, DCR, and DoR after administration. **Safety evaluation:** • Incidence and severity of all adverse events (AEs), adverse events of special interest (AESIs), serious adverse events (SAEs), and treatment-related adverse enevts (TRAEs). • To evaluate changes in vital signs, physical examination, and laboratory tests results before, during, and after the study treatment. **Immunogenicity evaluation (for IBI308 treatment group only):** • Anti-drug antibody (ADA) and neutralizing antibody (NAb). **Biomarker evaluation:** • Tumor tissue samples will be collected for tumor biomarker analyses, including

	PD-L1 expression and immune-related gene expression (e.g., expression levels of mRNAs of IDO1, CXCL9, CXCL10, HLA-DRA, STAT1, IFNG, etc.); • Blood samples of IBI308 treatment group will be collected for biomarker study, including but not limited to dynamic change analysis for PD-L1. **Quality of life:** • The quality of life and health status in IBI308 group and chemotherapy group during treatment will be evaluated based on EQ 5D-5L, EORTC QLQ-C30, and EORTC QLQ-LC13 scores.
Statistical methods	**Sample size estimation:** The primary efficacy endpoint is overall survival (OS). Assuming that $\alpha = 0.05$ (two-sided), power = 90%, IBI308-to-docetaxel survival hazard ratio HR = 0.63, endpoint events (death) are observed in 75% of the subjects, group assignment ratio is 1:1, the minimum estimated sample size is 266 cases; considering a certain dropout rate, a total of 290 cases are necessary for randomization, 145 cases in IBI308 group and 145 cases in the chemotherapy group. **Superiority hypothesis test:** This study adopts a superiority design and the primary efficacy endpoint is OS. Superiority hypothesis test: H0: HR $\geq$ 1, H1: HR < 1 Type I error rate (α) = 0.05 When the P $\leq \alpha$ (or the upper limit of confidence interval (CI) of HR < 1) is obtained via between-group comparison of OS of IBI308 and docetaxel based on the stratified Log-rank test, IBI308 can be considered superior to chemotherapy and is able to prolong the OS of the subject. **Interim analysis:** One interim analysis is designed in this study. The objective of the analysis is to evaluate the safety, and the analysis indicators are the safety indicators. At the time point of 50, the subjects completed 4 treatment cycles (every 3 weeks for one cycle) without considering the adjustment of α. **Primary efficacy endpoint:** The primary efficacy endpoint is OS. Kaplan-Meier method will be used to estimate median survival and its CI, 6-month, 9-month, and 12-month survival rates, and to plot survival curve; between-group comparison will be performed using stratified Log-Rank test; and stratified Cox proportional hazards model will be used to estimate HR and its CI.

	Secondary efficacy endpoints: Survival data: The analyses of PFS and DoR are the same as that of OS. The analyses of ORR and DCR will adopt Fisher's exact test for between-group comparison. **Safety data:** The incidence rates and severity of AEs will be summarized on a group-by-group basis, and abnormal changes in laboratory test indicators, vital signs, and physical examination will be described. **Immunogenicity data (for IBI308 treatment group only):** Data of ADA- and NAb-positive rates will be summarized. **Quality-of-life indicators:** The quality of life and health status in IBI308 group and chemotherapy group during treatment will be evaluated based on EQ 5D-5L, EORTC QLQ-C30, and EORTC QLQ-LC13 scores. **Biomarker:** Descriptive statistics for PD-L1 expression levels and distribution as well as immune-related gene expression results and distribution will be performed, and the potential correlation between the above indicators and efficacy will be explored.

Table 1. Schedule of study visits

Stage	Screening period	Treatment period				Safety follow-up[19]		Survival follow-up[20]
		Cycle 1	Cycle 2	Cycle 3	Cycle 4 and beyond			
Visit	1	2	3	4	5-N			
Day	Day -28 to -1	1	Day 22 (± 3 days)	Day 43 (± 3 days)	Every 3 weeks (± 3 days)	After the last dose Day 30 (± 3 days)	After the last dose Day 90 (± 7 days)	Every 60 days (± 7 days)
Standard study procedures								
Written ICF[1]	X							
Inclusion/exclusion criteria	X							
Demographics/medical history/previous medications[2]	X							
Vital signs[3]	X	X	X	X	X	X	X	
Weight/height[4]	X	X	X	X	X	X		
Physical examination	X		X	X	X	X	X	
ECOG PS score	X	X	X	X	X	X	X	
12-lead ECG[5]	X		X		X	X	X	
Routine blood test/Blood biochemistry/Routine urine test[6]	X		X	X	X	X	X	
Pregnancy test[7]	X					X		
Thyroid function[8]	X		X	X	X	X		
Immunogenicity (for IBI308 group only)[9]		X	X		X		X	
HIV, HBV, and HCV[10]	X							
AE evaluation[11]	X	X	X	X	X	X	X	

Stage	**Screening period**	**Treatment period**				**Safety follow-up[19]**		**Survival follow-up[20]**
		Cycle 1	**Cycle 2**	**Cycle 3**	**Cycle 4 and beyond**			
Visit	**1**	**2**	**3**	**4**	**5-N**			
Day	**Day -28 to -1**	**1**	**Day 22 (± 3 days)**	**Day 43 (± 3 days)**	**Every 3 weeks (± 3 days)**	**After the last dose Day 30 (± 3 days)**	**After the last dose Day 90 (± 7 days)**	**Every 60 days (± 7 days)**
Concomitant medications	X	X	X	X	X	X	X	
Survival condition		←	—	—	—	—	—	→
Subsequent anti-tumor therapy						X	X	X
Efficacy evaluation								
Tumor imaging evaluation[12]	X			X	X			
Randomization								
RAVE Balance central randomization[13]	X							
Study drug infusion								
IBI308 group: IBI308[14]		X	X	X	X			
Chemotherapy group: docetaxel[15]		X	X	X	X			
Quality of life evaluation[16]								
EQ 5D-5L, EORTC QLQ-C30, and QLQ-LC13 scales		X		X	X	X		
Biomarker study								
Collection of archived or fresh tumor tissue samples[17]	X							
Blood samples[18]		X		X	X			

Notes:

1. The ICF should be signed by subjects prior to any protocol-specified procedures.
2. Previous medications include treatment for the initial diagnosis, including chemotherapy, radiotherapy, and surgery.
3. Vital signs include body temperature, pulse, respiratory rate, and blood pressure.
4. Height will be measured during screening period only. Weight needs to be recorded before every planned dose during the study. If the weight fluctuation of a subject in docetaxel group is less than 10% compared to baseline (the day of the first dose), then the baseline weight will be used to calculate the dose. Otherwise, the actual dose will be calculated based on the weight of scheduled dosing days.
5. Schedule of 12-lead ECG test: during screening, prior to study medication (except cycle 1) every 2 cycles, and at the safety visits.
6. Routine blood tests include: red blood cell (RBC), Hemoglobin (HGB), white blood cell (WBC), Platelet (PLT), white blood cell (WBC) differentials [lymphocyte (LYM) and absolute neutrophil count (ANC)]. Blood biochemistry tests include: liver function [TBIL, ALT, AST, γ-glutamyltransferase (γ-GT), alkaline phosphatase (ALP), albumin (ALB), total protein (TP), and lactate dehydrogenase (LDH)], renal function [blood urea (UREA) or urea nitrogen (BUN) , Cr], blood electrolytes (Na, K, Cl, Mg, Ca, and P), amylase, and fasting blood glucose (FBG). Routine urine tests include pH, urine albumin (UALB), urine protein (UPRO), urine red blood cells (URBC), and urine glucose (UGLU). Routine blood test, blood biochemistry, and Routine urine tests will be carried out within 7 days prior to the first dose during screening, and then within 3 days prior to each dose as well as at safety follow-up visits. Tests will be conducted at each study site.
7. For female subjects of childbearing potential urine or serum pregnancy test will be performed within 3 days before the first dose and at the first safety follow-up visit. If the urine pregnancy test is not conclusive, then blood pregnancy test should be performed. The conclusion should be based on the blood pregnancy test. Tests will be conducted at each study site.
8. T3, T4, FT3, FT4, and TSH will be examined during screening; starting from cycle 2, thyroid function of IBI308 group must be examined within 3 days prior to dosing of study drug during each cycle and at the first safety follow-up visit. Tests will be conducted at each study site.
9. Immunogenicity assays will be performed in IBI308 treatment group within 1 h prior to IBI308 infusion in cycles 1, 2, 4, and every 4 cycles (cycles 8, 12, 16, and so on) thereafter, and at the second safety follow-up visit. Tests will be conducted in the central laboratory.
10. During screening, HIV antibody, Hepatitis B panel (HBsAg, HBsAb, HBcAb, HBeAg, and HBeAb), HBV DNA, and HCV antibody will be tested. HBV carriers are recommended to be monitored for virus activity regularly during the study. Tests will be conducted at each study site.
11. Safety evaluation of AEs and laboratory tests will be conducted based on NCI CTCAE v 4.03 (for the definitions, recording, causality determination, severity judgment, reporting time limit, and processing of AEs and SAEs, please refer to the protocol).

12. Tumor evaluation is based on RECIST v1.1 and iRECIST and conducted by the investigator, including the evaluation sites of neck, chest, abdomen, and pelvic cavity. According to the criteria in the RECIST v1.1, evaluations should be conducted at baseline (within 28 days prior to the first dose) and every 6 weeks (± 7 days), and then every 9 weeks (± 7 days) from 24 weeks after administration until PD, initiation of a new anti-tumor therapy, withdrawal of consent by the subjects, or death. Subjects in the IBI308 treatment group experiencing the first PD could continue the treatment with IBI308 based on the judgment of the investigator if they are clinically stable (see protocol for details). Subjects who discontinue the treatment due to causes other than PD still need to receive imaging evaluation as stipulated in the protocol after discontinuation until the occurrence of next event (initiation of a new anti-tumor therapy, PD, withdrawal of consentby the subjects, or death).
13. During screening, eligible subjects will be randomized at a ratio of 1:1 into IBI308 group or chemotherapy group. The stratification factor is ECOG score (0 or 1).
14. IBI308 200 mg, Q3W, until PD, death, intolerable toxicity, withdrawal of consent, initiation of a new anti-tumor therapy, or treatment discontinuation due to any other reason specified in the protocol. The administration on day 1 during cycle 1 must be completed within 3 working days after randomization.
15. Docetaxel 75 mg/m^2, Q3W, until PD, death, intolerable toxicity, withdrawal of consent, initiation of a new anti-tumor therapy, or treatment discontinuation due to any other reason specified in the protocol. The administration on day 1 during cycle 1 must be completed within 3 working days after randomization.
16. EQ 5D-5L, EORTC QLQ-C30, and EORTC QLQ-LC13 scales are adopted for evaluation of quality of life, and the evaluation will be conducted on the day of the first dose, at each imaging evaluation, and at the first safety follow-up visit.
17. During screening, subjects are required to provide qualified tumor tissue samples (previous or fresh) for PD-L1 and immune-related gene mRNA tests.
18. Subjects in the IBI308 group need to provide 10 mL of whole blood sample at each of the following time points: prior to the first dose, and at each efficacy evaluation during treatment before the initiation of the next treatment; the samples will be analyzed for tumor mutation burden (TMB) and circulating tumor cells (CTC), including but not limited to dynamic change of PD-L1.
19. The safety follow-up will be carried out at 30 (± 3) days and 90 (± 7) days after the last dose.
20. Survival follow-up will be carried out once every 60 (± 7) days. Telephone follow-up is allowed.

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List of Abbreviations and Definitions

Abbreviation	Definition
ADA	Anti drug antibody
AE	Adverse Event
AESI	Adverse Event of Special Interest
ALB	Albumin
ALK	Anaplastic lymphoma kinase
ALP	Alkaline phosphatase
ALT	Alanine transaminase
ANC	Absolute Neutrophil Count
AST	Aspartate amino transferase
CI	Confidence Interval
C_{max}	Maximum serum concentration of drug
Cr	Creatinine
CR	Complete Remission
CRA	Clinical Research Associate
CRO	Contract research organization
CSR	Clinical Study Report
CT	Computed tomography
CTC	Circulating tumor cell
CTCAE	Common Terminology Criteria for Adverse Events
DCR	Disease control rate
DLT	Dose-limiting toxicity
DoR	Duration of response
EC	Ethics Committee
ECG	Electrocardiogram
ECOG PS	Eastern Cooperative Oncology Group Performance Status
eCRF	Electrical Case Report Form
EGFR	Epidermal Growth Factor Receptor
EORTC QLQ-C30	European organization for research and Treatment of cancer quality of life questionnaire C30
EORTC QLQ-LC13	European organization for research and treatment of cancer quality of life questionnaire LC13
FAS	Full Analysis Set
FBG	Fasting Blood Glucos
FDA	Food and Drug Administration
FDG-PET	Fludeoxyglucose-Positron Emission-computed Tomography

Abbreviation	Definition
FT3	Free Triiodothyronine
FT4	Free Thyroxine
GCP	Good Clinical Practice
HBV	Hepatitis B virus
HCT	Hematocrit
HCV	Hepatitis C virus
HGB	Hemoglobin
HR	Hazard ratio
HIV	Human Immunodeficiency Virus
ICF	Informed Consent Form
iCPD	Immune confirmed progressive disease
ID	identity
IHC	immunohistochemistry
IDMC	independent data monitoring committee
IgG	Immunoglobulin G
irAE	Immune-related Adverse Event
IRR	Infusion related reactions
iRECIST	Immune Response Evaluation Criteria in Solid Tumours
iUPD	Immune unconfirmed progressive disease
IV	intravenous infusion
LDH	lactate dehydrogenase
LYM	lymphocyte
mRNA	Messenger RNA
MRI	Magnetic Resonance Imaging
NAb	Neutralizing Antibody
NCI	National Cancer Institute
NE	Not evaluatable
NMPA	National Medical Products Administration
NSCLC	non-small cell lung cancer
ORR	Objective Response Rate
OS	Overall Survival
PD	Progressive disease
PD-1	Programmed Cell Death 1
PD-L1	Programmed Cell Death Ligand 1
PFS	Progression Free Survival
PK	Pharmacokinetic

Abbreviation	Definition
PLT	Platelet
PR	Partial Remission
RBC	Red Blood Cell
RECIST	Response Evaluation Criteria in Solid Tumors
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SD	Stable Disease
sqNSCLC	Squamous non-small cell lung cancer
SS	Safety Set
$t_{½}$	half-life period
T3	triiodothyronine
T4	thyroxin
TBIL	Total Bilirubin
TEAE	Treatment Emergent Adverse Event
TMB	Tumor mutation burden
TP	Total Protein
TRAE	Treatment Related Adverse Event
TSH	Thyroid Stimulating Hormone
UALB	urinary albumin
UGLU	urinary glucose
ULN	Upper limits of normal
UPRO	urine protein
UREA	Urea
URBC	Urinary Red Blood Cells
WBC	White Blood Cells
γ-GT	γ-glutamyltransferase

1 Background

1.1 Disease Background

With prolonged mean life expectancy and changing lifestyle of human beings, malignant tumors have become a major life-threatening disease and pose serious threat to the health of Chinese people. In particular, lung cancer tops malignant tumors in terms of incidence rate and mortality due to large smoker population. Statistical data in 2015 show that 733,000 people developed lung cancer and 600,000 people died of lung cancer in China, and both the incidence rate and the mortality are top of the world[1]. Advanced squamous non-small cell lung cancer (sqNSCLC) is lack of effective therapies. The first-line standard therapy is platinum-based chemotherapy, and the second-line therapy is still docetaxel-based chemotherapy[2], which is limited in therapeutic effect and shows a median survival of about 6 months[2], indicating the presence of extremely unfulfilled medical demand. Recent years, there have seen rapid advancements in studies on inhibiting immune checkpoint to activate human autoimmune system which thereby exerts attack to tumor cells. Immune checkpoint inhibitors (PD-1/PD-L1 inhibitor) provide a new clinical therapy for non-small cell lung cancer (NSCLC), including sqNSCLC .

In Jan. 2015, a phase III clinical trial of Opdivo® (nivolumab), a PD-1 inhibitor from Bristol-Myers Squibb (BMS), in the treatment of sqNSCLC was prematurely terminated[2]. In this head-to-head study comparing nivolumab versus docetaxel in the second-line treatment, iDMC assessed that nivolumab treatment group had a OS obviously superior to that in docetaxel control group (median OS: 9.2 vs. 6.0 months; HR: 0.59, 95%CI: 0.44–0.79; $p < 0.001$), a longer PFS (median: 3.5 vs. 2.8 months; HR: 0.62, 95%CI: 0.47–0.81; $p < 0.001$), and a higher ORR (20% vs. 9%; $p = 0.008$)[2]. In Mar. 2015, FDA approved the use of nivolumab in subjects with advanced sqNSCLC who failed first-line therapy.

Based on the results of Keynote-010 study, PD-1 inhibitor Keytruda® (pembrolizumab) from Merck Sharp & Dohme (MSD) was also approved by FDA in 2015 for the use in the second-line treatment of PD-L1-positive NSCLC. In Keynote-010, a total of 1034 subjects were enrolled and randomized at a ratio of 1:1:1 to receive 2 mg/kg pembrolizumab, 10 mg/kg pembrolizumab, and 75 mg/m^2 docetaxel, respectively; the study showed that the median OS were 10.4, 12.7, and 8.5 months, respectively, indicating significantly improved OS in two pembrolizumab treatment groups versus docetaxel group[3].

Based on the results of POPLAR study and OAK study, Roche's PD-L1 antibody Tecentriq® (atezolizumab) was approved by FDA in 2016 for the use in second-line treatment of NSCLC. Both studies are randomized controlled studies of atezolizumab versus docetaxel in second- or over treatment of NSCLC, and the studies showed the median OS of 12.6 vs. 9.7 months[4] and 13.8 vs. 9.6 months[5], respectively.

Previous studies on causality of PD-L1 expression with prognosis of NSCLC showed inconsistence, which might be related to histological type and IHC PD-L1 antibody used. In the phase III study of nivolumab in second-line treatment of squamous non-small cell lung cancer (sqNSCLC), IHC staining was performed with 28-8 antibody and PD-L1 of each predetermined levels (1%, 5%, and 10%) showed neither prognostic effect nor predictive effect for any efficacy endpoint (OS, PFS, or ORR)[2]. Meanwhile, a retrospective study using 22C3 antibody also indicated that PD-L1 expression had no correlation with NSCLC prognosis[6].

1.2 Study Drug (IBI308)

1.2.1 Mechanism of action

Immune checkpoints can regulate or equilibrate intensity and extensiveness of immune response through mechanism of action of immunosuppression so as to prevent the body's normal cells or tissues from being damaged. However, tumor cells may escape from body immunosurveillance and avoid being eliminated utilizing the characteristics of immune checkpoints. Currently, multiple immune checkpoints have been found, among which CTLA-4 and PD-1/PD-L1 inhibitors have been applicable to clinical practice. Immune checkpoint inhibitors of PD-1/PD-L1 have good safety as well as a wide range of indications, and thus are considered having broad prospects for clinical application.

PD-1 is primarily expressed on the surfaces of activated T cells and has two ligands: PD-L1 and PD-L2. PD-L1 is the main ligand that is expressed on activated T cells, antigen-presenting cells, and tumor cells[7]. The binding of PD-1 to PD-L1 plays an important role in regulating the activation of T cells and maintaining peripheral immune tolerance. When T cells do not express PD-1, they interact with antigen-presenting cells to enable the activation and proliferation of T cells as well as the activation of cytokine secretion, which can kill the tumor cells. The activated T cells begin to express PD-1. After PD-1 binds to the ligand PD-L1 expressed on the surface of antigen-presenting cells or tumor cells, the inhibitory signal in the downstream of PD-1 inhibits the proliferation of T cells and activates the secretion of cytokines, thus weakens the function of T cells. Most tumor cells evade the attack of immune cells through this mechanism. The activity and ability to kill cancer cells of T cells can be restored by blocking the PD-1/PD-L1 interaction with drugs[8].

As of the end of 2017, 5 anti-PD-1/PD-L1 monoclonal antibodies had been approved by regulatory authorities including FDA for marketing, and they are: nivolumab (trade name: OPDIVO®, from BMS), pembrolizumab (trade name: KEYTRUDA®, from MSD), atezolizumab (trade name: TECENTRIQ®, from Roche), avelumab (trade name: BAVENCIO®, from Merck Serono & Pfizer), and duralumab (trade name: IMFINZI®, from Astra Zeneca). The indications include multiple tumors such as advanced melanoma, advanced NSCLC, advanced classical

Hodgkin's lymphoma, advanced renal cell carcinoma, advanced urothelial carcinoma, advanced head and neck cancer, colorectal cancer, gastric cancer, and liver cancer. In addition, many indications have been in phase III clinical studies or have been submitted for approval. The approval of these drugs confirms the important role of PD-1/PD-L1 immune checkpoint inhibitors in cancer immunotherapy. China has no PD-1/PD-L1 immune checkpoint inhibitor being marketed to date. It is of very important significance to encourage the development of such inhibitors and thereby to provide better alternative treatment for subjects with advanced lung cancer in China.

Recombinant fully human anti-PD-1 monoclonal antibody injection (R&D code: IBI308) is a recombinant fully human IgG4 monoclonal antibody. Multiple nonclinical *in vitro* tests have validated the effect of IBI308 in blocking PD-1 pathway, and multiple immune-functioning mouse tumor models also indicated the anti-tumor activity of IBI308 murine analogs (the study results are detailed in the Investigator's Brochure for details of the study results). The nonclinical study results indicated the development prospect of IBI308 in blocking the PD-1.

1.2.2 Clinical study results

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

PK evaluations on 1 mg/kg IBI308 were conducted in subjects (n = 3) with various tumors, among which preliminary results of a single dose showed that: The maximum body exposure during a single dosing was achieved right after the end of the infusion of 1 mg/kg IBI308; the drug rapidly completed distribution and proceeded with slow elimination ($t_{1/2}$ was about 17.3 d) after peaking, indicating classical PK two-compartment characteristics of monoclonal antibodies and elimination $t_{1/2}$ which was similar to the physiological $t_{1/2}$ of IgG4.

The preliminary results of pharmacodynamics (PD) study showed that: IBI308 at a dose of 1 mg/kg could rapidly (24 h) saturate the occupancy of peripheral PD-1 (95.8 ± 2.3%) and maintained the PD-1 occupancy with decreasing concentrations throughout the study (28 d, C28d: 3.70 ± 0.15 μg/mL). Steady state was expected to be achieved after continual dosing of 1

mg/kg IBI308 for 84 days (Q2W, 6 doses). On the premise of no significant variation in drug clearance profile in the subject, the expected steady-state trough concentration was around 13 μg/mL and the peripheral PD-1 receptor occupancy could be continuously maintained.

As of Oct. 30, 2017, neither DLT nor unexpected AE had been observed in the completed phase Ia study. A total of 267 tumor subjects received IBI308 therapy, and the overall safety profile was similar to those of anti-PD-1 monoclonal antibodies approved overseas.

1.3 Risk/Benefit Assessment

Considering the mechanism of action of IBI308 and the clinical safety information of products with similar mechanisms, the main AEs during this clinical trial will possibly be the immune-mediated inflammation resulted from the activation of immune system, e.g. pneumonia, colitis, hepatitis, renal insufficiency, and endocrine system inflammation. According to the available clinical data, anti-PD-1 monoclonal antibodies are well-tolerated despite of high incidence of adverse reactions. Treatment discontinuation due to adverse reactions only occur in a small number of subjects, and most events resolve after appropriate interventions. Early symptoms of immune related adverse events (irAEs) vary. Therefore, investigators must closely monitor early signs and symptoms of irAEs during the trial, make correct judgments timely, adjust the dose according to Section 5.4.1 in the protocol, and provide effective treatment measures to reduce risks to subjects. Besides, subjects with autoimmune diseases shall be excluded from the trial to avoid exacerbation of the original disease due to the activation of immune system.

Pharmacological and safety data of the phase Ia clinical trial of IBI308 indicate that IBI308 has definite pharmacological activity and good tolerability in subjects with advanced tumor.

The above data preliminarily demonstrate good safety and pharmacological activity of IBI308 as well as its significant anti-tumor activity in subjects with advanced sqNSCLC, and support clinical trials of IBI308 in Chinese subjects with advanced sqNSCLC.

2 Study Objective

2.1 Primary Objective

(1) To evaluate OS in subjects with advanced or metastatic sqNSCLC who have failed first-line platinum-based chemotherapy treated with IBI308 versus docetaxel.

2.2 Secondary Objectives

(1) To evaluate the objective response rate (ORR), disease control rate (DCR), duration of response (DoR), and progression free survival (PFS) of subjects with advanced/metastatic sqNSCLC who have failed first-line platinum-based chemotherapy treated with IBI308 versus docetaxel;

(2) To evaluate the safety in subjects with advanced/metastatic sqNSCLC who have failed first-line platinum-based chemotherapy treated with IBI308 versus docetaxel;

(3) To evaluate the influence on the quality of life in subjects with advanced/metastatic sqNSCLC who have failed first-line platinum-based chemotherapy treated with IBI308 versus docetaxel.

2.3 Exploratory Objectives

(1) To evaluate causalities of PD-L1 expression, immunity-related gene mRNA, and tumor mutation burden (TMB) with efficacy in subjects with advanced/metastatic sqNSCLC;

(2) To evaluate causality of dynamic PD-L1 expression on circulating tumor cell (CTC) surface with efficacy in the IBI308 group;

(3) To explore the application of Immune Response Evaluation Criteria in Solid Tumors (iRECIST) in the evaluations of PFS, ORR, DCR, and DoR of the IBI308 group.

3 Overall Study Design

3.1 Overall Design

This is a randomized, open-label, multicenter, parallel and phase III clinical trial comparing the efficacy and safety of IBI308 and docetaxel in the treatment of subjects with advanced or metastatic sqNSCLC who have failed first-line platinum-based chemotherapies (ORIENT-3) . This trial intends to enroll 290 subjects with advanced or metastatic sqNSCLC who have failed first-line platinum-based chemotherapies. The central randomization is adopted in this trial and the subjects will be stratified according to ECOG PS (0 or 1).

After the subjects with advanced or metastatic sqNSCLC who have failed prior first-line platinum-based chemotherapies sign the informed consent form (ICF) and are screened based on the inclusion/exclusion criteria, the eligible subjects will be randomized (1:1) to receive IBI308 (200 mg, IV, Q3W) or docetaxel (75 mg/m^2 IV, Q3W) until progressive disease (PD), death, intolerable toxicity, withdrawal of consent, initiation of a new anti-tumor therapy, or treatment discontinuation due to any other reason specified in the protocol.

This study will adopt RECIST v1.1 to carry out clinical tumor imaging evaluation. The tumor imaging evaluation will be conducted once every 6 weeks (± 7 days) depending on clinical situations of the subjects; and then once every 9 weeks (±7 days) after 24 weeks of administration until PD, initiation of a new anti-tumor therapy, withdrawal of consent by the subjects, or death. Subjects in the IBI308 treatment group experiencing the first PD could continue the treatment with IBI308 based on the judgment of the investigator if they are clinically stable (see Section 5.1.2 in the protocol for details). Subjects who discontinue the treatment due to causes other than PD still need to receive imaging evaluation as stipulated in the

protocol after discontinuation until the occurrence of next event (initiation of a new anti-tumor therapy, PD, withdrawal of consent by the subjects, or death).

After the study treatment is discontinued, 3 months of safety follow-up (30 ± 3 days and 90 ± 7 days after the last dosing) and survival follow-up (every 60 ± 7 days) will be carried out for the subjects.

Primary efficacy endpoint in this study is OS, which is defined as the time from randomization to death (subjects who do not die will be censored on the date of the latest known survival).

An independent data monitoring committee (IDMC) is set up in this study to conduct an interim safety analysis for the trial.

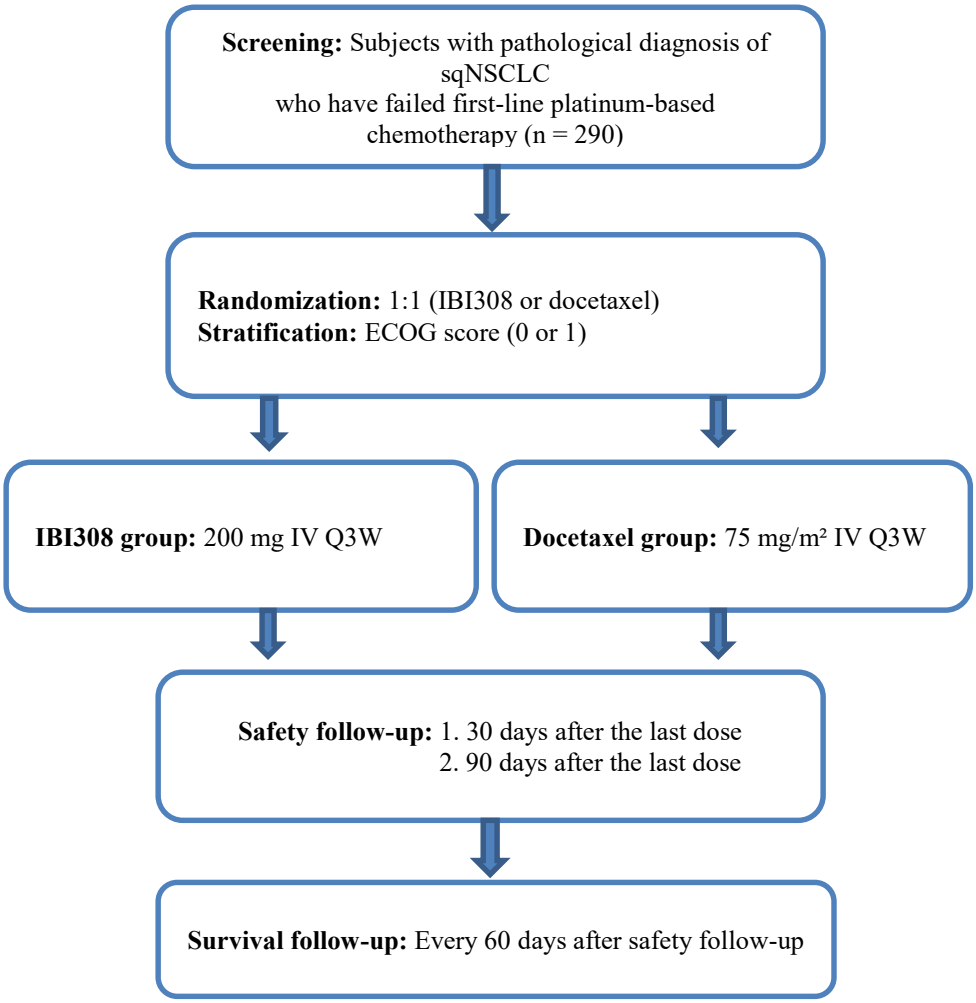

Figure 1. Schematic of CIBI308C301 study design and dosage regimen

3.2 Design Principles

3.2.1 Justification for open-label study design

Considering that the response of the subject to the drugs may vary significantly due to the different mechanism of action between IBI308 and docetaxel and thereby the effective blinding of subjects is unachievable, this trial adopts an open-label design instead of blinding.

IBI308 may cause autoimmune reactions involving corresponding tissues or organs of the body, and thus antihistamine and/or immunosuppressant (e.g., glucocorticoids) therapies are usually required.

Docetaxel may cause various allergic reactions (e.g., skin rash), fluid retention, and potential serious impairment of bone marrow, nervous system, liver, and kidneys. In addition, concurrent use of CYP3A4 inhibitors would increase exposure of docetaxel, and thereby the reduction of the dose of docetaxel is required when the inhibitors are used concurrently to avoid serious toxic side effects. Potential adverse reactions to docetaxel should be handled according to related instructions and clinical practice.

3.2.2 Justification for IBI308 monotherapy and dosage regimen

Safety and efficacy of anti-PD-1/PD-L1 monotherapy in second-line NSCLC have been fully demonstrated, and anti-PD-1/PD-L1 monotherapy has been listed as second-line standard therapy by National Comprehensive Cancer Network (NCCN). IBI308 is an anti-PD-1 monoclonal antibody and anti-tumor activity of IBI308 monotherapy has been validated in multiple immune-functioning mouse models (see Investigator's Brochure). In the phase I clinical study (CIBI308A101) of IBI308, the PD results showed that IBI308 had definite blocking effect against PD-1 receptor in the body. Therefore, this study will investigate efficacy and safety of IBI308 monotherapy in second-line sqNSCLC.

This study intends to adopt administration of IBI308 at 200 mg, Q3W. The selection of this administration method is mainly based on the safety and exposure (concentration)-response (PD-1 receptor occupancy) relationship data of the currently proceeding phase Ia study (CIBI308A101), combined with the nonclinical *in vitro*/*in vivo* PD data and relevant comparison data to similar drugs. On the premise that no significant variation occurs in drug clearance characteristics of subjects, IBI308 of 200 mg Q3W which is administered continuously for 84 days (4 doses) can achieve steady state with steady trough concentration of about 26 μg/mL and can maintain peripheral and target PD-1 receptor occupancy.

3.2.3 Justification for docetaxel as control drug

Advanced squamous non-small cell lung cancer (sqNSCLC) is lack of effective therapies and the first-line standard therapy is platinum-based chemotherapy. Docetaxel is one of the drugs which are approved for second-line treatment of NSCLC and can prolong the PFS and OS of subjects compared with best support care (BSC)[9] or active chemotherapy[10]. Meanwhile, docetaxel was used as control drug to compare with pemetrexed in a non-inferiority study, where docetaxel group had a median PFS of 2.9 months and median OS of about 8 months[11]. Pemetrexed was not approved for second-line treatment of sqNSCLC due to lack of efficacy. The studies on the erlotinib and gefitinib in second-line treatment of sqNSCLC were also conducted. Both of them showed nonuniform absorption levels in sqNSCLC subjects and thereby were not considered as second-line standard therapy. In summary, docetaxel is chosen as control drug in this study.

3.2.4 Rationale for treatment after progressive disease

Existing clinical data show that, a few subjects may experience "PD" (RECIST v1.1) after receiving PD-1 inhibitors prior to objective clinical objective response and/or stable disease (SD). However, continuous treatment may still bring clinical benefits[12]. The mechanism of action of this phenomenon may be worsening of intratumor inflammation which results increased tumors or even new lesions. Additionally, an anti-tumor immune response may take a certain time to develop. Therefore, subjects treated with IBI308 are allowed to continue study treatment with IBI308 after PD defined in RECIST v1.1 is preliminarily determined by the investigator, in case of potential clinical benefit (see Section 5.1.2 for details).

3.3 Independent Data Monitoring Committee

An independent data monitoring committee (IDMC) is set up in this study to conduct an interim safety analysis for the trial. The personnel composition, responsibilities, and procedures of the IDMC are detailed in the IDMC regulations.

4 Study Population

4.1 Inclusion Criteria

Subjects must meet the following inclusion criteria:

1. Cytologically or histologically diagnosed with sqNSCLC;
2. Locally advanced, metastatic, or recurrent (i.e., ineligible for radical radiochemotherapy phase IIIB, IIIC, or IV) NSCLC (as per UICC/AJCC staging system, version 8), including the following four situations:
    1) PD (RECIST v1.1) is observed during or after first-line platinum-based chemotherapy (including maintenance chemotherapy), and discontinuation, dose reduction, or replacement with any analogous drug for one of the medications is permitted in the first-line therapy;

2) Alternative systemic treatment regimen is required due to intolerable toxicity of first-line platinum-based chemotherapy regimen (at least one complete cycle of treatment is given);
3) Recurrent disease or metastasis is observed within 6 months after completion of platinum-based neoadjuvant/adjuvant chemotherapy (before or after radical surgery) or sequential/concurrent radical radiochemotherapy (platinum-based regimen);
4) Recurrent disease or metastasis is observed over 6 months after completion of platinum-based neoadjuvant/adjuvant chemotherapy (before or after radical surgery) or sequential/concurrent radical radiochemotherapy (platinum-based regimen), and PD is observed after or during platinum-based chemotherapy for the recurrent disease or metastasis;

3. With at least one measurable lesion (RECIST v1.1);
4. Males or females ≥ 18 and ≤ 75 years old;
5. ECOG PS score is 0 or 1;
6. Life expectancy ≥ 12 weeks;
7. Important organ and bone marrow functions meet the following requirements (excluding subjects who have received any cell therapy or growth factor therapy within 2 weeks prior to randomization):

1) Routine blood test: absolute neutrophil count (ANC) ≥ 1.5×10^9/L, platelet count (PLT) ≥ 100×10^9/L, and hemoglobin (HGB) ≥ 90 g/L (component blood transfusion shall not be carried out within 1 week prior to randomization);
2) Liver function: total bilirubin (TBIL) ≤ 1.5 × upper limit of normal (ULN), alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST) ≤ 2.5 × ULN, and serum albumin (ALB) ≥ 2.8 g/dL;
3) Renal function: serum creatinine (Cr) ≤ 1.5 × ULN, or creatinine clearance rate (CrCl) ≥ 40 mL/min (using standard Cockcroft-Gault equation):

$$\text{Female: CrCl} = \frac{(140 - \text{Age}) \times \text{Weight (kg)} \times 0.85}{72 \times \text{Cr (mg/dL)}}$$

$$\text{Male: CrCl} = \frac{(140 - \text{Age}) \times \text{Weight (kg)} \times 1.00}{72 \times \text{Cr (mg/dL)}}$$

8. The subjects and their sex partners should take a medically accepted contraceptive measure (intrauterine device (IUD), contraceptive agent or condom, etc.) during study treatment and within 6 months after completion of study treatment;
9. Subjects who have signed written ICFs, and are able to comply with the follow-up visits and relevant procedures required in the protocol.

4.2 Exclusion Criteria

Subjects should be excluded if any of the following exclusion criteria is met:

1. With known EGFR-sensitive mutation or ALK rearrangement;
2. Adenosquamous Carcinoma of Lung;
3. Have received anti-PD-1, anti-PD-L1, anti-CTLA-4 antibody or docetaxel therapy (not including docetaxel used in systemic treatment to cure any other malignant cancer and with potential dose-accumulating toxicity being eliminated);
4. Have received the following therapies:

- Systemic anti-tumor therapy, such as chemotherapy, targeted therapy, and immunotherapy (including treatments with Chinese herbal medicine indicated for cancer), within 3 weeks prior to randomization;
- Any investigational drugs within 4 weeks prior to randomization;
- A high dose of immunosuppressant (systemic glucocorticoid therapy using prednisone at a dose of over 10 mg/day or the equivalent dose, excluding a single dose of prednisone over 10 mg/day or the quivalent does and glucocorticoids used as prophylactics for hypersensitivity, such as medications prior to CT) within 4 weeks prior to randomization;
- Live attenuated vaccine within 4 weeks prior to randomization (or live attenuated vaccine that is planned during the study);
- Major surgery (e.g., open cavity, open chest, or open abdomen operation), or current non-healing surgical wounds, ulcers, or fractures, within 4 weeks prior to randomization.

5. Have received any prior anti-tumor therapy and developed adverse reaction, which has not recovered to CTCAE grade ≤ 1 yet (not including hair loss or laboratory tests of no clinical significance);
6. With active autoimmune disease (inherited or acquired), such as interstitial pneumonia, uveitis, enteritis, hepatitis, hypophysitis, vasculitis, nephritis, and thyroiditis (subjects with vitiligo or childhood asthma that has completely resolved and does not require any intervention after adulthood can be enrolled; subjects with hypothyroidism necessitating hormone replacement therapy only or type I diabete subjects with well-controlled insulin level can also be enrolled);
7. With known history of allotransplantation (except corneal transplantation) or allogeneic hematopoietic stem cell transplantation;
8. Allergic to monoclonal antibodies or any ingredient of docetaxel preparations;
9. Received chest radiotherapy over 30 Gy within 6 months prior to randomization or palliative radiotherapy at a dose of ≤ 30 Gy within 7 days prior to randomization (palliative radiotherapy for osteopathy or intracranial lesions is accepted);
10. Symptomatic central nervous metastasis and/or carcinomatous meningitis. Subjects with asymptomatic brain metastases or with stable symptoms after treatment of brain metastases are allowed to participate in this study as long as meeting all the following criteria: presence of measurable lesions outside the central nervous system (CNS); absence of metastases in midbrain, pons, cerebellum, medulla oblongata, or spinal cord; no history of intracranial hemorrhage; and no glucocorticoid therapy is currently required;
11. Afflicted with interstitial lung disease;

12. With superior vena cava syndrome that is contraindicated for infusion;
13. Clinically uncontrollable third space effusion, such as pleural effusion or ascites that cannot be controlled by drainage or other methods prior to enrollment;
14. Afflicted with other uncontrolled severe diseases, including but not limited to:

- Active or poorly controlled severe infections;
- HIV infected subjects (with positive anti-HIV antibody);
- Afflicted with acute or chronic active hepatitis B (HBV DNA > 1×10^3 copies/mL or > 200 IU/mL), or acute or chronic active hepatitis C (with positive HCV antibody);
- With active pulmonary tuberculosis, etc.;
- With class III–IV congestive heart failure (based on New York Heart Association Classification) or poorly controlled and clinically significant arrhythmia;
- Uncontrolled arterial hypertension (systolic blood pressure ≥ 160 mmHg or diastolic blood pressure ≥ 100 mmHg);
- With any arterial thrombosis, embolism, or ischemia within 6 months prior to enrollment, such as myocardial infarction, unstable angina, cerebrovascular accident, or transient cerebral ischemic attack, etc.;
- Tumor compresses peripheral important organs (such as esophagus) with associated symptoms;
- Uncontrolled hypercalcemia, or symptomatic hypercalcemia requiring further bisphosphonate therapy;
- With other concurrent malignant cancers (except cured cancers, such as cervical carcinoma in situ and non-melanoma skin cancer).

15. Acute or chronic diseases, psychiatric disorders, or laboratory abnormalities that may lead to the following consequences: increased study drug-related risks, or interference with interpreting study results, and considered ineligible for participating in the study by the investigators;
16. Pregnant or lactatingfemale subjects.

4.3 Restrictions During the Study

Female subjects of childbearing potential who are sexually active with nonsterilized male partners and nonsterilized male subjects who are sexually active with female partners of childbearing age must use at least one of the acceptable methods of effective contraception listed inTable 2, The contraception should be used from the beginning of the screening period to up to 180 days after the last dose of study drug; thereafter, the subject should discuss with a physician in charge about discontinuation of the contraceptive measures. Periodic abstinence, calendar-based method, and withdrawal method are not the acceptable forms of contraception.

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

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

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

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

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

[a]This method is also considered as a hormonal approach

4.4 Study Discontinuation/Withdrawal of Subjects

4.4.1 Discontinuation of any study drug by the subject

In case of any of the following situation, the subject "**must**" discontinue study drug:

- Discontinuation of study treatment required by the subject
- Any clinical AE, abnormal results of laboratory tests or concomitant diseases based on the judgment of the investigator, which indicate that subjects cannot acquire the greatest benefit if they continue to participate in the study
- Discontinuation of study required by the sponsor
- Discontinuation criteria specified in the study protocol
- Violation against the inclusion/exclusion criteria, which is likely to pose potential risk to the safety of subjects or affect the accuracy of study data; subjects are deemed unsuitable to continue participating in this study by the sponsor and the investigator;
- Subjects seriously violate the requirements of the study protocol, and are deemed unsuitable to continue participating in this study by the sponsor and the investigator;

- The subject is involved in any other type of clinical trial at the same time;

If subjects become pregnant, the investigator must report to the sponsor designee immediately. In most cases, the study drug will be permanently discontinued in an appropriate manner. If the investigator confirms the favorable benefit-to-risk ratio of further use of the study drug, then he/she must discuss with the sponsor designee on this issue.

All subjects who have discontinued the study drug have to be followed up according to the procedure specified in Table 1, unless the subject withdraws the ICF for all study procedures (including post-discontinuation study follow-up).

If a subject discontinues the study drug prior to study completion, then the reasons thereof must be recorded in the subject's medical record and entered on the corresponding page of Case Report Form (CRF).

4.4.2 Post-discontinuation study follow-up

In this study, OS is a primary endpoint. Study follow-up after completion are vital to safety of subjects and integrity as well as reliability of the study. All subjects who have discontinued the study drug must be further followed up to collect their prognoses and/or survival follow-up data according to the requirements specified in Table 1, until the death of subjects or the completion of the study.

For subjects lost to follow-up, the study site should try the best to contact the subjects and ascertain the reason for loss to follow-up, and then reschedule visits if possible. Meanwhile the date and method of contact shall be documented in the study documents.

4.4.3 Withdrawal of consent

If a subject who requests to discontinue study drug continues the study, he/she must be further followed up according to the procedures specified in the study protocol. There is only one exception, where a subject withdraws the consent definitely and further contact with the subject or any person authorized previously to offer this information is impossible. Where possible, the subject should give the investigator a **written** notice on the decision to withdraw theconsent of future follow-up. The investigator is required to elaborate the withdrawal of consent in details in the medical record to specify whether the subject just decides to discontinue the drug treatment or to withdraw from any study procedure/follow-up after discontinuation, and the above contents should be entered into the corresponding pages of CRF. The evaluation of survival situation (survival or death of the subject), if appropriate, can be conducted only as per the corresponding stipulation and using public information allowed in law.

5 Study Drugs and Other Treatment

5.1 Treatment Regimen

5.1.1 Treatment regimen

Study drugs in this study refer to IBI308 and docetaxel, and other medications during the study are non-study drugs. The treatment regimen is shown in the table below.

Table 3. Dosage of study drugs and treatment regimen

Groups	Treatment regimen	Duration of administration
IBI308 group	200 mg, IV for about 1 h, Q3W	Until PD, death, intolerable toxicity, withdrawal of consent, initiation of a new anti-tumor therapy, or treatment discontinuation due to ant other reason specified in the protocol (whichever occurs first); eligible subjects can continue the treatment with IBI308 after the first PD (see Section 5.1.2).
Docetaxel[a]	75 mg/m^2, IV for about 1 h, Q3W	Until PD, death, intolerable toxicity, withdrawal of consent, initiation of a new anti-tumor therapy, or treatment discontinuation due to any other reason specified in the protocol (whichever occurs first).

[a]The study site will determine the actual drug dose that a subject should receive by calculating the body surface area on the scheduled administration day in each cycle. The maximum body surface area adopted by the protocol is 2.0 m^2. For subjects with a body surface area > 2.0 m^2, the staff of the study site will calculate the dose based on a body surface area of 2.0 m^2. For convenience, the protocol allows for a deviation of ±5% of the total infusion dose each time.

5.1.2 Continued treatment after progressive disease

During the treatment with IBI308, if subjects continued the treatment with IBI308 after they are judged to have PD for the first time as per RECIST v1.1, the following criteria must be met:

1. The investigator believes that the subjects may enjoy clinical benefits from continued study treatment, and the disease does not show rapid progression;
2. The subjects can tolerate the study drug;
3. Stable ECOG PS scores;
4. Will not delay the treatment of serious complications requiring urgent intervention (such as metastasis in the CNS);
5. Before continuing treatment with IBI308, the subjects must be fully informed and the investigator must elucidate all foreseeable risks or discomforts and alternative treatments.

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

Data from subjects who continue IBI308 treatment after initial PD shall be collected. Refer to Table 1 for collection of data variables. The treatment will continue until no clinical benefit, death, intolerable toxicity, withdrawal of consent, or initiation of a new anti-tumor therapy (whichever occurs first) based on the judgment of the investigator.

For subjects who continue IBI308 treatment after initial PD, treatment shall be discontinued if clinical symptoms worsen with the absence of imaging evidence of further PD, and the subjects

should be recorded as "deterioration of clinical symptoms". In this case, the investigator should continue imaging evaluation as described in Section 6.3.

5.2 Study Drug (IBI308)

5.2.1 Description

The study drug is a recombinant fully human anti-PD-1 monoclonal antibody injection (hereinafter referred to as IBI308).

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

IBI308 is a clear, colorless liquid and is free of foreign matters, flocs, and precipitation.

IBI308 is manufactured by Innovent Biologics (Suzhou) Co., Ltd.

5.2.2 Labels

The smallest packaging unit is one box. Each box contains 2 vials of IBI308 injection. The IBI308's package contains the drug name, drug number, dosage form, strengths, drug code, batch number, shelf life, storage conditions, dosage and administration, precautions, and sponsor's information. The label on the vial contains the same information as the outer package except for dosage form and precautions. Both package and vial shall be labeled " for clinical study only".

5.2.3 Storage

To be stored at 2–8 ℃ protected from light. The shelf life is 24 months. If any quality problems such as turbidity and precipitation are observed in the injection, the vialshould be sealed immediately and notify the sponsor.

5.2.4 Preparation and infusion

The preparation and infusion of IBI308 are as follows:

1. Completely withdraw the contents of two vials of IBI308 injection and transfer them into a 100 mL IV infusion bag containing 0.9% (w/v) sterile normal saline, then document the start time of the preparation.
2. The IV bag is gently inverted to mix the solution, ensuring uniformity of the contents. No vigorous shaking is allowed to avoid foam.
3. Administer with a 0.2–1.2 μm in-line filter the infusion time is recommended to be

controlled within 30–60 min). Document the start and stop time of infusion.

Note: Before preparation, make sure that the IBI308 injection is clear without any quality issues such as turbidity or precipitation; make sure that the time from withdrawing IBI308 from the first vial to the end of infusion is no more than 24 h (storage conditions for the prepared solution is 2–8 °C in the fridge); avoid mixing with other drugs; do not administer as an IV push.

5.3 Study Drug (Docetaxel)

5.3.1 Description

Docetaxel is an approved anti-tumor drug and will be provided by the sponsor after re-labeling. The study site should store, prepare, and administer these drugs according to the approved prescribing information. Strengths: 20 mg/0.5 mL, 40 mg/1 mL, or 80 mg/2 mL.

5.3.2 Pretreatment prior to administration of docetaxel

Dexamethasone (8 mg, Bid, Po) should be administered one day prior to chemotherapy, on the day of chemotherapy, and the next day after chemotherapy. Alternatively, dexamethasone could be administered according to the study site's standard directions for dexamethasone.

5.4 Dose Adjustments

5.4.1 General principles

- On the first dosing day of study drug, the subject's hematologic, hepatic, and renal function pre-dose must meet the requirements, and all other toxicities must resolve to NCI CTCAE v4.03 grade 0–1 or baseline levels (excluding alopecia and fatigue).
- All the dose adjustments should be documented, including the reasons and actions taken.

5.4.2 IBI308 administration adjustments

Dose adjustments of IBI308 are not permitted throughout the trial. The IBI308 administration adjustment protocol (only for AEs related to IBI308 as determined by the investigator) is shown in Table below.

Table 4. IBI308 dose adjustment protocol

AE	Severity level	Dose adjustments
Pneumonia	Grade 2 pneumonia	Interruption[a]
	Grade 3 or 4 pneumonia	Permanent discontinuation

AE	Severity level	Dose adjustments
Diarrhea/enterocolitis	Grade 2 or 3 diarrhea or enterocolitis	Interruption[a]
	Grade 4 diarrhea or enterocolitis	Permanent discontinuation
Dermatitis	Grade 3 dermatitis	Interruption[a]
	Grade 4 dermatitis	Permanent discontinuation
Hepatitis	Grade 2 AST, ALT, or TBIL elevation for subjects with normal AST, ALT, or TBIL at baseline; AST, ALT, or TBIL elevation by ≥ 50% (meeting the criteria for grade 2) lasting for < 7 days for subjects with AST, ALT, or TBIL > ULN at baseline	Interruption[a]
	Grade 3 or 4 AST, ALT, or TBIL elevation for subjects with normal AST, ALT or TBIL at baseline; AST, ALT, or TBIL elevation of ≥ 50% (reaching the requirements of grade 3 or 4) for ≥ 7 days for subjects with AST, ALT, or TBIL > ULN at baseline	Permanent discontinuation
Hypophysitis	Grade 2 hypophysitis	Interruption[b]
	Grade 3 or 4 hypophysitis	Permanent discontinuation
Adrenocortical insufficiency	Grade 2 adrenocortical insufficiency	Interruption[b]
	Grade 3 or 4 adrenocortical insufficiency	Permanent discontinuation
Hyperthyroidism	Grade 3 or 4 hyperthyroidism	Permanent discontinuation
Type I diabetes	Grade 3 hyperglycemia	Interruption[b]
	Grade 4 hyperglycemia	Permanent discontinuation
Renal insufficiency	Grade 2 or 3 Cr elevation	Interruption[a]

AE	Severity level	Dose adjustments
	Grade 4 Cr elevation	Permanent discontinuation
Neurotoxicity	Grade 2 neurotoxicity	Interruption[a]
	Grade 3 or 4 neurotoxicity	Permanent discontinuation
Infusion reactions	Grade 3 or 4 infusion reaction	Permanent discontinuation

a: Resume the administration after symptoms improve to grade 0–1 or baseline levels.

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

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

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

5.4.3 Docetaxel

5.4.3.1 Dose delay

Administration of docetaxel should be delayed in case of the following circumstances:

- Any grade ≥ 2 non-skin drug-related AE, except the following events:
  - Grade 2 drug-related fatigues or abnormal results of laboratory tests does not require treatment delay
- Any grade 3 drug-associated skin AE
- Any grade ≥ 3 drug-related abnormal results of laboratory tests, excluding the following

circumstances of lymphocytopenia, neutrophil count, AST, ALT or TBIL:

- Grade 3 lymphocytopenia does not require administration delay
- No dose should be administered in case of neutrophil count < 1500 cells/mm^3
- No dose should be administered in case of TBIL > ULN, or AST and/or ALT > 1.5 × ULN with ALP > 2.5 × ULN

- Any AE, abnormal result of laboratory tests, or concurrent disease, which require delay of the study drug, based on the judgment of the investigator.

Subsequent doses may be reduced according to Section 5.4.3.2.

Subjects who are treated with docetaxel may need to use growth factors (including G-CSF and erythropoietin). The specific administration is decided by the investigator.

5.4.3.2 Dose reduction

Dose reduction may be required for docetaxel, and the actual practice will be carried out according to the table below.

Table 5. Docetaxel dose reduction procedure

Dose	**Docetaxel**
Starting dose	75 mg/m²
The first dose reduction	55 mg/m²
The second dose reduction	37.5 mg/m²
The third dose reduction	Discontinuation of docetaxel

Does adjustments of docetaxel are required for subjects who experience the following circumstances during docetaxel treatment: neutropenia with fever, neutrophil count < 500 cells/mm³ for over 1 week despite of support care with growth factors, severe or cumulative skin reaction, or grade 3/4 non-hematological toxicity. Subjects should delay the treatment as per Section 5.4.3.1 and then resume administration at a dose reduced by one level (55 mg/m²). If such AEs occur after the first dose reduction, then another reduction to 37.5 mg/m² is permitted. If the third dose reduction is required, then the subject should discontinue docetaxel treatment and proceed to follow-up stage.

Subjects who experience grade ≥ 3 peripheral neuropathy or meet other criteria described in Section 5.4.3.4 should discontinue docetaxel treatment and proceed to follow-up stage.

5.4.3.3 Criteria for resumption of docetaxel treatment

After drug-related AE resolves to grade ≤ 1 or baseline level, the subject could resume docetaxel treatment, except for the following circumstances:

- Subjects with grade 2 fatigue could resume the treatment;
- Subjects with the absence of grade 3 drug-associated skin AE while the presence of grade 2 skin toxicity could resume the treatment;
- Subjects with decreased neutrophil count or increased TBIL, AST or ALT must meet the criteria for resumption of treatment established according to the black box warning in the prescribing information of docetaxel;
- Subjects who meet discontinuation criteria (Section 5.4.3.4) as determined based on values of grade 2 elevations in AST/ALT and TBIL should permanently discontinue the study drug;

If treatment delays for a period > 6 weeks, then the subject must permanently discontinue the study treatment, except for the situations specified in Section 5.4.3.4.

The resumption of docetaxel treatment should follow the dose reduction recommendation described in Section 5.4.3.2.

5.4.3.4 Criteria for discontinuation of docetaxel

Administration of docetaxel should be permanently discontinued in case of the following circumstances:

- Any grade ≥ 3 peripheral neuropathy;
- Any grade ≥ 3 non-skin drug-related AE lasting for > 7 days, except the following abnormal results of laboratory tests:
  - Grade 3 drug-related abnormal results of laboratory tests does not require treatment delay, except for the following situations:
    - Grade 3 drug-related thrombocytopenia with hemorrhage requiring discontinuation;
    - Any drug-related abnormal results of liver function test (LFT) which meet the following criteria requires discontinuation:
      - ALT or AST > 5 × ULN lasting for > 2 weeks
      - AST or ALT > 10 × ULN
      - TBIL > 5 × ULN
      - AST or ALT > 3× ULN with TBIL > 2 × ULN
- Any grade 4 drug-related AE or abnormal results of laboratory tests, except the following events that do not require discontinuation:
  - Grade 4 neutropenia lasting for ≤ 7 days

- Grade 4 lymphocytopenia or leukopenia
- Solitary grade 4 electrolyte imbalance/abnormality which has no clinical sequela and can be corrected by using corresponding supplementary therapy/pertinent handling within 72 h after onset.

- Dose delay for a period > 6 weeks, except the following circumstances:
  - The dose lay for > 6 weeks is allowed if the reason thereof is unrelated with the drug and the approval is obtained from the sponsor's medical manager. The subjects who experience dose delay for > 6 weeks must consult with the sponsor's medical manager prior to resumption of the treatment. Tumor evaluation should continue according to the study protocol despite of the dose delay.
- Continued docetaxel treatment may cause any AE, abnormal results of laboratory tests, or concurrent disease, which will pose considerable clinical risk to the subject, based on the judgment of the investigator.

5.5 Principles of Managing Immune Checkpoint Inhibitor Toxicities

The mechanism of action of IBI308 is to stimulate T-cell activation and proliferation, which could result in immune hyperfunction and thereby lead to autoimmune disease involving multiple systems. Autoimmune AEs such as immune-related pneumonitis, diarrhea/enterocolitis, renal insufficiency, skin rash, hepatitis, endocrine disorders, and peripheral or central neuritis have been observed in the clinical application of other immune checkpoint inhibitors such as ipilimumab, nivolumab, pembrolizumab, and atezolizumab. Once subjects developed the above AEs in this study, monitoring on signs and symptoms as well as relevant examinations should be performed to identify the cause. If an alternative cause is not found (such as PD, concomitant medications, or infection) and glucocorticoids and/or other immunosuppressants are required (endocrine events such as hyperthyroidism/hypothyroidism, hypophysitis, type I diabetes, and adrenal insufficiency which may not require immunosuppressants are still considered related to immune hyperfunction caused by IBI308), then any AE described above is considered related to immune hyperfunction caused by IBI308 and should be diagnosed as an irAE.

Management for irAE is shown in Appendix 6.

5.6 Concomitant Treatment

5.6.1 Therapies prohibited during study drug treatment

- Other therapies to treat tumors such as chemotherapy, immunotherapy, targeted therapy, and traditional Chinese medicine with anti-tumor potency.
- Immunomodulators and high-dose glucocorticoids (except for those to treat subjects

with AEs).

- Immunoglobulins.
- Live attenuated vaccine.

5.6.2 Therapies permitted during study drug treatment

- Medications that meet the protocol requirements, as determined by the investigator (e.g. concomitant medication used for disease-related symptoms and treatment-related AEs).
- Subjects who need medications for a long time due to pre-existing diseases, such as hypertensive and diabetes mellitus, can continue the use of drug.
- Locoregional surgery or radiotherapy (the radiotherapy field does not cover lungs) used for isolated lesions (excluding target lesions) during the study treatment.
- Supportive care for relieving tumor-related symptoms, such as bisphosphonate treatment for bone metastases.
- Use of locoregional corticosteroids, such as dermal, ocular, nasal, and inhaled corticosteroids.
- Prophylactic use of anti-emetics, glucocorticoids, or other therapies indicating toxicities for chemotherapy group.
- Use of colony-stimulating factors according to relevant guidelines for chemotherapy group.

5.6.3 Drug-drug interactions

- IBI308: no available data on drug interactions at present.
- Docetaxel: Subjects in docetaxel group should avoid being given potent CYP3A4 inhibitors (see details in the package insert of docetaxel) during the study. These drugs include (but are not limited to):
  - Ketoconazole
  - Itraconazole
  - Clarithromycin
  - Atazanavir
  - Indinavir
  - Nefazodone
  - Nelfinavir

- Ritonavir
- Saquinavir
- Telithromycin
- Voriconazole

Excessive grapefruits, lime and its products and juice made from these fruits are not encouraged for subjects in docetaxel group.

5.7 Treatment Compliance

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

5.8 Drug Return and Destruction

After confirmation by clinical research associate (CRA), the containers, vials, infusion bags, and syringes of used and partially used study drugs can be destroyed on-site or recycled according to the appropriate guidelines and operating procedures established by study sites and local agencies.

Upon the completion or discontinuation of the study, all unused or expired study drugs must be returned to the sponsor for destruction. Arrangements for the return of IBI308 will be made by the CRA designated by the sponsor.

5.9 Study Drug Records

The designee of local study site should make timely records of receipt, dispensing, using, storing, destroying, returning, and damaging the study drugs in accordance with the relevant regulations and guidelines as well as the requirements of operation processes of this study.

5.10 Complaint Handling

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

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

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

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

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

6 Study Evaluations and Procedures

6.1 Enrollment and Randomization

6.1.1 Subject enrollment and randomization procedures

The investigator will enroll the subjects by the following steps:

1. Obtain the ICF signed by the subjects prior to any study-related procedures.
2. Confirm the subjects' eligibility by the principal investigator or trained designee after reviewing the inclusion/exclusion criteria.
3. Randomize the subjects by central randomization and with stratification factor of ECOG score (0 or 1).

Subjects who have failed to meet the criteria (screen failures) can be re-screened. If re-screening is considered, the investigator must contact the sponsor's medical manager. Each subject can be re-screened once. The subjects must sign the ICF again and receive a new identification number when they are re-screened.

6.1.2 Enrollment error handling

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

6.2 Study Plan and Schedule

6.2.1 Screening period

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

- Signing of ICF
- Confirming the inclusion/exclusion criteria

- Recording the demographics, medical history, and previous medications
- Recording vital signs, height, and body weight
- Physical examination
- ECOG PS score
- 12-lead ECG
- Routine blood test/blood chemistry/urinalysis (within 7 days prior to the first dose)
- Pregnancy test (within 3 days prior to the first dose)
- Thyroid function
- HIV antibody, hepatitis B panel (HBsAg, HBsAb, HBcAb, HBeAg, and HBeAb), HBV DNA, and HCV antibody
- AE evaluation
- Concomitant medications
- Tumor imaging evaluation
- Archived or fresh tumor tissue sample
- RAVE Balance randomization

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

6.2.2 Baseline (prior to day 1 of cycle 1)

- Recording the vital signs
- Body weight
- ECOG PS score
- Immunogenicity
- AE evaluation
- Concomitant medications
- EQ 5D-5L, EORTC QLQ-C30, and EORTC QLQ-LC13 scales
- Blood sampling for biomarkers

6.2.3 Treatment visits

- Recording of vital signs and body weight; if the weight fluctuation is less than 10%

compared to baseline (the day of the first dose) in the docetaxel group, the baseline weight will be used to calculate the dose. Otherwise, the actual dose will be calculated based on the weight of scheduled dosing days.

- Physical examination
- ECOG PS score
- 12-lead ECG
- Routine blood test/blood biochemistry/Rutine urine test
- Thyroid function
- Immunogenicity (for IBI308 group only)
- AE evaluation
- Concomitant medications
- Tumor imaging evaluation
- Administration of investigational drug
- EQ 5D-5L, EORTC QLQ-C30, and EORTC QLQ-LC13 scales
- Blood sampling for biomarkers
- Survival condition

The schedule of visits is shown in Table 1.

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

6.2.4 Safety follow-up

Two safety follow-ups will be carried out. The first visit will be conducted 30 (± 3) days after the last dose, and the second visit will be conducted 90 (± 7) days after the last dose. The following contents should be included:

- Recording the vital signs
- Body weight
- Physical examination
- ECOG PS score
- 12-lead ECG
- Routine blood test/blood biochemistry/Routine urine test

- Thyroid function
- Pregnancy test (at the first visit only)
- Immunogenicity (in IBI308 group at the second visit only)
- AE evaluation
- Concomitant medications
- Subsequent anti-tumor therapy (if applicable)
- Survival condition
- EQ 5D-5L, EORTC QLQ-C30, and EORTC QLQ-LC13 scales

Subjects terminating treatment prematurely need to complete the above safety follow-ups, too. Tests related to premature treatment termination should be carried out on D21–D30 after the last dose, and their results can be documented as the results of the first safety follow-up.

Prior to initialization of therapy with other anti-tumor drugs, the above safety follow-ups have to be done first. If therapy with other anti-tumor drugs starts within 90 days after the last dose, then the second safety follow-up 90 days after the last dose is not required. The investigator may conduct the second safety follow-up because of reasons including AEs of special interest.

6.2.5 Survival follow-up

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

6.3 Efficacy Evaluation

The method for evaluation of tumor burden during each subsequent follow-up should be the same as the one used at the baseline (CT/MRI). Sites to be evaluated in each subject include neck, chest, abdomen, and pelvic cavity, and based on symptoms and signs of each subject, other involving sites (e.g., brain) will be examined. Baseline evaluation is conducted within 28 days prior to the first dose of the study treatment. The investigator can evaluate the imaging results within 28 days prior to the enrollment.

Once every 6 weeks (± 7 days) after the first dose of investigational drug, tumor imaging evaluation will be carried out; 24 weeks after the first dose of investigational drug, tumor imaging evaluation can be conducted once every 9 weeks (± 7 days), until PD, initiation of a new anti-tumor therapy, withdrawal of the informed consent forms (ICFs) by the subjects, or death. Subjects in IBI308 treatment group whose imaging PD is initially documented will be evaluated

once, and part of the subjects meeting particular requirements are permitted to continue receiving the treatment with the investigational drug after PD (refer to Section 5.1.2). For subjects who discontinue the treatment for reasons other than imaging PD, an imaging evaluation should be carried out at the end of the treatment as per the protocol, until the occurrence of any of the following events: initiation of a new anti-tumor therapy, PD, withdrawal of consent by subjects, and death.

The subject may continue the treatment if PD cannot be confirmed by the investigator, especially for non-target lesions and new lesions, until the occurrence of clinical symptoms or the next scheduled evaluation time point when the imaging evaluation will be performed again. If repeated scans confirm PD, then the PD should be recorded using the date of the initial scan.

In this study, the tumor evaluations, as the primary analysis, are performed based on RECIST v1.1 at the study site. Refer to Appendix 3 for the evaluation methods.

6.4 Safety Evaluation

6.4.1 Routine laboratory safety evaluation

Table 6. Routine laboratory safety evaluation

Routine blood test	RBC, HGB, WBC, PLT, LYM, and ANC
Blood biochemistry	TBIL, ALT, AST, γ-GT, ALP, ALB, TP, LDH, UREA/BUN, Cr, Na, K, Cl, Mg, Ca, P, amylase, and FBG
Routine urine test	PH, UALB, UPRO, URBC, and UGLU

6.4.2 Physical examination

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

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

6.4.3 12-lead ECG

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

The subjects are required to rest in supine position for at least 5 minutes prior to 12-lead ECG. All 12-lead ECGs should be performed while the subjects are resting in the supine position. Further ECG is performed if clinically indicated, such as a cardiac AE. The investigator should review the ECG on the day it is performed, and document the results on the ECG. The same

method of evaluation is used throughout the study.

Investigator should evaluate all ECGs based on the types of abnormalities with or without clinical significance. For a clinically significant abnormality, investigator should record the result as an AE in eCRF.

6.4.4 Vital signs

Vital signs will be performed in accordance with the schedule of visits (Table 1). Vital signs include body temperature, pulse, respiratory rate, and blood pressure.

Additional monitoring of vital signs is allowed based on standard clinical practice or clinical needs.

Additional records for vital signs may be collected in medical record when an AE/SAE occurs (if applicable). The time and date of collection and measurement should be recorded in an appropriate section of the eCRF

6.4.4.1 Pulse and blood pressure

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

6.4.4.2 Body temperature and respiratory rate

The body temperature and respiratory rate should be collected prior to the infusion on the scheduled administration day.

6.4.5 Weight and height

Height will be measured only during screening.

Weight needs to be recorded before every planned dose during the study. If the weight fluctuation of a subject in docetaxel group is less than 10% compared to baseline (the day of the first dose), then the baseline weight will be used to calculate the dose. Otherwise, the actual dose will be calculated based on the weight of scheduled dosing days.

6.4.6 Pregnancy test

Urine or serum human chorionic gonadotropin (hCG) pregnancy test will be performed in female subejects of childbearing age (for the definition, refer to Section 4.3) within 3 days prior to the first dose of investigational drug. For the result of urine hCG of positive or inconclusive, a serum β-hCG pregnancy test is performed. Result of the serum pregnancy test is determinative. For the serum β-hCG result of positive, the subject is not eligible or discontinued participating in the study. A repeated test is performed for the suspected pregnancy during the study.

6.4.7 Other safety inspections

- HIV antibody

- Hepatitis B: hepatitis B panel (HBsAg, HBsAb, HBcAb, HBeAg, and HBeAb) and HBV DNA.
- Hepatitis C: HCV antibody.
- Thyroid function: T3, T4, TSH, FT3, and FT4.

6.5 Immunogenicity

Immunogenicity assays will be performed in IBI308 treatment group only, within 1 h prior to IBI308 infusion in cycles 1, 2, 4, and every 4 cycles (cycles 8, 12, 16, and so on) thereafter, and during the second safety follow-up. Tests will be conducted in the central laboratory.

ADA titer should be tested for each subject in IBI308 treatment group, and ADA-positive serum samples should be further tested for neutralizing antibodies (NAbs).

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

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

6.6 Quality of Life Evaluation

Quality of life evaluation will be performed on the day of the first dose, during each imaging evaluation, and at the first safety follow-up using EQ 5D-5L, EORTC QLQ-C30, and EORTC QLQ-LC13 scales.

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

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

6.7 Biomarker Analysis

When permitted by the EC, subjects who meet the inclusion criteria are required to provide diagnosed tumor tissues at the baseline. For the acceptable tumor tissues, including the archived tumor tissues or those newly collected and prepared during the screening period, at least 8

unstained sections of 4–5 microns will be required for PD-L1 assay and expression level assay of immune-related mRNA (including but not limited to expression levels of messenger RNA of IDO1, CXCL9, CXCL10, HLA-DRA, STAT1, and IFNG).

Subjects in the IBI308 group need to provide 10 mL of whole blood sample at each of the following time points: prior to the first dose, and at each efficacy evaluation during treatment before the initiation of the next treatment; the samples will be analyzed for tumor mutation burden (TMB) and circulating tumor cells (CTC), including but not limited to dynamic change of PD-L1.

6.8 Storage and Destruction of Biological Samples

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

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

7 Safety Reports and AE Management

7.1 Definition of AEs

An adverse event (AE) is defined as any adverse medical event that is observed in the period from the signing of the ICF to 90 days after the last dose of the investigational drug, regardless of whether or not considered as related to the investigational drug. Not all laboratory test abnormalities/vital sign abnormalities should be reported as AEs, and only the laboratory test abnormalities/vitals sign abnormalities meeting any of the followings can be reported as AEs: for AEs, including but not limited to the followings:

(1) Worsening of pre-existing (prior to enrollment) medical conditions/diseases (including symptoms, signs, and laboratory test abnormalities);

(2) Any new adverse medical conditions (including symptoms, signs, and newly diagnosed diseases);

(3) Abnormal laboratory test results/vital sign abnormalities (including infusion-related reactions) accompanied with clinical symptoms or resulting in change of investigational drug (e.g., temporary or permanent discontinuation);

(4) Abnormal laboratory test results requiring medical intervention or change of both treatment;

(5) Other clinically significant laboratory abnormalities judged by the investigator.

7.2 Definition of SAEs

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

(1) Death, except for the cases caused by PD.

(2) Life-threatening (a life-threatening event is defined as an AE when the subject is at immediate risk of death at the time, but does not include the case that may lead to death only when the event worsens).

(3) Requires hospitalization or prolonged hospitalization, excluding the followings:

- Hospitalization at a rehabilitation institution
- Hospitalization at a sanatorium
- General emergency admission
- Day surgery (e.g., outpatient/same-day/ambulatory surgery)
- Hospitalizations or prolonged hospitalizations unrelated to worsening of an AE are not considered as SAEs. Hospitalization due to pre-existing disease, without new AEs or exacerbation of pre-existing disease (e.g., hospitalization to examine laboratory abnormalities that have been persistent before the study); hospitalization for administrative reasons (e.g., annual routine physical examinations); hospitalizations during the study as specified in the protocol (e.g., hospitalization performed in accordance study protocol); elective hospitalization unrelated to worsening of AEs (e.g., elective surgery); scheduled treatment or surgical procedures, which should be documented in the entire study protocol and/or individual subject's baseline information; and hospitalization merely due to the use of blood products.

(4) Resulting in permanent or severe disability/incapacity.

(5) Resulting in congenital abnormalities/birth defects.

(6) Other important medical events: These events are defined as events that may jeopardize the subjects and require medical or surgical interventions to prevent one of the other outcomes listed in the definition above.

7.3 Criteria for Severity Levels of AEs

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

AEs not included in CTCAE v4.03 are graded in accordance with the following CTCAE principles:

(1) Grade 1 mild; asymptomatic or mild signs; clinical or diagnostic observations only; medical intervention not indicated.

(2) Grade 2 moderate; minimal, local or non-invasive intervention indicated; limiting age-appropriate instrumental activities of daily living (e.g., cooking, shopping, using telephone and managing money).

(3) Grade 3 severe or clinically significant but not immediately life-threatening; hospitalization or prolonged hospitalization indicated; disabling; limiting self-care activities of daily life (e.g., bathing, dressing and undressing, feeding self, using toilet, and taking medications), but not bedridden.

(4) Grade 4 life-threatening consequences; urgent intervention indicated.

(5) Grade 5 death related to AE.

7.4 Correlation Between AEs and Investigational Drug

The relationship between the investigational drug and AEs can be determined by the classification and the criteria in the followings:

Table 7. Correlation determination between AEs and investigational drug

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

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

7.5 Documentation of AEs

The investigator should document AEs or SAEs using medical terms/concepts. Avoid colloquialisms/abbreviations. All the AEs (including SAEs) should be documented in the AE form of the eCRF.

If any clinically significant laboratory test abnormality or vital sign abnormality is manifestation of a disease or syndrome (e.g., cholecystitis-induced elevations in ALP and bilirubin exceeding 5 times ULN), then such diagnosis (i.e., cholecystitis) will be documented in the AE form of the eCRF only. Otherwise, such laboratory test abnormalities or vital sign abnormalities should be documented in the AE form of the eCRF, and any laboratory value being higher or lower than normal reference range should be indicated (e.g., "serum potassium increased" rather than "serum potassium abnormality" should be documented). If there is a standard clinical term corresponding to such laboratory test abnormality or vital sign abnormality, then the clinical term (e.g., "anemia" rather than "hemoglobin decreased") should be documented in the eCRF. The same laboratory test abnormality or vital sign abnormality with clinical significance is found in multiple follow-ups, unless change in severity or etiology, should not be repeatedly documented as an AE or SAE in the eCRF.

7.5.1 Collection and time of AEs

The investigator should learn about AEs by asking the subjects non-leading questions.

All the AEs, including SAEs, that occur from the signing of the ICF to 90 days after the last dose are collected, regardless of whether they are observed by the investigator or self-reported by the subject. If the subject initiates a therapy with other anti-tumor drugs within 90 days after the last dose of the investigational drug, then only AEs considered related to the drug are required to be collected.

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

7.5.2 AE follow-up

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

investigational drug.

7.5.3 Contents of AE documentation

Investigator should document all the AEs, including the diagnosis (document signs and symptoms including the laboratory abnormalities if there is no diagnosis), time and date of occurrence (if applicable), CTCAE grade of severity and changes in severity (events ≥ grade 3), whether it is an SAE, whether it is an AE of special interest (AESI), measures taken for the investigational drug, treatment for the AE and outcome of the event, and relationship between the event and investigational drug.

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

Descriptions of the AE are as follows:

Diagnosis, symptoms, and signs

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

AEs secondary to other events

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

document them as separate events in the eCRFs.

Ongoing or recurrent AEs

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

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

Laboratory test abnormalities

All clinically significant laboratory test abnormalities are reported as AEs. The investigator has responsibilities for reviewing all the laboratory test abnormalities and determining whether the abnormalities should be reported as AEs.

Death

During the entire course of the study, all the deaths that occur within 90 days after the last dose are documented in the "Death Report Form" in the eCRFs and reported to the sponsor promptly, regardless of the causality with the investigational drug.

When documenting death events, for the death with a known cause, the cause of death should be documented as an AE and the outcome of the AE should be death, and the event should also be reported as an SAE (death caused by tumor progression will not be documented and reported as an AE/SAE, but the investigator should document the death in the "Death Report Form" of the eCRF and inform the sponsor promptly). For the death with an unknown cause, the AE should be documented as "death with an unknown cause" in the AE form of the eCRF, and reported as an SAE. Further investigation should be performed next to identify the exact cause of death.

If the death is definitely caused by tumor progression, then it should not be documented and reported as an AE/SAE; nonetheless, the investigator should document the death in the "Death Report Form" of the eCRF and inform the sponsor promptly.

Pre-existing medical conditions

Symptoms/signs presenting during the screening period will be recorded and reported as AEs only if the severity level, frequency, or property becomes aggravated (except for worsening of the studied disease). The relative change from previous conditions should be documented, such as "increased frequency of headaches".

Progressive disease

A progressive disease is defined as the worsening of subject condition caused by the primary tumor that the investigational drug is targeting, the appearance of new lesions, or the progression

of the primary lesion. PD will not be reported as an AE. Any deaths, life-threatening events, hospitalizations or prolonged hospitalizations, permanent or significant disability/incapacity, congenital anomaly/birth defects, or other important medical events caused by PD will not be reported as SAEs.

Overdose

A dose exceeding the dose specified in the study protocol is called overdose. In the event of overdose accompanied with an AE, the AE should be documented. When overdose is accompanied with an SAE, the SAE should be reported quickly in accordance with SAE procedures.

7.6 Expedited Reporting of SAEs and Pregnancy

SAE reporting:

SAEs that occur from the signing of ICF within 90 days (inclusive) since the last dose must be reported. The investigator must fill out the "SAE Report Form" from NMPA, regardless of whether it is an initial report or a follow-up report, and sign and date the form. The investigator must report the SAE to the sponsor, NMPA, and EC within 24 hours of noticing the event.

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

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

When submitting the SAE report by mail, it is recommended for the investigator to encrypt the report file and send the report file and password in different emails.

The investigator should also report the event to the NMPA, health administration department, and EC in accordance with the regulations.

Pregnancy

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

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

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

The investigator must conduct visits on the outcome of the pregnancy until 8 weeks after the subject gives birth. The outcome should be reported to the sponsor.

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

If the subject also experiences an SAE during the pregnancy, the "SAE Report Form" from NMPA should also be filled out and reported in accordance with SAE procedures.

7.7 Abnormal Hepatic Function

Drug-induced liver injury is considered if abnormal AST and/or ALT levels are accompanied with abnormal elevation of TBIL, and the following conditions are met without other possible causes. Such cases should always be considered as important medical events.

Table 8. Liver injuries required to be reported as SAEs

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

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

Other than repeated AST and ALT tests, albumin, creatine kinase, total bilirubin, direct and indirect bilirubin, gamma-glutamine transferase, prothrombin time (PT)/international normalized ratio (INR), and alkaline phosphatase should also be tested. Detailed medical history should include history of alcohol, acetaminophen, soft drugs, various supplements, family diseases, occupational exposure, sexual behavior, travel, contact with a patient with jaundice, surgery, blood transfusion, hepatic diseases, or allergic diseases. Further tests may also include detection of acute hepatitis A, B, C, and E and hepatic imaging (such as biliary tract). If a retest shows consistency with the criteria outlined in Table 8 and there are no other possible causes, the possibility of drug-induced liver injury should be considered before all the results of etiological tests are accessible. These potentially drug-induced liver injury should be reported as SAEs.

7.8 Management of Drug-Related Toxicities

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

7.8.1 Immune-related adverse event

Since the mechanism of action of IBI308 involves T-cell activation and proliferation, immune related adverse events (irAEs) are likely to be observed during this study, the definition of irAE is shown in Section 5.5. Signs and symptoms of irAEs should be monitored.

Refer to Section 5.4.2 for dose adjustments of IBI308 and principles of AE management and Appendix 6 for management for irAE.

7.8.2 Adverse events of special interest (AESIs)

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

AESIs for this study include the following:

- Grade 3 or greater infusion reactions
- Grade 2 or greater diarrhea, colitis, uveitis, and interstitial pneumonia
- Other grade 3 or greater immune-related adverse events

8 Statistics

8.1 Statistical Analysis Plan

The final analysis was planned to be performed when 75% of the subjects had an endpoint event (death), or 18 months after the last subject was enrolled.

The drafting of a detailed statistics analysis plan (SAP) will be started after the enrollment of the first subject, and the final draft will be determined before database locking. All analyses and the expression methods for the results will be detailed in the SAP.

8.2 Hypothesis Test

This study is a superiority design to compare IBI308 and chemotherapeutic drugs. The superiority hypothesis test is adopted:

H0:HR $\geq$ 1; H1:HR < 1

Type I error rate α = 0.05 (bilateral). The stratified log-rank test is used to compare the OS of IBI308 and docetaxel groups:

If the P value is $\leq \alpha$, (or the upper limit of confidence interval of HR < 1), then it can be considered that the superiority of IBI308 over docetaxel is valid.

8.3 Statistical Populations

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

1) SS: subjects who receive at least one dose of the investigational drug.
2) Full analysis population: randomized subjects.
3) PPS: a subset of the FAS, including subjects with good compliance and no serious protocol violations or prohibited medications.

8.4 Statistical Analysis Methods

8.4.1 General method of statistical analysis

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

All statistical analyses will be carried out using SAS 9.2 or above.

The significance level of the comparison between groups: $\alpha = 0.05$ (bilateral). If the P value $\leq$ 0.05, the difference between groups can be considered statistically significant.

8.4.2 Analysis of the primary endpoint

OS: the time from randomization to the death of the subject. If the subject is still alive at the end of the study, the known "last date of subject survival" will be used as the censoring date.

In OS analysis, Kaplan-Meier will be used to estimate the median overall survival (mOS) and its confidence interval, and the survival graph will be plotted. A stratified log-rank test will be used to compare the PFS between groups. Stratified Cox proportional hazards model will be used for HR estimation, with randomization stratification factors added into the model. In OS analysis, RMST will also be used to compare inter-group differences in case of the inconformity between the potential HR and constant HR.

Survival rates at 6, 9, and 12 months are estimated by Kaplan-Meier.

8.4.3 Analysis of the secondary endpoints

All efficacy endpoints are evaluated based on the RECIST v1.1:

(1) Progression free survival (PFS)

PFS: The time from randomization to first PD (imaging). For subjects died of any cause before PD, the PFS is the time from randomization to death. Subjects who do not have PD or die will be censored on the date of their last imaging evaluation. Subjects who do not receive any imaging evaluation after baseline will be censored on the date of randomization.

In PFS analysis, Kaplan-Meier will be used to estimate the median progression free survival (mPFS) and its 95% CI, and the survival graph will be plotted. A stratified log-rank test will be used to compare the PFS between groups.

(2) Overall response rate (ORR)

$ORR = \frac{CR + \text{Number of subjects with PR}}{\text{Total number of subjects}} * 100\%$ Binomial distribution will be used to calculate the 95% CI, inter-group difference and the 95% CI of the inter-group difference. Fisher's exact probability test will be used for comparison between groups.

(3) Disease control rate (DCR)

$DCR = \frac{CR + PR + \text{Number of subjects with SD}}{\text{Total number of subjects}} * 100\%$ Binomial distribution will be used to calculate the 95% CI, inter-group difference and the 95% CI of the inter-group difference. Fisher's exact probability test will be used for comparison between groups.

(4) Duration of response (DoR)

For subjects achieved CR or PR, DoR: the time from the date of the first response to PD or death. For subjects without PD or death, the censoring date is the date when the last imaging evaluation is done.

Kaplan-Meier will be used to estimate median duration of remission (mDoR) and its 95%CI, and the survival graph will be plotted. A stratified log-rank test will be used to compare the PFS between groups.

8.4.4 Analysis of quality-of-life questionnaire

The quality of life and health status in IBI308 group and chemotherapy group during treatment will be evaluated based on EQ 5D-5L, EORTC QLQ-C30, and EORTC QLQ-LC13 scores.

8.4.5 Biomarker analysis

- Tumor tissue samples are collected for tumor biomarker analysis, including but not limited to the expression level of PD-L1 and immune-related genes in tumor samples (including but not limited to the expression levels of mRNAs of IDO1, CXCL9, CXCL10, HLA-DRA, STAT1 and IFNG), to analyze the relationship between the above biomarkers and efficacy.
- Blood samples of the IBI308 group are collected for circulating tumor cell (CTC) analysis, including but not limited to the dynamic changes of PD-L1 and the efficacy levels at different expression levels of PD-L1.

8.4.6 Safety analysis

The safety analysis will be performed based on SS. Safety parameters include AEs, laboratory tests, vital signs, ECG, and immunogenicity.

8.4.6.1 Drug exposure

The drug exposure, duration of treatment (number of treatment cycles) of the subjects will be summarized.

8.4.6.2 Adverse event

All the AEs will be coded according to MedDRA.

The incidence rate of AEs, TEAEs, ADRs, immune-related adverse events (irAE), adverse events of special interest (AESI), SAEs, and AEs leading to study termination are summarized respectively (frequency). The distributions of severity levels of TEAE, ADR, irAE, and AESI are summarized by SOC and PT in MedDRA coding according to NCI CTCAE v4.03.

Subjects who discontinue the treatment due to AEs, develop SAEs, or die will be listed (including at least the followings: start date and end date of the AEs, severity levels, relationship with investigational drug, measures taken, and outcome).

8.4.6.3 Laboratory test

Measurements and changes before and after treatment in routine blood test and blood chemistry parameters will be described using mean ± SD, maximum, minimum, and median. Normal and abnormal changes after treatment will be described using a cross-classification table.

Urinalysis: A cross-classification table will be used to describe normal and abnormal changes after treatment.

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

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

8.4.6.4 ECG

Descriptive statistics will be performed on ECG parameters and changes from baseline. A cross-classification table will be used to describe normal and abnormal changes after treatment and data lists will be provided.

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

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

Abnormal changes from baseline in physical examination will be tabulated

8.4.6.6 Immunogenicity indicators

The positive rates of ADA and NAb will be calculated. Subjects' antibody titer will be tabulated.

8.4.7 Compliance analysis

The frequency and proportion of subjects who violate the expected dosing regimen will be summarized.

The proportion of subjects who are given 80–120% of the dose of the investigational drug specified in the protocol will be summarized.

The proportions of the subjects who complete the study and who complete different treatment cycles will also be summarized.

8.4.8 Subjects' baseline characteristics

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

8.4.9 Interim analysis

One interim analysis is designed in this study. The objective of the analysis is to evaluate the safety, and the analysis parameters are the safety parameters. At the time point of 50, the subjects completed 4 treatment cycles without considering the adjustment of α.

8.4.10 Subgroup analysis

An efficacy analysis of PD-L1 positive subjects;

A subgroup analysis based on random stratification factors and other prognostic factors (PS score).

A subgroup analysis based on baseline characteristics of subjects and other potential factors with clinical significance.

The subgroup analysis to be carried out will be defined in detail in the statistical analysis plan.

8.4.11 Multiple comparisons and adjustments

This study is a phase III clinical study, and the interim analysis is a safety analysis. As efficacy endpoints are not involved, no α adjustment will be performed.

All the secondary efficacy endpoints are analyzed only once in this study, and the comparison of the secondary endpoints is controlled by step-down method for α: If the P value of the OS inter-group comparison $\leq \alpha$, the comparison of the PFS between groups is conducted. If the P value of PFS inter-group comparison is $\leq \alpha$, the comparison of the ORR between groups is conducted. If

the P value of ORR inter-group comparison is ≤ α, the comparison of the DCR between groups is conducted. If the P value of the inter-group comparison of any endpoint is > α, the subsequent endpoint is compared nominally between groups.

8.4.12 Eligible subject data lists

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

PFS, OS and other data of all subjects at the end of the study (PD date, date of death, PFS, OS)

8.4.13 Exploratory analysis

Relationship between different expression levels of PD-L1 and efficacy.

The parameters of the clinical benefit evaluation are based on the iRECIST, including ORR, DoR, PFS and DCR.

The relationship between the level of each biomarker and the efficacy endpoints.

8.5 Sample Size Determination

The primary efficacy endpoint is overall survival (OS). Assuming that α = 0.05 (bilateral), power = 90%, IBI308-to-docetaxel survival hazard ratio HR = 0.63, endpoint event (death) is observed in 75% of the subjects, group assignment ratio is 1:1, and the minimum estimated sample size is 266 cases; considering a certain dropout rate, a total of 290 cases are required for enrollment, 145 cases in IBI308 group and 145 cases in the chemotherapy group. The deadline for final data will be determined in advance based on the OS incidence in all subjects observed during the study before the preset number of events is reached.

8.6 Methods for Controlling Bias

8.6.1 Randomization and blinding

In this study, subjects are randomized into groups using RAVE Balance, and the random stratification factor is ECOG PS score (0 or 1). The investigator or qualified designee will log into the system via their respective password. The system will assign each subject a unique random code and also obtain the name of the investigational drug to be received by the subject through RAVE Balance. The independent statistician in charge of randomization will generate a randomization table of subjects (subject random code) based on a 1:1 ratio of IBI308 and docetaxel, and the subject random code will be submitted to the randomization system in the form of an electronic document.

This is an open-label, unblinded study.

8.6.2 Blinding maintenance evaluation

The investigational drug is not blind in this study.

IDMC will be used in the interim analysis of the primary efficacy endpoint (OS) and safety.

8.6.3 Unblinding and emergency unblinding

N/A

9 Quality Assurance and Quality Control

According to the GCP guidelines, sponsor is responsible for implementing and maintaining the study quality and quality control system in accordance with the corresponding standard operation procedures to ensure that the implementation of the clinical trials, the authenticity of data and that the collection, recording and reporting of clinical trial data comply with requirements in the protocol, GCP and corresponding regulations.

9.1 Clinical Monitoring

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

Before the start of the study, the CRA will assess the qualifications of each study site, and report issues related to facilities, technical equipment, or medical staff to the sponsor. During the study, the CRA is responsible for the monitoring of whether the written ICFs from all subjects have been obtained and whether the data records are correct and complete. Also, the CRA will compare the data entered into the eCRFs with the source data, and inform the investigator of any error or omission. The CRA will also control study center's adherence to with the protocol and study procedures, arrange for the supply of the investigational drug and clinical trials, and ensure that the drug is kept under prescribed conditions.

The monitoring visit will be conducted in accordance with applicable statutes and regulations. Each site receives regular monitoring visits from the time the subjects are enrolled. After each visit to the study site, the CRA should submit a written report to the sponsor.

9.2 Data Management/Coding

This study will use an electronic data acquisition (EDC) system, and the study data will be recorded in the eCRFs by the investigator or its authorized personnel. Before the initiation of the study site or data entry, the investigator and authorized personnel will be properly trained and appropriate security measures will be taken for the computers and other equipment.

Data entry into the eCRFs should be completed as soon as possible during or after the visit. The eCRFs should be updated at any time to ensure that they reflect the latest developments of the subjects. To avoid the differences in outcome evaluations by different evaluators, the baseline and all the subsequent efficacy and safety evaluations of a given subject shall be performed by the same individual. The investigator shall review the data to ensure the accuracy and correctness of all data entered into the eCRFs. During the study, the investigator should document any evaluations that are not conducted, or any information that is not available, applicable, or known. The investigator needs to sign all verified data electronically.

The CRA will review the eCRFs, and assess the completeness and consistency. The CRA will also compare the eCRFs with the source documents to ensure the consistency of critical data. All data entry, correction and modification will be performed by the investigator or the designee. The data in the eCRFs are submitted to the data server and any modification to the data should be recorded in the audit trail, including reasons, operator names, time and dates of modifications. The roles and permission levels of the personnel responsible for data entry will be determined in advance. The CRA or data manager will submit data queries in the EDC system, and study personnel shall respond to the queries. The EDC system will record the audit trail of each query, including the name of the investigator, as well as the time and date.

Unless otherwise specified, the eCRF should be considered simply as a form for data collection and not a source document. The source documents are all records used by the investigator or hospital, which are related to the subjects and are able to demonstrate the presence, inclusion/exclusion criteria, and participation of the subjects, including laboratory records, ECG results, pharmaceutical records, and subject folders.

The investigator should be responsible for maintaining all source documents and offering the documents to the CRA for review during each visit. In addition, the investigator must submit a complete eCRF for each enrolled subject, regardless of the duration of participation. The protocol numbers and subject numbers of all supporting documents (such as laboratory records or hospital records) submitted with the eCRFs should be carefully verified. All the personal privacy information (including the subjects' names) should be deleted or made illegible to protect the privacy of the subjects. The investigator should verify that the record has been reviewed and that the data are accurate with an electronic signature. The electronic signature is completed with the investigator's user ID and password. The system automatically attaches the date and time of the signature. The investigator shall not share the user ID and password with other personnel. If data in the eCRF need to be modified, the procedures defined by the EDC system have to be followed. All modifications and reasons for the changes are recorded in the audit trail.

AEs, and concurrent diseases/medical history will be coded. The medical dictionary used for coding will be described in the "Clinical Study Report" (CSR).

9.3 Quality Assurance Audit

During the course of the study, the sponsor or the representative authorized by the sponsor may perform quality assurance audits on the study sites, database and related study documents. At the same time, the corresponding regulatory authorities may also inspect the study sites, database and related study documents at their own discretion. The investigator must inform the sponsor immediately when an inspection notice is received from the regulatory authorities.

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

10 Ethics

10.1 Ethics Committee

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

The study site must follow the requirements of the EC in the study site. Protocol revisions, ICF or recruitment materials should be submitted to the EC for approval. Local safety reports should be made and updated regularly in accordance with the regulations from the EC, and the final report should be submitted. All the above documents and EC approvals must be provided to the sponsor or designee.

10.2 Ethics Conduct of the study

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

The GCP is an international ethical and scientific specification for designing, conducting, recording and reporting clinical trials that involve the participation of human subjects. This study will be conducted in accordance with the GCP and relevant national regulations and in accordance with the relevant ethical principles of the Declaration of Helsinki to protect the rights, safety, and health of the subjects.

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

10.3 Subject Information and Informed Consent

Prior to undergoing any study procedure, the ICF should be used to explain to potential participants the potential risks and benefits of this study. The informed consent form should be in a language that is simple and be easy to understand. The ICF statement should clarify that ICF is voluntarily signed and the risks and benefits of participating in this study should be clearly outlined. The subject may withdraw from the study at any time. The investigator may only enroll a subject after fully explaining the details of the study, answering questions to the subject's satisfaction, giving the subject sufficient time for consideration, and obtaining written ICF from the subject or his/her legal representative. All signed ICFs must be kept in the investigator's files or in the subject's folder.

The investigator is responsible for explaining the contents of the ICF and obtaining the ICF signed and dated by the subject or his/her legal representative prior to starting the study. The investigator should provide the subject with a copy of the signed ICF. The investigator must document the informed consent process in the source document of the trial.

10.4 Data Protection of Subjects

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

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

11 Study Management

11.1 Data Processing and Record Keeping

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

The study documents should be retained properly for future access or data traceability. Safety and environmental risks should be considered when retaining documents.

The documents associated with the study may only be destroyed with the written consent of the sponsor and the investigator. The investigator/study site may transfer the study documents to other parties that comply with the record-keeping requirements or to another location that meet record-keeping requirements only after notifying the sponsor and obtaining the written consent.

11.2 Source Data/File Access

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

11.3 Protocol Revisions

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

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

11.4 Responsibilities of the Investigator

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

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

11.5 Publication of Study Data

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

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

The sponsor has the right to announce or publish information or data related to the trial or to report it to the drug administration. If the Sponsor needs to display the name of the investigator in a publication or advertisement, the consent of the investigator should be obtained.

Financing and Insurance

The sponsor will purchase insurance for subjects participanting in this study in accordance with local regulations and the minimum requirements. Insurance-related terms will be saved in the study folder.

12 References

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13 Appendix

Appendix 1: Signature Page for Investigator

Protocol Title:

A Randomized, Open-Label, Multicenter, Parallel, and Phase III Clinical Trial (ORIENT-3) Comparing the Efficacy and Safety of IBI308 and Docetaxel in the Treatment of Subjects with Advanced or Metastatic Squamous Non-Small Cell Lung Cancer Who Have Failed Platinum-Based First-Line Chemotherapies

Protocol No.: CIBI308C301

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

Instructions for the Investigator: Please sign and date this signature page, type the investigator's name and job title, as well as the name of the study site, and return this document to Innovent Biologics (Suzhou) Co., Ltd.

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

Signature of Investigator: _____ Date: _____

Name (Print): _____

Job Title: _____

Name/Address of Study Site: _____

_____

_____

Appendix 2: ECOG PS Scoring Criteria

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

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Appendix 3: Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST v1.1)

The following is an excerpt from the RECIST v1.1.

1 MEASURABILITY OF TUMOR AT BASELINE

1.1 Definitions

At the baseline level, tumor lesions/lymph nodes will be categorized into measurable and non-measurable ones according to the following definitions:

1.1.1 Measurable lesion

Tumor lesion: At least one diameter line that can be accurately measured (recorded as the maximum diameter), and its minimum length is as follows:

- 10 mm by CT scan (with a slice thickness of no more than 5 mm)
- 10 mm caliper measurement by clinical exam (lesions which cannot be accurately measured with calipers should be recorded as non-measurable)
- 20 mm by chest X-ray
- Malignant lymph nodes: To be considered pathologically enlarged and measurable, a lymph node must be ≥ 15 mm in minimum diameter when assessed by CT scan (CT scan slice thickness is recommended to be no greater than 5 mm). At baseline and follow-up, only the minimum diameter will be measured and followed up.

1.1.2 Non-measurable lesion

All other lesions, including small lesions (with the maximum diameter of < 10 mm or the minimum diameter of a pathological lymph of ≥ 10 mm to < 15 mm) and non-measurable lesions. Non-measurable lesions include: meningeal disease, ascites, pleural or pericardial effusion, inflammatory breast cancer, cancerous lymphangiitis of the skin/lung, abdominal masses that cannot be diagnosed and followed up by imaging, and cystic lesions.

1.1.3 Special considerations for lesion measurement

Bone lesions, cystic lesions, and lesions with prior locoregional treatment must be specified:

Bone lesions:

- Bone scan, PET scan, or plain film are not suitable for measuring bone lesions, but can be used to confirm the presence or disappearance of bone lesions;

- In case of osteolytic lesions or mixed osteolytic/osteogenic lesions that have a definite soft tissue composition with the soft tissue composition meeting the above measurability definition, these lesions can be considered as measurable lesions provided that they can be evaluated using tomographic imaging techniques such as CT and MRI;
- Osteogenic lesions are non-measurable lesions.

Cystic lesions:

- A lesion that meets the definition criteria for simple cysts in radiography should not be considered as a malignant lesion because it is a simple cyst by definition, which should be neither a measurable lesion nor a non-measurable lesion;
- If such lesion is cystic metastatic and meets the above measurability definition, it can be regarded as a measurable lesion. However, if noncystic lesions are present in the same patient, these are preferred for selection as target lesions.

Lesions with prior local treatment:

- Tumor lesions situated in a previously irradiated area, or in an area subjected to other loco-regional treatment, are usually not considered measurable unless there has been demonstrated progression in the lesion. The conditions under which these lesions are measurable should be detailed in the study protocol.

1.2 Description of Measurement Method

1.2.1 Measurement of lesions

When performing clinical evaluation, all tumor measurements should be recorded in metric notation. All baseline assessments of tumor lesion size should be possibly completed within 28 days (4 weeks) before the start of treatment.

1.2.2 Assessment method

The same technique and method should be used for baseline assessment and subsequent measurement of lesions. Except for lesions that cannot be evaluated by imaging, while the clinical examination is applicable only, other lesions must be evaluated by imaging.

Clinical lesions: Clinical lesions can only be considered as measurable lesions (such as skin nodules) when they are on the surface and have a measured diameter of ≥ 10 mm. For subjects with skin lesions, it is recommended to use color photos containing the size of the lesion measured by ruler as an archive. When the lesion can be evaluated by both imaging and clinical examination, imaging evaluation should be used whenever possible since it is more objective and may also be reviewed at the end of the study.

Chest X-ray: Chest CT is preferred over chest X-ray when progression is an important endpoint, particularly in identifying new lesions. Chest X-ray examination is only applicable when the boundary of the measured lesion is clear and the lungs are well ventilated.

CT and MRI: CT is the best currently available and repeatable method for efficacy evaluation. This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is.≤ 5 mm. When CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situations (e.g. for body scans).

Ultrasound: Ultrasound should not be used as a measurement method to measure the lesion size. Ultrasonic examination can not be repeated after the measurement due to its operational dependency, and cannot guarantee that the same technique and measurements will be taken from one assessment to the next. If new lesions are identified by ultrasound in the course of the trial, CT or MRI should be used for confirmation. If there is concern about radiation exposure at CT, MRI may be used instead of CT in selected instances.

Endoscopy and laparoscopy: These techniques are not recommended for objective evaluation of tumors, but they can be used to confirm the CR results when biopsy specimens are obtained, or to confirm the relapse in trials where the endpoint is defined as a relapse or surgical resection after CR.

Tumor markers: Tumor markers cannot be used alone to evaluate objective tumor response. However, if the marker level exceeds the ULN at baseline, it must be returned to normal when used to evaluate a CR. Since the tumor markers are varied from diseases, it needs to be considered when writing measurement criteria in the protocol. Specific criteria for CA-125 response (recurrent ovarian cancer) and PSA (recurrent prostate cancer) response have been published. In addition, the International Gynecologic Cancer Society (IGCS) has prepared the criteria for CA-125 progression, which will soon be added to the objective evaluation criteria for tumors in the first-line treatment of ovarian cancer.

Cytological/histological technologies: Under certain circumstances specified in the protocol, these technologies can be used to identify PR and CR (e.g., residual benign tumor tissue is often present in the lesions of germ cell tumors). When exudation may be a potential side effect of a certain therapy (such as treatment with a taxane compound or an angiogenesis inhibitor), and the tumor can be measured meeting the criteria for response or disease stabilization, the occurrence of tumor-related exudation during treatment or aggravation can be confirmed by cytological technologies to distinguish response (or SD) and PD.

2 ASSESSMENT OF TUMOR REMISSION

2.1 Assessment of All Tumors and Measurable Lesions

In order to evaluate the objective response or possible future progress, it is necessary to perform a baseline assessment of the total tumor burden of all tumor lesions, which then should be used as the references for the subsequent measurement results. In clinical protocols with objective response as the primary treatment endpoint, only subjects with measurable lesions at baseline can be enrolled. Measurable lesion is defined by the presence of at least one measurable lesion. For trials with PD (time of PD or degree of progression on a fixed date) as the primary endpoint of treatment, the inclusion criteria for subjects with or without measurable lesions must be specified in the protocol.

2.2 Baseline Documentation of Target and Non-Target Lesions

When there are more than one measurable lesions in the baseline assessment, all lesions should be recorded and measured, and the total number should not exceed 5 (not more than 2 per organ), since the target lesion represents all involved organs (i.e., for subjects with 1 or 2 involved organs only, at most 2 or 4 target lesions can be selected for baseline measurement).

Target lesions must be selected based on size (the maximum diameter), and can represent all involved organs, and measurements must have well repeatability. Sometimes when the largest lesion cannot be measured repeatedly, the lesion with the maximum diameter may be selected again.

Special attention should be paid to the lymph nodes defined as normal tissues that can be identified by imaging, even if there is no signs of tumor metastasis. Pathological nodes which are defined as measurable and may be identified as target lesions must meet the following criteria: the minimum diameter by CT scan of ≥ 15 mm. Only the minimum diameter should be measured at the baseline. Usually, radiologists will use the minimum diameter of a nodule to determine whether the nodule has metastasized. The nodule size is generally expressed in 2-D data of imaging (either an axial plane in CT or one of the axial, sagittal, or coronal plane in MRI). The minimum value is the minimum diameter. For example, a 20 mm × 30 mm abdominal nodule with a minimum diameter of 20 mm can be considered as a malignant, measurable nodule. In this example, 20 mm is the measured value of the nodule. Nodules with a diameter of ≥ 10 but < 15 mm should not be considered as target lesions. Nodules with a diameter of < 10 mm should be not classified as pathological nodules, requiring no further records or observations.

The sum of the calculated diameters of all target lesions (including the maximum and the minimum diameters of non-nodular lesions) will be reported as the sum of the diameters at the baseline. If the lymph node diameter is included, as mentioned above, only the minimum

diameter is counted. The sum of the baseline diameters will be used as a reference value for the disease at the baseline.

All the remaining lesions, including pathological lymph nodes, can be considered as non-target lesions and no measurement is required, but such lesions should be recorded during baseline assessment. For example, such lesions can be recorded as "presence", "absence", or "definitive progression" in rare cases. Extensive target lesions can be recorded with target organs (such as massively enlarged pelvic lymph nodes or large-scale liver metastases).

2.3 Response Criteria

2.3.1 Assessment of target lesions

Complete response (CR): All target lesions should be disappeared, with the minimum diameter of all pathological lymph nodes (including target and non-target nodules) reducing to < 10 mm.

Partial response (PR): The sum of target lesion diameters is reduced by at least 30% compared to the baseline level.

PD: The minimum value of the sum of all measured target lesion diameters throughout the study should be used as a reference, with increases in the diameter of at least 20% compared to the baseline level (if the baseline measurement is the minimum value, it should be used as a reference); otherwise, the absolute value of the sum of the diameter must be increased by 5 mm (the appearance of one or more new lesions is also considered to be PD).

SD: Due to neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, the minimum sum of diameters can be taken as reference in this study.

2.3.2 Considerations for non-target lesion assessment

Lymph nodes: Even if the lymph nodes are identified as target lesions of a decrease of less than 10 mm, the actual minimum diameter value corresponding to the baseline must be recorded for each measurement (consistent with the anatomical plane at baseline measurement). In other words, if the lymph node is a target lesion, even if the criteria for CR are reached, a CR cannot be determined due to the definition of < 10 mm of the minimum diameter of a normal lymph node. Target lymph node lesions that need to be specifically recorded in specific locations in the eCRF by other recording methods: For CR, the minimum diameter of all lymph nodes must be < 10 mm; for PR, SD, and PD, the actual measured minimum diameter of the target lymph node will be included in the sum of the target lesion diameters.

Target lesions that are too small to be measured: In clinical studies, all lesions (nodules or non-nodules) recorded at baseline should be recorded again in subsequent assessments, even if these lesions are very small (as small as 2 mm, for example). However, in some cases, the lesion may be too small so that the CT scan image is very blurry, and it is difficult for the radiologist to

define the measurement value. Therefore, such lesion may be reported as "too small to be measured". In this case, it is very important to record a value on the eCRF. If it is the opinion of the radiologist that the lesion has probably disappeared, the measurement value should be recorded as 0 mm. If the lesion does exist but with a blurry image so that an exact measurement value cannot be obtained, the default recording should be 5 mm. (Note: This is unlikely to occur in lymph nodes, because a lymph node normally has a measurable size, or it is often surrounded by fat tissues as in the retroperitoneal cavity; but if the measurement value of such node cannot be obtained, the default recording should also be 5 mm). The default value of 5 mm is determined by the cutting thickness of the CT scan (which will not change due to different cutting thickness values of CTs). Since the same measurement value is hardly possible to occur twice, providing the aforesaid default value can reduce the risk of erroneous assessment. But it needs to be reiterated that if the radiologist can provide the exact measured size of the lesion, the actual value must be recorded, even if the diameter of the lesion is less than 5 mm.

Separated or combined lesions: When a non-nodular lesion is presented in parts, the maximum diameter of each separated part is added to calculate the sum of the lesion diameters. Similarly, for combined lesions, they can be distinguished by the plane between the combined parts, and then calculate the maximum diameter of each. However, if the combination is inseparable, the maximum diameter should be taken as the maximum diameter of the entire combined lesion.

2.3.3 Assessment of non-target lesions

This section defines the response criteria for non-target lesions. While some non-target lesions may actually be measurable but without measurement requirements, such lesions should be assessed only qualitatively at time points specified in the protocol.

CR: All non-target lesions are disappeared and the levels of tumor markers are recovered to normal. All lymph nodes must be non-pathological in size (with the minimum diameter of < 10 mm).

Incomplete response/non-progressive disease: At least 1 non-target lesion is found with/without persistent tumor marker levels that exceed normal levels.

PD: Definitive progression of existing non-target lesions. Note: A PD will be considered if at least 1 new lesion is found.

2.3.4 Special considerations regarding the assessment of non-target lesion progression

The supplementary explanation for the non-target lesion progression is as follows: When the subject has measurable non-target lesions, if a clear definition of progress is to be made on the basis of the non-target lesions, the overall non-target lesions must have deteriorated to the extent that the treatment must be terminated even if the target lesions are evaluated as stable or PR.

However, the general increase in the size of one or more non-target lesions is often insufficient to meet the criteria for PDs. Therefore, when the target lesion reachs stable or PR, it is very rare that the change of non-target lesions alone can define the overall tumor progression.

When all of the subject's non-target lesions are not measurable: This is applicable to some phase Ⅲ trials provided that the presence of a measurable lesion is required in the inclusion criteria. However, the overall assessment is also based on the aforesaid requirements since no measurement value can be obtained for the lesion. The assessment of the exacerbation of non-target lesions is a major challenge (by definition: all non-target lesions must not be measurable), and thus when the changes in non-target lesions lead to an increase in the overall disease load equivalent to the PD of target lesions, an effective test method should be established for assessment according to the definitive progressions of non-target lesions. For example, the lesion can be described as an increase in tumor burden equivalent to an additional 73% increase in volume (equivalent to a 20% increase in the diameter of a measurable lesion); or a peritoneal effusion from "minor" to "major"; or a lymphatic lesion from "local" to "extensive"; or in the protocol as "sufficient to cause changes in the therapy". Other examples include a pleural effusion from "trace" to "major", lymphatic involvement spreading from the primary site to a distant site, or lesions described in the protocol as "requiring changes in the treatment". If a definitive progression has been found, the subject should be generally considered as having PD at the time point of the finding. It is best to have objective criteria applicable to the assessment of non-measurable lesions. Notably, the additional criteria must be reliable.

2.3.5 New lesions

The appearance of new malignant lesions can be an indication for the progression of the disease. Therefore, it is critical to perform a certain assessment for such new lesions. Currently, there is no specific criteria for imaging tests of these lesions, while the findings for new lesions should be definitive. For example, the progression cannot be attributed to differences in imaging technologies, changes in imaging morphology, or other lesions except tumors (such as some "new bone lesions" that are simply the cure or the recurrence of the underlying lesions). This is of great importance when the patient is partially or completely responded to the treatment for his/her lesions at baseline. Specifically, a necrosis of a liver lesion may be defined as a new cystic lesion in the CT report, but it is not.

Lesions that have been detected during follow-up but not found at baseline will be considered as new lesions, and will be an indication for a PD. For example, for a subject who is found to have visceral lesions during the baseline examination, and then metastases by a head CT or MRI, the subject's intracranial metastatic lesion will be considered as the rationale for the determination of PD, even if no cranial examination is performed at baseline.

If a new lesion is not definitive due to its small size or other reasons, further treatment and follow-up evaluation are required to confirm whether it is a new lesion. If the lesion is confirmed to be a new one by repeated examinations, the time of the initial finding should be counted as the start of the PD.

Generally, the FDG-PET assessment of lesions requires additional tests for supplemental confirmation, and it is reasonable to combine the results from FDG-PET tests and those from CT tests (especially for new suspicious diseases). New lesions can be identified by FDG-PET tests based on the following procedures:

In case of negative FDG-PET test results at baseline in combination with positive results from subsequent follow-up FDG-PET tests, a PD is indicated.

In case of no FDG-PET tests at baseline in combination with positive results from subsequent FDG-PET tests:

A PD can be proved if new lesions determined by the subsequent FDG-PET test results which are positive are consistent with those determined by CT test results.

Otherwise, the CT tests should be performed again for confirmation of new lesions with positive test results of FDG-PET found in follow-ups (if confirmed, the time of abnormality found by previous FDG-PET tests should be counted as the start of the PD).

And no progression should be determined in case of consistency between the subsequent FDG-PET test results which are positive and those of existing lesions determined by CT tests.

2.4 Evaluation of Optimal Overall Efficacy

The evaluation of the best overall response refers to the best response recording from the start to the end of the study, while any necessary conditions must also be taken into account for confirmation. Sometimes, the therapeutic response will appear after the end of treatment. As a result, it should be clearly specified in the protocol that whether the efficacy evaluation after the treatment is counted in the evaluation of the best overall response. Also in the protocol, it must be specified that how any new therapy before progression affects the best response. The best response from the subjects mainly depends on the results of target and non-target lesions and the manifestations of new lesions. In addition, the response depends on the nature of the study, as well as the requirements and measurement criteria in the protocol. Specifically, the response from the subjects is the primary endpoint in non-randomized studies where the confirmation of PR or CR is required for the evaluation of the best overall response.

2.4.1 Time point response

It is assumed that there will be an efficacy evaluation at each time point defined in the protocol. Table 1 summarizes the overall efficacy evaluation at each time point for subjects with measurable lesions at baseline.

If no measurable lesions (no target lesions) are found in subjects, see Table 2 for the corresponding evaluation.

2.4.2 Description of missing evaluations and non-evaluable cases

If the imaging or measurement of the lesions of a subject cannot be performed at a specific time point, the subject should then be determined non-evaluable at that time point. If only part of the lesions of a subject can be evaluated in an evaluation, the case should then be determined as non-evaluable at that time point, unless there is evidence to prove that the missing lesions will not affect the efficacy evaluation at the specified time point. In addition, such case may be an indication for a PD. For example, a subject has 3 lesions with a sum of diameters of 50 mm at the baseline level, but only 2 are subsequently determined evaluable, with a sum of diameters of 80 mm, and then the subject will be evaluated as having a PD, regardless of the effects of the missing lesion.

2.4.3 Optimal overall response: at all time points

Once all data of the subjects are available, their optimal overall response can be determined.

Evaluation of the optimal overall response when the confirmation of complete or partial response (CR/PR) is not required in the study: The best response in the study refers to the optimal response at all time points (for example, SD is the efficacy evaluation for the subjects in cycle 1, PR for cycle 2, and PD for the last cycle. However, the optimal overall response should be evaluated as PR). When the optimal overall response is evaluated as SD, the minimum time from the baseline level specified in the protocol must be met. If not, the SD result will not be accepted and the optimal overall response from the subjects will depend on the subsequent evaluations. For example, if the response from the subjects is evaluated as SD in cycle 1 and PD in cycle 2, but the minimum time requirement of SD is not met, the optimal overall response will be evaluated as PD. Similarly, if the response from the subjects is evaluated as SD in cycle 1, followed by a loss to follow-up, the subjects will be considered non-evaluable.

Evaluation of the optimal overall response when the confirmation of CR/PR is required in the study: The complete or partial response can be determined only if the CR/PR criteria required by the study are met by each subject, and at a subsequent time point (usually 4 weeks later) specifically mentioned in the protocol, the efficacy is confirmed again. In this case, the optimal overall response can be found in the description of Table 3.

2.4.4 Special notes on efficacy evaluation

When nodular lesions are included in the overall target lesion assessment and the diameters of such lesions are reduced to the "normal" level (< 10 mm), a scan report of the lesion size will still be provided. In order to avoid overestimating the condition indicated by the increase in nodule size, the measurement result will still be recorded even if the size is normal. As mentioned above, this suggests that the measurement results from subjects who are evaluated as CR will not be recorded as 0 in the eCRF.

If the efficacy confirmation is required during the study, the optimal overall response will be more difficult to be evaluated at the repeated "non-measurable" time points. For these missing data/evaluations, it must be stated in the analysis plan of the study that they can be explained clearly when determining efficacy. In most studies, for example, the response from a subject in PR-NE-PR can be considered as the efficacy confirmation.

When a subject experiences a overall deterioration of the health status requiring discontinuation of the treatment, but no objective evidences are obtained, it should be reported as a symptomatic progression. In addition, the cases with objective progression should be possibly assessed even after the treatment is terminated. Symptomatic deterioration is not an assessment description of objective response, but the reason for the discontinuation of the treatment. In this case, the objective response will be assessed by the target and non-target lesions shown in Tables 1 to 3.

The assessment should be based on the early progression as required by the definition, but early deaths or non-evaluable cases are defined as special cases for studies, which should be specifically described in each of the study protocol (depending on the treatment intervals and cycles).

Sometimes, it may be difficult to distinguish local lesions from normal tissues. When such definition is the basis for the assessment of CR, we recommend a biopsy before evaluating the efficacy by CR of local lesions. When the abnormal imaging results of the local lesions in some subjects are considered as indications for lesion fibrosis or scarring, the FDG-PET should be taken as criteria similar to biopsy, in order to confirm the efficacy by CR. In this case, the application of FDG-PET should be prospectively described in the protocol, and supported by the report of the specialty medical literatures. However, it must be realized that false positive results can be obtained in the CR assessment due to the limitations of FDG-PET and biopsy themselves (including the resolution and sensitivity).

Table 1. Time point efficacy: subjects with target lesions (including or excluding non-target lesions)

Target lesion	Non-target lesion	New Lesion	Overall response
CR	CR	No	CR
CR	Non-CR/non-PD	No	PR
CR	NE	No	PR
PR	Non-progressive or not completely evaluable	No	PR
SD	Non-progressive or not completely evaluable	No	SD
Not completely evaluable	Non-progressive	No	NE
PD	Any	Yes or no	PD
Any	PD	Yes or no	PD
Any	Any	Yes	PD
CR = complete response	PR = partial response	SD = stable disease	PD = progressive disease; NE = non-measurable

Table 2. Time point efficacy: subjects with non-target lesions only

Non-target lesion	New lesion	Overall response
CR	No	CR
Non-CR/non-PD	No	Non-CR/non-PD
Not completely evaluable	No	NE
PD that cannot be determined	Yes or no	PD
Any	Yes	PD

Note: "Non-CR/non-PD" is preferred over SD for non-target disease. Since SD is increasingly used as an endpoint for efficacy evaluation, the efficacy by non-CR/non-PD is determined for cases without specified measurable lesions.

For indefinite progression findings (such as very small and uncertain new lesions; and cystic or necrotic changes in the underlying lesions), the treatment can be continued until the next assessment. If a PD is confirmed in the next assessment, the date when a suspected progression is found previously will be taken as the date of the progression.

Table 3. Optimal overall responses required to be confirmed for efficacy by CR and PR

Overall response at the first time point	Overall response at the subsequent time points	Optimal overall response
CR	CR	CR
CR	PR	SD, PD, or PR[a]
CR	SD	If SD meets the minimum time requirement, it should be the result otherwise PD
CR	PD	If SD meets the minimum time requirement, it should be the result otherwise PD
CR	NE	If SD meets the minimum time requirement, it should be the result otherwise NE
PR	CR	PR
PR	PR	PR
PR	SD	SD
PR	PD	If SD meets the minimum time requirement, it should be the result otherwise PD
PR	NE	If SD meets the minimum time requirement, it should be the result otherwise NE
NE	NE	NE

Note: CR = complete response; PR = partial response; SD = stable disease; PD = progressive disease; NE = non-evaluable. SUP. "a": If CR is definitely confirmed at the first time point, for subjects who are found to have any disease at the subsequent time points, the evaluation results at the subsequent time points should still be PD (due to the recurrence of the disease after CR) even if the PR criteria are met according to the efficacy from the baseline. The optimal response will be determined by whether SD is observed at the minimum treatment interval. The first evaluation result may be CR in some cases, while small lesions are indicated by scanning at the subsequent time points. Consequently, the efficacy in the subjects at the first time point should actually be PR rather than CR. In this case, the initial CR result should be changed to PR, for which the optimal response will be PR.

2.5. Frequency of Tumor Re-Evaluation

The frequency of the tumor re-evaluation during the treatment will be determined according to the treatment regimen while being consistent with the type and schedule of the treatment. For the phase III trial, it is rational to perform a follow-up every 6–9 weeks (the time is designed at the end of a cycle), for which the time interval may be adjusted depending on special protocols or circumstances. In the protocol, it must be specified that which tissue sites are assessed at the baseline level (usually those that are most likely to be closely related to the metastatic lesion of the studied tumor type), along with the frequency to repeat the evaluation. Normally, both the target and non-target lesions should be evaluated in each assessment, while some non-target lesions may be less frequently evaluated under optional circumstances, such as bone scans that are only required when the evaluation of the efficacy by the target disease is confirmed as CR or when a progressive bone disease is suspected.

After treatment, the tumor re-evaluation will be determined by whether the response rate or the time to an event (progression/death) is used as the endpoint of the clinical trial. If the time to an event (such as TTP/DFS[1]/PFS) is used as the endpoint, the routine re-evaluation should be performed as required by the protocol. Especially in randomized comparison studies, pre-defined evaluations should be included in the schedule (e.g., 6–8 weeks during treatment, or 3–4 months after treatment) and not be affected by other factors, such as delayed treatment, dosing intervals, and any other events that may bring imbalanced treatment arms in the timing of disease evaluation.

2.6. Confirmation of Efficacy Evaluation/Response Period

2.6.1. Confirmation

For non-randomized clinical studies with efficacy as the primary endpoint, the efficacy by PR and CR must be confirmed to ensure that the efficacy results are not obtained from inaccurate evaluations. This allows reasonable explanations for the results when the historical data are available, but the efficacy results based on the historical data should also be confirmed. In all other cases, such as randomized trials (phase Ⅱ or Ⅲ) or studies with either SD or PD as the primary endpoint, there are no more requirements for an efficacy confirmation since it is a valueless practice when explaining the trial results. Nevertheless, eliminating the requirement for efficacy confirmation will make the review at the study site even more important in preventing deviations, especially for unblinded studies.

In the case of SD, the measurement that meets the SD criteria specified in the protocol must be obtained at least once in the shortest time interval (generally no shorter than 6–8 weeks) after the start of the study.

2.6.2 Overall response period

The overall response period refers to the time from the first measurement consistent with the criteria for CR or PR (whichever is obtained first) to the time when the recurrence or progression of the disease is firstly recorded (the minimum measurement recorded in the study is used as a reference for determination of PD). The overall response duration refers to the time from the first measurement consistent with the criteria for CR to the time when the recurrence or progression of the disease is firstly recorded.

2.6.3 Stable disease period

The stable disease period refers to the time from the start of the treatment to the occurrence of a PD (which should be started from the time of randomization in randomized trials) while using the minimum sum in the study as a reference (if the baseline sum is the minimum value, it is used as a reference for PD calculation). The clinical association of SD period varies with

different studies and diseases. For a specific trial using the proportion of subjects with SD for a minimum period of time as an endpoint, it should be specified in the protocol that the minimal time interval between two measurements defined by SD.

Note: The DOR and SD as well as the progression-free survival (PFS) are influenced by the frequency of the follow-up after baseline evaluation. It is not in the scope of the guidelines to define a standard follow-up frequency. A number of factors should be considered for the follow-up frequency, such as the type and staging of the disease, treatment cycles, criteria, and specifications. When a comparison across studies is required, the accuracy limitations of the corresponding measurement endpoints should also be considered.

2.7. PFS/TTP

2.7.1. Phase II clinical trial

This guideline is mainly about using objective response as a study endpoint in phase II clinical trial. In some cases, the response rate may not be preferred when evaluating the potential anti-cancer activities of new drugs/new regimens. In such cases, PFS/PPF results at the cut-off time points can be considered as suitable alternative indicators for being the signal source to identify the biological activity of the new drug. However, such evaluations obviously are questionable in an uncontrolled trial given that the seemingly valuable observations may be related to the patient screening and other biological factors rather than the effect of drug intervention. Therefore, it is preferable to have a randomized control designed for the phase II clinical trials using the objective response as endpoint. However, for certain tumors with consistent clinical manifestations (usually in persistent and poor conditions), it is also acceptable to have non-randomized trials. Yet in such cases without a positive control, close attention should be paid to recording for efficacy evidences when assessing the expected PFS or PPF results.

Appendix 4: Immune Response Evaluation Criteria in Solid Tumors (iRECIST)

iRECIST: Efficacy Evaluation Guidelines for Immunotherapy in Clinical Trials (Appendix) (Excerpt)

1. iRECTIST EFFICACY EVALUATION

Immunotherapy may promote the infiltration of immune cells, resulting in a transient increase in tumor volume or enabling falsely undetectable lesions. A large degree of consistency can be found between this version and RECIST v1.1; however, the evaluation of cases that may not reflect the true progression of the tumor, such as increased tumor load or the appearance of new lesions, has been adjusted.

The key differences are explained below. All efficacy indicators evaluated using iRECIST will be prefixed with "i". The efficacy of iRECIST at each time point and the best overall response will be recorded separately.

1.1. Confirmation of Progression

Unlike RECIST v1.1, iRECIST requires confirmation of PD and introduces iUPD (unconfirmed progression) and iCPD (confirmed progression) standards. Scans to confirm progression can be performed as early as 4 weeks after iUPD and no later than 8 weeks after iUPD.

If the tumor load still increases compared with the last measurement result, it is judged as iCPD. For specific evidences, refer to one or more of the following:

- On the basis of PD (compared to the lowest point) of target lesions, non-target lesions or new lesions that meet the definition of RECIST v1.1, the tumor load continues to increase
  - Target lesion deterioration, manifested by an increase in the absolute value of the sum of the measured values by at least 5 mm
  - The progression of non-target lesions is definitive, manifested by increased tumor load
  - The increase of previously discovered new lesions (the absolute value of the sum of the measured values of new target lesions increases by at least 5 mm) or other new lesions are discovered
- Other lesions (target lesions, non-target lesions, or new lesions) with no previous tumor progression are found to meet the RECIST v1.1 progression criteria, including the discovery of other new lesions

If iUPD is not confirmed in the next evaluation, the corresponding efficacy evaluation result will be recorded (if iUPD still meets and does not deteriorate, it will be recorded as iUPD, if it meets the criteria of iSD, iPR or iCR compared to the baseline, it will be recorded as the corresponding result). As shown in Table 2, in the case where iUPD's next efficacy evaluation does not reach iCPD, the previous iUPD does not affect the recording of iCR, iPR, or iSD at a later evaluation time point or at the time of the best overall response.

1.2. New Lesion

New lesions shall be measured and evaluated according to the RECIST v1.1 (up to 5 lesions, no more than 2 per organ, with a longest diameter of at least 10 mm [lymph node lesion with a minimum diameter of at least 15 mm]), and clearly marked as a new ones from previous ones.

New lesions should meet the definition of new target lesions or non-target lesions, and be recorded as iUPD (or iCPD). The measurement of such target lesions should not be calculated as the sum of the measured values of target lesions defined at baseline. The measurement results of these new target lesions should be recorded in a separate CRF.

PD can be confirmed based on the following conditions: An imaging evaluation performed at least 4 weeks (not more than 8 weeks) after iUPD found that the absolute value of the sum of the measured values of the new target lesion increased by at least 5 mm or the new non-target lesion increase in volume (no explicit increase required) or other new lesions appear.

All subjects will define the immune best overall response (iBOR) from the beginning of treatment to the end of treatment according to Table 3.

2. TIME TO RESPONSE AND STABLE DISEASE (RECIST V1.1 and iRECIST)

The time to response will be calculated from the time that the CR/PR or iCR/iPR is met (whichever occurs first) until relapse or a PD is found, and the minimum measurement value (including baseline) during the study period is also recorded as a reference.

The time to SD will be calculated from the time that the SD/PR or iCR/iPR is met (whichever occurs first) until a PD is found, and the minimum measurement value (including baseline) during the study period is also recorded as a reference.

Table 1. RECIST v1.1 and iRECIST

	RECIST v1.1	**iRECIST**
Definitions for measurable and non-measurable lesions; number and location of target lesions	The lesion with the maximum diameter longer than or equal to 10 mm should be defined as a measurable lesion (15 mm for lymph node lesions); up to 5 lesions (2 per organ); other lesions for non-target lesions (the minimum diameter of a lymph node lesion should be ≥ 10 mm)	No change; but the new lesion will be recorded separately in the CRF according to the RECIST v1.1 (the sum of the measured values of the target lesion at baseline is not counted)

	RECIST v1.1	**iRECIST**
CR, PR, or SD	Unrecordable PD before CR, PR, or SD	IUPD (one or more) before iCR, iPR or iSD, but no iCPD
Confirmation of CR or PR	For non-randomized trials only	Same as RECIST v1.1
Confirmation of SD	Not necessary	Same as RECIST v1.1
New lesion	Evaluated as PD while no measurement required	Evaluated as iUPD while recorded as iCPD for the next evaluation if conditions are met • Occurrence of other new lesion or • increased volume of new lesions (the sum of the measured values of new target lesions increased by ≥ 5 mm or any new non-target lesion increased) New lesions that have never been recorded before can also be confirmed as iCPD
Independent blind review and central image acquisition	Recommended in some cases	Recommended in all cases (without independent review)
Confirmation of PD	Not required (unless indefinitive)	Required
Consider the patient's clinical status	Not in the evaluation	Continue the medication after iUPD based on the stability of the patient's clinical status (see definition)

CR: complete response; PR: partial response; SD: stable disease; PD: progressive disease; iCR: immune complete response; iPR: immune partial response; iSD: immune stable disease; iUPD: immune unconfirmed progressive disease; iCPD: immune confirmed progressive disease.

Table 2. iRECIST efficacy records at different evaluation time points

Efficacy evaluation at this time				
Target lesion*	**Non-target lesion***	**New lesion***	**Efficacy evaluation result**	
			Without previous iUPD**	**With previous iUPD**, ***
iCR	iCR	No	iCR	iCR
iCR	Non-iCR/Non-iUPD	No	iPR	iPR
iPR	Non-iCR/Non-iUPD	No	iPR	iPR
iSD	Non-iCR/Non-iUPD	No	iSD	iSD

Efficacy evaluation at this time				
Target lesion*	**Non-target lesion***	**New lesion***	**Efficacy evaluation result**	
			Without previous iUPD**	**With previous iUPD**, *****
iUPD is unchanged or reduced from the last evaluation	iUPD is unchanged or reduced from the last evaluation	Yes	NA	In case of a new lesion which has been diagnosed before or observed with increase (an increase in SOM of ≥ 5 mm or new increase in non-target lesion), it can be confirmed as an iCPD. In case of no changes in a new lesion compared to the lase evaluation (volume or quantity), the new lesion should also be recorded as iUPD
iSD, iPR, iCR	iUPD	No	iUPD	The increase in the volume of non-target lesions (no definitive PD in accordance with RECIST v1.1 is required) can be confirmed as iCPD, otherwise it is still iUPD
iUPD	Non-iCR/Non-iUPD; iCR	No	iUPD	In case of meeting the following conditions, then it is confirmed to be iCPD, otherwise iUPD: • Except for a target lesion with an increase in SOM ≥ 5 mm, the target lesion should also be recorded as iUPD
iUPD	iUPD	No	iUPD	In case of meeting the following conditions, then it is confirmed to be iCPD, otherwise iUPD: • A previous target lesion of iUPD with an increase in SOM of ≥ 5 mm and/or • an increase in non-target lesion of iUPD (previous evaluation — without definitive PD)
iUPD	iUPD	Yes	iUPD	In case of meeting the following conditions, then it is confirmed to be iCPD, otherwise iUPD: • A previous target lesion of iUPD with an increase in SOM of ≥ 5 mm and/or

Efficacy evaluation at this time				
Target lesion*	**Non-target lesion***	**New lesion***	**Efficacy evaluation result**	
			Without previous iUPD**	**With previous iUPD**, *****
				• The non-target lesion of iUPD with an increase in size (definitive PD is not required) and/or • an increase in volume or quantity of a new lesion with history
Non-iUPD/PD	Non-iUPD/PD	Yes	iUPD	In case of meeting the following conditions, then it is confirmed to be iCPD, otherwise iUPD: • an increase in volume or quantity of a new lesion with history
*Refer to the principles in RECIST v1.1. In case of no false progression, the regulations on CR, PR, and SD in RECIST v1.1 are consistent those in iRECIST .** For any type of lesion.*** Found in the most recent assessment before this one.				

iCR: immune complete response; iPR: immune partial response; iSD: immune stable disease; iUPD: immune unconfirmed progressive disease; iCPD: immune confirmed progressive disease; SOM: sum of measured values; NA: not applicable: NE: non-evaluable

Table 3. Best overall response by iRECIST

Best overall response					
Evaluation 1	**Evaluation 2**	**Evaluation 3**	**Evaluation 4**	**Evaluation 5**	**Immune best overall response**
iCR	iCR, iPR, iUPD, NE	iCR, iPR, iUPD, NE	iUPD	iCPD	iCR
iUPD	iPR, iSD, NE	iCR	iCR, iUPD, NE	iCR, iPR, iSD, iUPD, iCPD, NE	iCR
iUPD	iPR	iPR, iSD, iUPD, NE	iPR, iSD, iUPD, NE, iCPD	iPR, iSD, iUPD, NE, iCPD	iPR
iUPD	iSD, NE	iPR	iPR, iSD, iUPD, NE	iPR, iSD, iUPD, iCPD, NE	iPR
iUPD	iSD	iSD, iUPD, NE	iSD, iUPD, iCPD, NE	iSD, iUPD, iCPD, NE	iSD
iUPD	iCPD	Any	Any	Any	iCPD
iUPD	iUPD (without iCPD)	iCPD	Any	Any	iCPD
iUPD	NE	NE	NE	NE	iUPD

- For example only — May be multiple cases following the same principle
- This table is assumed to be following a randomization study design without confirmation of CR or PR
- For subjects with only non-target lesions at baseline, the evaluation at each time point is only recorded as iCR or non-CR/non-PD, but it is not reflected in the table for convenience

iCR: immune complete response; iPR: immune partial response; iSD: immune stable disease; iUPD: immune unconfirmed progressive disease; iCPD: immune confirmed progressive disease; SOM: sum of measured values; NA: not applicable: NE: non-evaluable

Appendix 5: List of Pre-Existed Autoimmune Diseases Prior to Enrollment

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

Autoimmune diseases include but are not limited to:

Acute sporadic encephalomyelitis
IgA nephropathy
Addison's disease
Inflammatory bowel disease
Alopecia
Interstitial cystitis
Ankylosing spondylitis
Myasthenia gravis
Antiphospholipid antibody syndrome
Lupus
Aplastic anemia
Lyme disease (chronic)
Asthma
Meniere's syndrome
Autoimmune hemolytic
Anemia
Corneal ulcer
Autoimmune hepatitis
Localized autoimmune hypophysitis
Multiple sclerosis
Autoimmune hypoparathyroidism
Myasthenia gravis
Autoimmune myocarditis
Neuromuscular ankylosis
Autoimmune ovaritis
Myoclonus syndrome
Autoimmune orchitis
Optic neuritis
Autoimmune thrombocytopenia purpura
Ord's thyroiditis
Bechet disease
Pemphigus
Bullous pemphigoid
Pernicious anemia
Celiac disease
Multiple arteritis
Chronic fatigue syndrome
Polyarthritis
Chronic inflammation demyelinating
Polyneuropathy
Autoimmune syndrome
Churg-Strauss syndrome
Primary biliary cirrhosis
Crohn's disease
Psoriasis dermatomyositis
Rett syndrome
Type I Diabetes
Rheumatoid arthritis
Autonomic dysfunction
Sarcoidosis
Eczema
Scleroderma
Sjogren syndrome
Bullous dermolysis
Stiff-person syndrome
Pemphigus during pregnancy
Takayasu arteritis
Giant cell arteritis
Ulcerative colitis
Pulmonary hemorrhage-glomerulonephritis syndrome
Vitiligo
Graves’ disease
Vogt-Kovanagi-Harada disease
Guillain-Barre syndrome
Vulvodynia
Hashimoto's disease
Wegener's granulomatosis
Kawasaki disease

Appendix 6: Management for irAE

Table 1. Dose adjustments and toxicity management of major potential irAEs

<table>
<tr><th></th><th colspan="2">AE Grade/Dose Adjustments</th><th>Toxicity Management</th></tr>
<tr><td rowspan="5">General principles</td><td colspan="2">AEs are graded according to NCI CTCAE v4.03</td><td rowspan="5">It is recommended to manage irAEs according to the guideline in this table.
− Subjects should be fully evaluated to rule out any alternative causes (e.g., PD, concomitant medication, infection)
− The event is an irAE if there are no clear alternative causes and treatment with corticosteroids is required
− Consider symptomatic and local treatment for low grade events (grade 1 or 2, unless otherwise stated)
− Consider systemic glucocorticoid therapy for persistent low grade events (grades 1–2) or severe events (≥ grade 3)
− If the event re-occurs or worsens during tapering of glucocorticoids, the glucocorticoid dose should be increased until symptoms are stabilized or improved, then tapering with a lower rate
− Once persistent clinical improvement is observed, subjects receiving glucocorticoids IV can start tapering the dose or switch to an equivalent dose of glucocorticoid PO at an earlier time (a lower bioavailability of oral administration should be considered)
− For events that unresponsive to glucocorticoid treatment, consider a stronger immunosuppressants, e.g. TNF blockers (e.g. infliximab) or mycophenolate mofetil, after discussing with the physicians
− For grade 3/4 local inflammation of lesions (such as local pain, irritation, and rash), IBI308 may be continued as determined by the investigator</td></tr>
<tr><td>Grade 1</td><td>No dose adjustments required</td></tr>
<tr><td>Grade 2</td><td>Interrupt
• If worsens, treat as a grade 3/4 event
• If reduces to grades 0–1 or baseline, continue the treatment at the next scheduled date</td></tr>
<tr><td>Grade 3</td><td>Interrupt or permanently discontinue the treatment</td></tr>
<tr><td>Grade 4</td><td>Permanent discontinuation</td></tr>
</table>

	AE Grade/Dose Adjustments		**Toxicity Management**
Pneumonia	Any grade		– Monitor signs and symptoms of pneumonitis or interstitial lung disease (e.g. new shortness of breath, cough, chest pain or exacerbation of existing symptoms and signs), evaluate subjects by imaging, pulmonary function, and other examinations – Initial examination may include clinical evaluation, arterial oxygen saturation, laboratory tests, and high-resolution CT scans
	Grade 1	No dose adjustments required. However, consider interrupting the treatment based on clinical needs and during diagnostic tests for other causes	For grade 1 events: – Monitor signs and symptoms and arterial oxygen saturation for 2–4 days – Perform other laboratory tests if clinically indicated – Consider consulting a respirologist and infectious diseases specialist
	Grade 2	Interrupt • If worsens, treat as a grade 3/4 event • If reduces to grades 0–1 or baseline, continue the treatment at the next scheduled date	For grade 2 events: – Monitor signs and symptoms daily, consider hospitalization – Discuss with the sponsor's medical manager, and consider systemic glucocorticoid treatment – Repeat imaging if clinically indicated – If no improvement is seen within 3–5 days, consider other tests and increasing the glucocorticoid dose – If no improvement is seen within 3–5 days, consider a stronger immunosuppressant (e.g. infliximab) – Once improved, taper glucocorticoids within ≥ 4 weeks, and consider prophylactic antibiotics – Consider consulting a respirologist and infectious diseases specialist

	AE Grade/Dose Adjustments		Toxicity Management
	Grade 3 or Grade 4	Permanent discontinuation	For grade 3–4 events: – Discuss with the sponsor's medical manager – Consider consulting a respirologist and infectious diseases specialist – Hospitalization – Supportive care (oxygen) – Begin systemic glucocorticoid treatment based on experience – If no improvement is seen within 3–5 days, consider other tests and stronger immunosuppressants (e.g. infliximab) – Once improved, taper glucocorticoids within ≥ 4 weeks, and consider prophylactic antibiotics
Diarrhea or Enterocolitis	Any grade		– Monitor possible signs and symptoms related to diarrhea/enterocolitis (abdominal pain, enterospasm, changes in bowel habits, melena, mucous stool, bloody stool, or muscle guarding) – Subjects should be fully evaluated to rule out any alternative causes (e.g., PD and infection) – If alternative causes cannot be determined, consider glucocorticoid treatment for low grade events to prevent from escalating to high grade – Use analgesics with caution (may mask the symptoms of perforation and peritonitis)
	Grade 1	No dose adjustments required	For grade 1 events: – Closely monitor symptom exacerbation – Consider symptomatic treatment, including fluid replacement, electrolyte replacement, diet modifications, and loperamide administration
	Grade 2 or 3	Interrupt • If worsens, treat as a	For grade 2–3 events: – Consider symptomatic treatment, including fluid replacement, electrolyte replacement, diet modifications, and

	AE Grade/Dose Adjustments		Toxicity Management
		grade 3/4 event • If reduces to grades 0–1 or baseline, continue the treatment at the next scheduled date	loperamide and/or budesonide administration – If the event persists for > 3–5 days or worsens, consider systemic corticosteroid treatment – If no improvement is seen within 3–5 days, consider other tests and increasing the glucocorticoid dose – If no improvement is seen or exacerbation occurs within 3–5 days, consider other tests and stronger immunosuppressants (e.g. infliximab) – If not reduces to grade ≤ 1 within 3–4 days, discuss with the sponsor's medical manager – Once improved, taper glucocorticoids within ≥ 4 weeks, and consider prophylactic antibiotics
	Grade 4	Permanent discontinuation	For grade 4 events: – Monitor frequency and volume of bowel movement, maintain hydration – If applicable, perform emergency GI consultation and lower GI endoscopy and imaging to confirm the presence of intestinal perforation – Begin systemic glucocorticoid treatment based on experience – If no improvement is seen within 3–5 days, consider increasing the glucocorticoid dose – If no improvement is seen within 3–5 days, consider other immunosuppressants (e.g. infliximab, but not in subjects with perforations or sepsis) – Once improved, taper glucocorticoids within ≥ 4 weeks, and consider prophylactic antibiotics

	AE Grade/Dose Adjustments		Toxicity Management
Hepatitis (ALT, AST, or TBIL increased)	Any grade		– Closely monitor hepatitis-related signs and symptoms (e.g., jaundice, tea-colored urine, nausea, emesis, loss of appetite, hepatalgia, and hemorrhagic tendency) – Monitor and evaluate hepatic function – Evaluate alternative causes (e.g. viral hepatitis, PD, concomitant medication) – The dose adjustments and toxicity management in this table are applicable only to subjects with normal ALT, AST, and TB at baseline; for subjects with ALT, AST, or TB > ULN at baseline, interrupt the drug if ALT, AST, or TB elevation of ≥ 50% for < 7 days and discontinue permanently if ALT, AST, or TB elevation of ≥ 50% for ≥ 7 days. Toxicities should be managed based on the investigator's clinical judgment
	Grade 1	No dose adjustments required	For grade 1 events: – Continue monitoring hepatic function according to protocol
	Grade 2	Interrupt • If worsens, treat as a grade 3/4 event • If reduces to grades 0–1 or baseline, continue the treatment at the next scheduled date	For grade 2 events: – If not reduces to grade ≤ 1 within 3–4 days, discuss with the sponsor's medical manager – For ALT, AST, or TBIL elevations, retest hepatic function within 3–4 days and increase monitoring frequency – If the event persists for > 3–5 days or worsens, consider systemic corticosteroid treatment – If no improvement is seen within 3–5 days, consider other tests and increasing the glucocorticoid dose – If no improvement is seen within 3–5 days, consider stronger immunosuppressants (e.g. mycophenolate mofetil)

	AE Grade/Dose Adjustments		Toxicity Management
			– Once improved, taper steroids within ≥ 4 weeks, and consider prophylactic antibiotics
	Grade 3 or 4	Permanent discontinuation	For grade 3–4 events: – Discuss with the sponsor's medical manager – Begin systemic glucocorticoid treatment based on experience – If no improvement is seen within 3–5 days, consider stronger immunosuppressants (e.g. mycophenolate mofetil) – If no improvement is seen within 3–5 days, consider other immunosuppressants based on local guidelines – If applicable, consult a gastroenterologist, perform abdominal examination and imaging – Once improved, taper glucocorticoids within ≥ 4 weeks, and consider prophylactic antibiotics
Dermatitis	Any grade		– Monitor signs and symptoms or dermatitis, e.g. rash, exudation, hypopigmentation, photaesthesia, and pruritus – If there is formation of bullae, contact the sponsor's medical manager – Consult a dermatologist – Perform skin biopsy when necessary
	Grade 1	No dose adjustments required	For grade 1 events: – Consider symptomatic treatment, including oral antipruritic agents (e.g. diphenhydramine or hydroxyzine) and local treatment (e.g. urea cream or topical glucocorticoids)
	Grade 2	No dose adjustments required • For a refractory (> 1–2 weeks) grade 2 event,	For grade 2 events: – Consider symptomatic treatment including oral antipruritic agents and

	AE Grade/Dose Adjustments		Toxicity Management
		interrupt until reduces to grades 0–1 or baseline, continue the treatment at the next scheduled date	local treatment – Consider a medium-potency topical glucocorticoid – If no improvement or deterioration is seen with 3–5 days, discuss with the sponsor's medical manager and consider systemic glucocorticoid treatment – Consult a dermatologist – Consider skin biopsy if persists for > 1–2 weeks or relapses – Once improved, taper glucocorticoids within ≥ 4 weeks, and consider prophylactic antibiotics
	Grade 3	Interrupt • If worsens, treat as a grade 4 event • Permanently discontinue if a grade 3 rash does not reduce to grades 0–1 or baseline within 30 days	For grade 3–4 events: – Discuss with the sponsor's medical manager – Consider hospitalization – Monitor affected area (rule of nine) – Consult a dermatologist – If clinically feasible, consider skin biopsy (preferably more than once) – Begin systemic glucocorticoid treatment based on experience – If no improvement is seen within 3–5 days, consider other tests and increasing the glucocorticoid dose – Once improved, taper glucocorticoids within ≥ 4 weeks, and consider prophylactic antibiotics
	Grade 4	Permanent discontinuation	
Hypopituitarism	All grades		– Monitor signs and symptoms of endocrine disorders, including weakness, fatigue, drowsiness, nausea, emesis, chills, changes in bowel habits, behavioral changes, mental state changes, hypotension, hypoglycemia, dizziness, headache, impaired vision, low libido in males, irregular menstruation in females – Subjects should be fully evaluated to rule out any alternative causes (e.g., PD, brain

	AE Grade/Dose Adjustments		Toxicity Management
			metastasis, and infection) – Monitor and evaluate pituitary function: TSH, FT3, FT4, adrenocorticotropic hormone, cortisol, luteinizing hormone, follicle stimulating hormone, growth hormone, prolactin, Na^+, blood glucose, estradiol, testosterone, and other laboratory parameters related to endocrine disorders. Perform functional tests when necessary (including adrenocorticotropic hormone [ACTH] stimulation test and insulin-induced hypoglycemia test) – Consider pituitary MRI – Consider consulting an endocrinologist – Consider testing for autoantibodies
	Grade 1	No dose adjustments required	For grade 1 events: – Monitor pituitary function – Subjects should be fully evaluated to rule out any alternative causes – Consider consulting an endocrinologist based on clinical indications
	Grade 2	Interrupt • If worsens to grades 3–4, permanently discontinue • If reduces to grades 0–1 or baseline, continue the treatment at the next scheduled date	For grade 2–4 events: – Discuss with the sponsor's medical manager – Consult an endocrinologist – Hospitalization when necessary – Evaluate endocrine function, consider pituitary MRI if clinically indicated – Begin hormone replacement therapy when necessary (cortisone replacement therapy should begin one week prior to levothyroxine treatment) – Begin immunosuppressive therapy based on experience, consider systemic glucocorticoid treatment – Once improved, taper glucocorticoids within ≥ 4 weeks (the dose of cortisone used for hormone replacement may be adjusted accordingly, but subjects whose endocrine function do not recover require
	Grade 3 or 4	Permanent discontinuation	

	AE Grade/Dose Adjustments		Toxicity Management
			long-term treatment); consider prophylactic antibiotics when tapering to prevent opportunistic infections
Adrenal insufficiency	Any grade		– Monitor signs and symptoms of endocrine disorders, including fatigue, pigmentation, loss of appetite, hypotension, and weakness – Subjects should be fully evaluated to rule out any alternative causes – Monitor and evaluate adrenal function: cortisol, adrenocorticotropic hormone, blood sodium, blood potassium, blood glucose, and other endocrine laboratory indexes suspected to be related to adrenal function. The ACTH stimulation test should be performed when necessary – Immunosuppressive therapy when necessary – Hormone replacement therapy (cortisone) when necessary – Consider consulting an endocrinologist – Consider testing for autoantibodies
	Grade 1	No dose adjustments required	For grade 1 events: – Monitor adrenal function – Consider consulting an endocrinologist based on clinical indications
	Grade 2	Interrupt • If worsens to grade 3 or 4, permanently discontinue • If reduces to grades 0–1 or baseline, continue the treatment at the next scheduled date	For grade 2 events: – Discuss with the sponsor's medical manager – Evaluate adrenal function, begin hormone replacement therapy when necessary

	AE Grade/Dose Adjustments		Toxicity Management
	Grade 3 or Grade 4	permanent discontinuation	For grade 3–4 events: – Discuss with the sponsor's medical manager – Consult an endocrinologist – Consider systemic corticosteroid treatment – Begin corticosteroids with mineralocorticoid activity immediately for adrenal crisis, severe dehydration, hypotension, or shock – Once improved, taper glucocorticoids within ≥ 4 weeks (the dose of cortisone used for hormone replacement may be adjusted accordingly, but subjects whose endocrine function do not recover require long-term treatment); consider prophylactic antibiotics when tapering to prevent opportunistic infections
Hyperthyroidism/ hypothyroidism	Any grade		- Monitor signs and symptoms of thyroid dysfunction, e.g. hyperthyroidism (palpitations, sweating, increased appetite and bowel movement, and weight loss) and hypothyroidism (general weakness, fatigue, cold, memory loss, and constipation) - Subjects should be fully evaluated to rule out any alternative causes - Monitor and evaluate thyroid function - Consider consulting an endocrinologist - Consider testing for thyroid autoantibodies (antithyroglobulin antibodies, anti-thyroid peroxidase antibodies, and thyroid-stimulating hormone receptor antibodies)
	Grade 1 or 2	No dose adjustments required	For grade 1-2 events: - Monitor thyroid function and thyroid autoantibodies regularly - L-thyroxine replacement therapy or anti-thyroid medications when necessary

	AE Grade/Dose Adjustments		Toxicity Management
	Grade 3 or 4	Hyperthyroidism • Permanent discontinuation Hypothyroidism • No dose adjustments required	For grade 3–4 events: – Discuss with the sponsor's medical manager – Monitor thyroid function and thyroid autoantibodies – Consult an endocrinologist *Hyperthyroidism* – Anti-thyroid medications – Consider β-blockers for tachycardia *Hypothyroidism* – L-thyroxine replacement therapy
Type I Diabetes	Any grade		– Monitor signs and symptoms closely, e.g. polyuria, polydipsia, polyphagia, fatigue, weakness, and weight loss – Subjects should be fully evaluated to rule out any alternative causes – Monitor and assess pancreas islet function: blood glucose, insulin, c-peptide, β-cell autoantibodies, blood ketones, and other endocrine laboratory parameters related to type I diabetes
	Grade 1 or 2	No dose adjustments required	For grade 1-2 events: – Monitor and assess pancreas islet function – Start insulin therapy when necessary
	Grade 3	Interrupt • Resume treatment after blood glucose is under control	For grade 3–4 events: – Consult with the sponsor's medical manager – Monitor and assess pancreas islet function – Consider consulting an endocrinologist – Blood glucose control with insulin, adjust insulin dose accordingly – If ketoacidosis occurs, subjects should be hospitalized to receive insulin, fluid replacement, and alkali therapy
	Grade 4	Permanent discontinuation	

	AE Grade/Dose Adjustments		Toxicity Management
Renal Insufficiency (Creatinine Elevated)	Any grade		– Monitor signs and symptoms closely (e.g. oliguria, dark urine, anemia, fatigue, and weight loss) – Subjects should be fully evaluated to rule out any alternative causes – Monitor and evaluate renal function – Consider consulting a nephrologist – Consider kidney biopsy when necessary to distinguish between inflammatory and non-inflammatory causes
	Grade 1	No dose adjustments required	For grade 1 events: – Monitor creatinine levels Q1W – If creatinine level returns to baseline level, resume routine creatinine monitoring according to the study protocol
	Grade 2 or 3	Interrupt • If reduces to grades 0–1, continue the treatment at the next scheduled date • If persists for > 7 days or worsens, treat as a grade 4 event	For grade 2–3 events: – Discuss with the sponsor's medical manager – Monitor creatinine levels every 2–3 days – Begin systemic glucocorticoid treatment based on experience – If reduces to grade 1, taper glucocorticoid for at least 1 month**,** consider prophylactic antibiotic to prevent infections – Consider kidney puncture biopsy – Consult a nephrologist
	Grade 4	Permanent discontinuation	For grade 4 events: – Discuss with the sponsor's medical manager – Monitor creatinine levels once daily – Begin systemic glucocorticoid treatment based on experience – If reduces to grade 1, taper glucocorticoid for at least 1 month**,** consider prophylactic antibiotic to prevent infections – Consult a nephrologist – Consider kidney puncture biopsy

	AE Grade/Dose Adjustments		Toxicity Management
Immune-related neurotoxicities (except for myasthenia gravis and Guillain-Barre syndrome)	Any grade		− Monitor the subject's systemic symptoms (headache, nausea, dizziness, behavioral changes, or weakness) − Subjects should be fully evaluated to rule out any alternative causes (e.g., PD, infection, metabolic syndrome, and medications) − Consider appropriate diagnostic tests (e.g. electromyography and nerve conduction study) − If applicable, begin symptomatic treatment and consult a neurologist
	Grade 1	No dose adjustments required	− Closely monitor signs and symptoms
	Grade 2	Interruption • If reduces to grades 0–1, continue the treatment at the next scheduled date • If worsens, treat as a grade 3 event	For grade 2–4 events: − Discuss with the sponsor's medical manager − Consider consulting a neurologist − Hospitalization when necessary − Manage neuropathy and neuropathic pain with appropriate medications (e.g. gabapentin, duloxetine, etc) − Consider systemic corticosteroid treatment − If no improvement is seen within 3–5 days, consider other tests and immunosuppressants (e.g., intravenous immunoglobulin G, IVIgG) − Once stabilized, taper glucocorticoids within ≥ 4 weeks
	Grade 3 Grade 4	Permanent discontinuation	
Immune-related peripheral neuropathy, e.g. Guillain-Barré syndrome and myasthenia gravis	Any grade		− Monitor signs and symptoms closely (myasthenia gravis: eye or limb soreness and discomfort, blurred vision, fatigue, which worsens as the day goes on; Guillain-Barrésyndrome: sudden and severe nerve pain, paralysis of the limbs, and prickling or burning sensation in the limbs) − Timely diagnosis of immune-related peripheral neuropathy is very important,

	AE Grade/Dose Adjustments		Toxicity Management
			as subjects may suffer from unpredictable acute compensation, which may lead to severe disease or death.Pay special attention to signs and symptoms that may indicate serious consequences, e.g. significant dysphagia, rapidly progressive weakness, respiratory insufficiency, or autonomic dysfunction – Neuroelectrophysiological tests should be performed to rule out any alternative causes (e.g., PD, infection, metabolic syndrome, and medications). It is worth noting that cancer itself and cancer treatment can affect neural function. The diagnosis of immune-related peripheral neuropathies is thus difficult. Neurological consultation should be actively carried out – Plasmapheresis or IVIgG should be considered for subjects with Guillain-Barrésyndrome (glucocorticoids are generally ineffective)
	Grade 1	No dose adjustments required	For grade 1 events: – Discuss with a physician – Monitor signs and symptoms – Consider consulting a neurologist
	Grade 2	Interruption • If reduces to grades 0–1, continue the treatment at the next scheduled date • If worsens, treat as a grade 3–4 event	For grade 2–4 events: – Discuss with the sponsor's medical manager – Monitor signs and symptoms – Consult a neurologist – Hospitalization when necessary – Manage neuropathy and neuropathic pain with appropriate medications (e.g., gabapentin and duloxetine) *Myasthenia gravis* – Glucocorticoids may be used to treat myasthenia gravis (should be used under the supervision of a neurologist since corticosteroids, especially high-dose, may
	Grade 3 or 4	Permanent discontinuation	

	AE Grade/Dose Adjustments		Toxicity Management
			result in initial deterioration of symptoms) – Subjects intolerant to glucocorticoids may be treated with plasmapheresis or IVIgG – For myasthenia gravis-like neurotoxicities, consider acetylcholinesterase inhibitors in addition to glucocorticoids *Guillain-Barre syndrome* – Plasmapheresis or IVIgG should be considered for subjects with Guillain-Barrésyndrome (glucocorticoids are generally ineffective)

Table 2. Dose adjustments and toxicity management of other potential irAEs

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

***Note: For laboratory abnormalities, the event should be determined based on clinical signs/symptoms and the clinical judgment of the investigator**

Table 3. Dose adjustments and toxicity management of infusion reactions

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