CLINICAL STUDY PROTOCOL

Study Title:	A Randomized, Double-Blind, Phase III Study to Compare the Efficacy and Safety of IBI308 in Combination with Gemcitabine and Platinum-Based Chemotherapy Vs. Placebo in Combination with Gemcitabine and Platinum-Based Chemotherapy in the First-Line Treatment for Patients with Advanced or Metastatic Squamous Non-Small Cell Lung Cancer (ORIENT-12)
Protocol Number:	CIBI308C303
Version and Date:	Nov. 27, 2019/Version 2.3
Product Name:	Sintilimab (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 + 86 021-31652896 hui.zhou@innoventbio.com

Sponsor's Signature Page

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Project Number: CIBI308C303

Title	Name (regular script)	Signature	Date
Vice President of Medical Science and Strategic Oncology Department	Zhou Hui		
Senior Biostatistics Director	Sun Xing		

Protocol Synopsis

Protocol no.	CIBI308C303
Sponsor	Innovent Biologics (Suzhou) Co., Ltd.
Investigational drug	IBI308
Active ingredient	Recombinant fully human anti-PD-1 monoclonal antibody
Study title	A Randomized, Double-Blind, Phase III Study to Compare the Efficacy and Safety of IBI308 in Combination with Gemcitabine and Platinum-Based Chemotherapy Vs. Placebo in Combination with Gemcitabine and Platinum-Based Chemotherapy in the First-Line Treatment for Patients with Advanced or Metastatic Squamous Non-Small Cell Lung Cancer (ORIENT-12)
Study phase	Phase III
Expected study duration	Approximately 23 months
Study objectives	Primary objective: • To compare the progression free survival (PFS) of patients with advanced or metastatic squamous non-small cell lung cancer (NSCLC) receiving IBI308 in combination with gemcitabine and platinum-based chemotherapy vs. placebo in combination with gemcitabine and platinum-based chemotherapy as first-line treatment based on the "Response Evaluation Criteria in Solid Tumors" (RECIST, V1.1). Secondary objectives: • To compare the overall survival (OS) between the two groups; • To compare the objective response rate (ORR) between the two groups based on RECIST V1.1; • To compare the disease control rate (DCR) between the two groups based on RECIST V1.1; • To compare the time to response (TTR) between the two groups based on RECIST V1.1; • To compare the duration of response (DOR) between the two groups based on RECIST V1.1; • To evaluate the safety and tolerability characteristics of IBI308 in combination with gemcitabine and platinum-based chemotherapy. Exploratory objectives: • To explore potential biomarkers in tumor tissues that can predict the efficacy of IBI308, including but not limited to immunohistochemistry assay of programmed cell death ligand 1 (PD-L1) expression and RNA assay in tumor samples;

	• To explore potential biomarkers in peripheral blood that can predict the efficacy of the IBI308 group, including but not limited to the T-cell receptor (TCR) and circulating tumor DNA (ctDNA) assay; • To compare the quality of life of patients treated with IBI308 in combination with chemotherapy vs. placebo in combination with chemotherapy by using the "Lung Cancer Symptom Scale" (LCSS) and "European Organization for Research and Treatment of Cancer Quality of Life Questionnaire" (EORTC QLQ-C30); • To explore the PFS of subjects in the control group after crossover treatment with IBI308; • To explore the population PK characteristics of IBI308.
Study design	This is a randomized, double-blind, multi-center, phase III study to compare the efficacy and safety of IBI308 in combination with gemcitabine and platinum-based (cisplatin or carboplatin) chemotherapy vs. placebo in combination with gemcitabine and platinum-based (cisplatin or carboplatin) chemotherapy in first-line treatment of previously untreated Chinese subjects with advanced or metastatic squamous NSCLC. Subjects in this study will receive treatment with either IBI308 in combination with gemcitabine and platinum (cisplatin or carboplatin) or placebo in combination with gemcitabine and platinum (cisplatin or carboplatin) for 4 or 6 cycles, followed by maintenance therapy with IBI308 or placebo, respectively, until progressive disease (PD), intolerable toxicity, initiation of new anti-tumor therapy, withdrawal of informed consent form (ICF), loss to follow-up, death, or other conditions requiring treatment discontinuation as judged by the investigator, whichever occurs first. The maximum duration of treatment with IBI308 is 24 months. In this study, a total of 348 previously untreated subjects with advanced or metastatic squamous NSCLC will be randomized in a 1:1 ratio to the test group and the control group, 174 subjects in the test group and 174 subjects in the control group (in the actual study, if the actual number of enrolled subjects is different from the number of planned enrollment due to unforeseen reasons, such as the enrollment speed faster than the requirements of the protocol, the end date of screening should be determined in advance to ensure that the number of actually enrolled subjects does not exceed the number of planned enrollment by 10%, i.e., a maximum of 382 subjects should be enrolled, 191 in each group). Randomization stratification factors include staging (stage IIIB/IIIC vs. stage IV), platinum-based medications (cisplatin vs. carboplatin), and PD-L1 expression level (< 1% vs. ≥ 1%). The primary study endpoint is PFS assessed by the Independent Radiographic Review Committee (IRRC) based on RECIST V1.1. An interim analysis will be performed during the study and the results and reports will be submitted to the Independent Data Monitoring Committee (IDMC), which will judge whether the trial is valid according to the estimated valid cut-off value and give advice to the sponsor on whether the study data can be submitted in advance. The IDMC charter will be finalized and approved by IDMC and sponsor prior to the interim analysis. The responsibilities of IDMC members and associated procedures will be defined in the IDMC charter.

Sample estimation	IBI308 is expected to prolong PFS of subjects from 5.5 months to 7.9 months (HR = 0.7). With the enrollment time of 15 months, the total study time of 23 months, power of 82%, one-sided $\alpha = 0.025$ and considering a monthly dropout rate of 0.5%, a total of 348 subjects (174 in the test group and 174 in the control group) are needed to be randomized to achieve the 264 PFS events required in the trial. In the actual study, if the actual number of enrolled subjects is different from the number of planned enrollment due to unforeseen reasons, such as the enrollment speed faster than the requirements of the protocol, the end date of screening should be determined in advance to ensure that the number of actually enrolled subjects does not exceed the number of planned enrollment by 10%, i.e., a maximum of 382 subjects should be enrolled, 191 in each group. An interim analysis will be performed when 70% of PFS events (i.e., 185 PFS events) occur. Superiority in efficacy of the test group over the control group will be determined using Lan-deMets spending function and O'Brien-Fleming boundary in the interim analysis. One-sided P value for the interim analysis is 0.0074. If the actual interim analysis time point in the study differs from the planned (185 PFS events), the P value for the interim analysis should be adjusted according to the Lan-deMets spending function and O'Brien-Fleming. Final PFS analysis is expected to be performed about 8 months after enrollment of the last subject. If the interim analysis results fail to reach statistical significance, and the PFS events at the final analysis are significantly more than the estimated, the P value of the final analysis will be recalculated using the Flexible spending function according to the α value actually spent in the interim analysis, so as to ensure that the overall type I error is controlled at a one-sided level of 0.025. In the interim analysis, with one-sided $\alpha = 0.0074$, if HR $\leq$ 0.698 is observed for the test group of IBI308 in combination with gemcitabine and cisplatin or carboplatin chemotherapy vs. the control group of placebo in combination with gemcitabine and cisplatin or carboplatin chemotherapy, it is demonstrated that the superiority has been concluded in the interim analysis. For the secondary endpoint OS, no formal sample size calculation will be made, and the analysis is expected to be performed 1 year after the last subject is enrolled. This study is expected to be conducted in 30–40 sites of China.
Inclusion criteria	1) Sign the written informed consent form (ICF) prior to any trial-related procedure; 2) Aged $\geq$ 18 years and $\leq$ 75 years; 3) With a life expectancy of more than 3 months; 4) With at least one measurable lesion confirmed by the investigator according to RECIST V1.1. Measurable lesions located in the radiation field of previous radiotherapy or subjected to locoregional therapy can be selected as target lesions if PD is confirmed; 5) Patients with histologically or cytologically confirmed locally advanced (stage IIIB/IIIC), metastatic or recurrent (stage IV) squamous NSCLC who cannot receive surgery or radical concurrent chemoradiotherapy, based on the "8th Edition of the TNM Classification for Lung Cancer" issued by the International Association for the Study of Lung Cancer and the American Joint Committee on Cancer Classification; 6) With an Eastern Cooperative Oncology Group Performance Status score (ECOG PS score) of 0 or 1;

	7) Have not received any prior systemic anti-tumor therapy for advanced/metastatic disease; for patients who have received prior platinum-based adjuvant chemotherapy/radiotherapy, neoadjuvant chemotherapy/radiotherapy, or radical chemoradiotherapy for PD, they are eligible for the study if PD occurs at > 6 months after the last treatment; 8) With adequate hematologic function, defined as ANC ≥ 1.5×10^9 /L, platelet count ≥ 100×10^9 /L, and hemoglobin ≥ 90 g/L (no blood transfusion history within 7 days); 9) With adequate hepatic function, defined as TBIL level ≤ 1.5 × upper limit of normal (ULN) and aspartate amino transferase (AST) and alanine transaminase (ALT) levels ≤ 2.5 × ULN for all patients, or AST and ALT levels ≤ 5 × ULN for patients with liver metastases; 10) With adequate renal function, defined as clearance of creatinine (CCr) ≥ 50 mL/min (Cockcroft-Gault formula); 11) With adequate coagulation function, defined as international normalized ratio (INR) or prothrombin time (PT) ≤ 1.5 × ULN; for subjects receiving anticoagulant therapy, INR/PT within the range proposed for anticoagulant drugs is acceptable; 12) Female subjects of childbearing age should be tested negative for urine or serum pregnancy within 3 days before the first dose of the study drugs. A blood pregnancy test is required if the urine pregnancy test is inconclusive; 13) For male and female patients at risk of conception, highly effective contraception measures (failure rate < 1% per year) should be taken until at least 180 days after discontinuation of the study treatment; Note: Abstinence is acceptable as a method of contraception if it is the usual lifestyle and preferred method of contraception for the subject.
Exclusion criteria	1) Non-squamous NSCLC in histology. The dominant cell morphology must be identified for mixed cell type (patients with squamous cell carcinoma components > 50% can be enrolled); patients with small cell carcinoma, neuroendocrine carcinoma, and sarcoma components cannot be included; 2) Patients with known epidermal growth factor receptor (EGFR)-sensitive mutation or anaplastic lymphoma kinase (ALK) rearrangement; 3) Currently participating in an interventional clinical study, or treated with another study drug or investigational device within 4 weeks before the first dose; 4) Previously received the following therapies: anti-PD-1, anti-PD-L1, or anti-PD-L2 agents or agents targeting another stimulation or synergistically inhibiting T-cell receptor (TCR) (e.g., CTLA-4, OX-40, and CD137); 5) Received proprietary Chinese medicines with anti-tumor indications or immunomodulators (thymosin, interferon, interleukin, etc.) within 2 weeks prior to the first dose, or received a major surgery within 3 weeks prior to the first dose; 6) With active hemoptysis, active diverticulitis, abdominal abscess, gastrointestinal obstruction, and peritoneal metastases requiring clinical intervention; 7) Have undergone solid organ transplantation or hematologic transplantation;

	8) With clinically uncontrolled pleural effusion/ascites (patients who do not need effusion drainage or have no significant increase in effusion 3 days after stopping drainage can be enrolled); 9) With a tumor compressing the surrounding important organs (such as esophagus) with relevant symptoms, compressing the superior vena cava, or invading the mediastinal great vessels, heart, etc.; 10) With Class III–IV congestive cardiac failure (based on New York Heart Association Classification) or poorly controlled and clinically significant arrhythmia; 11) With any arterial thrombosis, embolism, or ischemia within 6 months prior to enrollment, such as myocardial infarction, unstable angina, cerebrovascular accident, and transient ischemic attack. With a history of deep venous thrombosis, pulmonary embolism, or any other serious thromboembolic events within 3 months prior to enrollment (implantable port or catheter-related thrombosis, or superficial venous thrombosis is not considered as "serious" thromboembolism); 12) With known allergy to the active ingredients and/or any excipient of IBI308, gemcitabine, cisplatin, or carboplatin; 13) With active autoimmune disease requiring systemic treatment (e.g., use of disease-modifying drugs, corticosteroids, or immunosuppressive agents) within 2 years before the first dose. Replacement therapy (e.g., thyroxine, insulin, or physiologic doses of corticosteroids for adrenal or pituitary insufficiency) is not considered systemic; 14) Patients requiring long-term systemic use of corticosteroids. Patients requiring intermittent use of bronchodilators, inhaled corticosteroids, or local injection of corticosteroids for COPD or asthma can be included in the study; 15) Full recovery (i.e., ≤ grade 1 or reaching the baseline, excluding asthenia or alopecia) from toxicity and/or complications caused by any intervention has not achieved before the start of treatment; 16) Diagnosed with other malignant tumors within 5 years before the first dose, excluding radically cured cutaneous basal cell carcinoma, cutaneous squamous cell carcinoma, and/or radically resected carcinoma *in situ*. For other malignant tumors or lung cancer diagnosed more than 5 years before the first dose, pathological or cytological diagnosis should be performed for recurrent and metastatic lesions; 17) Symptomatic central nervous system (CNS) metastasis. Patients 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 of the following criteria: presence of measurable lesions outside the CNS; absence of metastases in midbrain, pons, cerebellum, meninges, medulla oblongata, or spinal cord; maintain clinical stable condition for at least 2 weeks; discontinue hormone therapy 14 days prior to the first dose of the study drugs; 18) With a history of non-infectious pneumonia requiring corticosteroid therapy within 1 year prior to the first dose or with non-infectious pneumonia at present; 19) With an active infection requiring treatment or have used systemic anti-infective drugs within one week prior to the first dose;

	20) With known psychiatric disorder or substance abuse that could affect the compliance with trial requirements; 21) With a known history of human immunodeficiency virus (HIV) infection (i.e., HIV 1/2 antibody positive), known syphilis infection (syphilis antibody positive), and active pulmonary tuberculosis; 22) With untreated active hepatitis B; Note: Subjects with hepatitis B who meet the following criteria are also eligible for inclusion: Hepatitis B virus (HBV) load must be less than 1000 copies/mL (200 IU/mL) or below the lower limit of detection (LLD) prior to the first dose, and subjects should receive anti-HBV treatment to avoid virus reactivation throughout the chemotherapeutic period of the study; For subjects with HBcAb (+), HBsAg (−), HBsAb (−), and HBV load (−), close monitoring is required instead of prophylactic anti-HBV treatment to avoid virus reactivation; 23) Subjects with active hepatitis C virus (HCV) infection (HCV antibody positive and HCV-RNA level above the LLD); 24) Have received live vaccines within 30 days prior to the first dose; Note: Seasonal inactivated influenza virus vaccines for injection are allowed, while live attenuated influenza vaccines for intranasal use are not acceptable; 25) With any medical history, disease, treatment, or laboratory abnormal finding that would interfere with the trial results or prevent the subject from participating in the whole trial, or the investigator believes that participation in this study is not in the best interest of the subject; 26) With local or systemic diseases not attributable to malignancy, or with cancer-related secondary diseases, which would result in a high medical risk and/or uncertainty in survival evaluation.
Study drugs and administration	1. IBI308: 10 mL:100 mg, 200 mg, IV infusion on day 1, Q3W. 2. IBI308 placebo: 10 mL/vial, 2 vials, IV infusion on day 1, Q3W. 3. Gemcitabine: 200 mg/vial or 1 g/vial, 1 g/m^2, IV infusion on day 1 and day 8, Q3W. 4. Cisplatin: 20 mg/vial, 75 mg/m^2, IV infusion on day 1, Q3W. 5. Carboplatin: AUC 5 mg/mL/min, IV infusion on day 1, Q3W.
Evaluation criteria	**Efficacy evaluation:** • Efficacy evaluation is based on RECIST V1.1. PFS, OS, ORR, TTR, DOR, and DCR after administration will be evaluated. **Safety evaluation:** • Incidence, relationship with the investigational drug, and severity level of all adverse events (AEs), treatment related adverse events (TRAEs), immune related adverse events (irAEs), and serious adverse events (SAEs);

	• Number of subjects discontinuing study treatment due to the above AEs; • Positive rates of anti-drug antibodies (ADAs) and neutralizing antibodies (NAbs); • Changes in vital signs, physical examination, and laboratory tests results before, during, and after the study treatment will be evaluated.
Statistical methods	The primary objective of this study is to confirm that compared with placebo in combination with gemcitabine and cisplatin or carboplatin chemotherapy, IBI308 in combination with gemcitabine and cisplatin or carboplatin chemotherapy can prolong the progression free survival (PFS). The primary endpoint PFS is analyzed at approximately 23 months after the start of the trial (i.e., at the end of the study, expected to be at approximately 8 months after randomization of the last subject). An interim analysis will be performed when 70% of PFS events (i.e., 185 PFS events) occur. In order to strictly control the overall type I error rate at a one-sided level of 0.025, superiority in efficacy of the test group over the control group will be determined using Lan-deMets spending function and O'Brien-Fleming boundary in the interim analysis. One-sided P value for the interim analysis is 0.0074. **Efficacy evaluation:** A stratified log-rank test will be used to compare the OS between groups. The median PFS and corresponding 95% CI will be estimated via the Kaplan-Meier method, and survival curves will be plotted. The between-group HR and corresponding 95% CI will be estimated with a stratified COX proportional hazards model, with the randomization stratification factor as the stratification factor. The COX proportional hazards model will also be used to assess the effects of various covariates possibly related to prognosis and efficacy prediction on the estimated treatment effect HR. A stratified log-rank test will be used to compare the OS between groups. The median OS and corresponding 95% CI will be estimated via the Kaplan-Meier method, and survival curves will be plotted. The between-group HR and corresponding 95% CI will be estimated with a stratified COX proportional hazards model, with the randomization stratification factor as the stratification factor. The COX proportional hazards model will also be used to assess the effects of various covariates possibly related to prognosis and efficacy prediction on the estimated treatment effect HR. For endpoints DOR and TTR, the Kaplan-Meier method will used to estimate medians and provide survival curves. The ORRs, DCRs, and corresponding 95% CIs of tumor response evaluation in each treatment cycle will be estimated for test group and control group. The difference between groups and corresponding 95% CI will be calculated. The quality of life scores will be standardized to convert raw scores into standardized scores ranging between 0–100. The results will be subjected to descriptive statistics and Wilcoxon test. The Eastern Cooperative Oncology Group Performance Status (ECOG PS) scores will be analyzed also using descriptive statistics and Wilcoxon test. **Safety evaluation:** The exposure of subjects to study drugs, the number of cycles completed by subjects in the two groups, dose adjustments during treatment, cumulative number of dose adjustments during treatment, etc. will be summarized.

	All AEs will be coded and categorized according to codes in the "Medical Dictionary for Regulatory Activities" (MedDRA), and graded by severity level according to the "Common Terminology Criteria for Adverse Events" (CTCAE V4.03). The incidences of AEs, TRAEs, irAEs, AEs leading to treatment discontinuation, AEs leading to study termination, AEs leading to death, grade 3 or greater AEs, and SAEs will be summarized; the number of subjects and percentages will be summarized by system organ classification (SOC), preferred term (PT), and group, and these AEs will be summarized by SOC, PT, severity level, and group. Measured values and changes from baseline of laboratory tests, vital signs, and ECG will be summarized using descriptive statistics. Baseline results and worst results during the study will be presented in cross tabulation. Immunogenicity data will be presented with descriptive statistics. The number and percentage of subjects who develop ADAs and NAbs during the study will be summarized by group. The analysis of pharmacokinetic (PK) data will include, but is not limited to, descriptive statistical analysis of IBI308 trough concentrations in cycles 1/3/11.

Table 1. Schedule of study visits

Stage	**Screening period**	**Combination therapy (21 days per cycle)**												**Maintenance therapy (21 days per cycle)**	**Safety visit[22]**	**Survival visits[23]**
		C1/D1	**C1/D8**	**C2/D1**	**C2/D8**	**C3/D1**	**C3/D8**	**C4/D1**	**C4/D8**	**C5/D1**	**C5/D8**	**C6/D1**	**C6/D8**			
Day	**-28 ~-1**	**1**	**8**	**22**	**29**	**43**	**50**	**64**	**71**	**85**	**92**	**106**	**113**		**Day 30 after the last dose**	**Every 90 days**
Time window (day)	**NA**	**+2**	**±2**	**±3**	**±2**	**±3**	**±2**	**±3**	**±2**	**±3**	**±2**	**±3**	**±2**	**± 3 days**	**± 3 days**	**± 7 days**
Standard study procedures																
Written ICF[1]	X															
Inclusion/exclusion criteria	X															
Demographics/medical history/previous therapies for lung cancer[2]	X															
Previous and concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Vital signs[3]	X	X		X		X		X		X		X		X	X	
Weight/height[4]	X	X		X		X		X		X		X		X	X	
Comprehensive physical examination	X														X	
12-Lead ECG[5]	X			X		X		X		X		X		X	X	
Survival condition																X

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		C1/D1	**C1/D8**	**C2/D1**	**C2/D8**	**C3/D1**	**C3/D8**	**C4/D1**	**C4/D8**	**C5/D1**	**C5/D8**	**C6/D1**	**C6/D8**			
Day	**-28 ~-1**	**1**	**8**	**22**	**29**	**43**	**50**	**64**	**71**	**85**	**92**	**106**	**113**		**Day 30 after the last dose**	**Every 90 days**
Time window (day)	**NA**	**+2**	**±2**	**±3**	**±2**	**±3**	**±2**	**±3**	**±2**	**±3**	**±2**	**±3**	**±2**	**± 3 days**	**± 3 days**	**± 7 days**
Laboratory evaluation																
Routine blood test[6]	X		X	X	X	X	X	X	X	X	X	X	X	X	X	
Blood chemistry[6]	X			X		X		X		X		X		X	X	
Urinalysis[6]	X			X		X		X		X		X		X	X	
Coagulation function[7]	X														X	
Pregnancy test[8]	X														X	
Thyroid function[9]	X			X		X		X		X		X		X	X	
Virological antibody test (HIV, HBV, and HCV)[10]	X															
Test HCV-RNA if positive for HCV antibody[11]	X			X		X		X		X		X		X	X	
Test HBV-DNA if positive for HBsAg and/or HBcAb[12]	X			X		X		X		X		X		X	X	
Blood myocardial enzyme and troponin[13]	X			X		X										

Stage	**Screening period**	**Combination therapy (21 days per cycle)**												**Maintenance therapy (21 days per cycle)**	**Safety visit[22]**	**Survival visits[23]**
		C1/D1	**C1/D8**	**C2/D1**	**C2/D8**	**C3/D1**	**C3/D8**	**C4/D1**	**C4/D8**	**C5/D1**	**C5/D8**	**C6/D1**	**C6/D8**			
Day	**-28 ~-1**	**1**	**8**	**22**	**29**	**43**	**50**	**64**	**71**	**85**	**92**	**106**	**113**		**Day 30 after the last dose**	**Every 90 days**
Time window (day)	**NA**	**+2**	**±2**	**±3**	**±2**	**±3**	**±2**	**±3**	**±2**	**±3**	**±2**	**±3**	**±2**	**± 3 days**	**± 3 days**	**± 7 days**
Safety monitoring																
ECOG PS score	X	X		X		X		X		X		X		X	X	
AE evaluation[14]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Quality-of-life questionnaires[15]		X				X				X				X	X	
Subsequent anti-tumor therapy															X	X
Efficacy evaluation																
Tumor imaging evaluation[16]	X					X				X				X	X	
PK and immunogenicity																
Immunogenicity[17]		X		X				X						X	X	
PK[18]		X		X				X						X		
Administration of study drugs[19]																
IBI308 or placebo		X		X		X		X		X		X		X		
Gemcitabine		X	X	X	X	X	X	X	X	X	X	X	X			
Cisplatin or carboplatin		X		X		X		X		X		X				

Stage	**Screening period**	**Combination therapy (21 days per cycle)**												**Maintenance therapy (21 days per cycle)**	**Safety visit[22]**	**Survival visits[23]**
		C1/D1	**C1/D8**	**C2/D1**	**C2/D8**	**C3/D1**	**C3/D8**	**C4/D1**	**C4/D8**	**C5/D1**	**C5/D8**	**C6/D1**	**C6/D8**			
Day	**-28 ~-1**	**1**	**8**	**22**	**29**	**43**	**50**	**64**	**71**	**85**	**92**	**106**	**113**		**Day 30 after the last dose**	**Every 90 days**
Time window (day)	**NA**	**+2**	**±2**	**±3**	**±2**	**±3**	**±2**	**±3**	**±2**	**±3**	**±2**	**±3**	**±2**	**± 3 days**	**± 3 days**	**± 7 days**
Biomarker study																
Archived or fresh tumor tissue sample[20]	X															
Whole blood[21]		X				X				X				X	X	

Note:

1. The ICF should be signed by subjects prior to any procedures outlined in the protocol.
2. Previous therapies for lung cancer: all treatments for lung cancer, including chemotherapy, radiotherapy, and surgery.
3. Vital signs include: body temperature, pulse, respiratory rate, and blood pressure.
4. Height is measured during screening period only. Body weight is measured prior to each dose. If the body weight of a subject fluctuates by less than 10% from the baseline (the day when the first dose of study drugs is given), the baseline body weight will be used to calculate the chemotherapeutic dose. Otherwise, the actual dose will be calculated based on the weight of scheduled dosing days.
5. Time of 12-lead ECG examinations: within 7 days before the first dose of study drugs during screening, within 3 days before each administration of study drugs from cycle 2 onwards, and during safety follow-up.
6. Routine blood test: red blood cell (RBC), hemoglobin (HGB), hematocrit (HCT), white blood cell (WBC), platelet (PLT), and WBC differential [lymphocyte, neutrophil, monocyte, eosinophil, and basophil]. Blood chemistry: hepatic function [TBIL, DBIL, ALT, AST, γ-GT, ALP, ALB, TP, LDH, and CK], renal function (UREA or BUN, and Cr), blood electrolytes (Na, K, Cl, Mg, Ca, and P), amylase, and fasting blood glucose (FBG). Urinalysis: pH, UWBC, UPRO, URBC, UGLU, and specific gravity. Subjects with ≥ 2+ urine protein in urinalysis during screening should undergo a 24-h urine protein quantitation test. The tests will be conducted within 7 days before the first dose of study drugs during screening, within 3 days before each administration of study drugs from cycle 2 onwards, and during safety follow-up. Tests will be conducted at each study site.

7. Coagulation function test: PT and INR. The test will be conducted within 7 days before the first dose of study drugs during screening and during the safety follow-up. Tests will be conducted at each study site.
8. Women of childbearing age will undergo urine or serum pregnancy test within 3 days before the first dose during screening and during the safety follow-up. 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.
9. The thyroid function test will be conducted within 28 days before the first dose, within 3 days before each administration of study drugs from cycle 2 onwards, and during the safety follow-up. T3/FT3, FT4, and TSH are examined during screening, and only TSH is examined from cycle 2 onwards. In case of any abnormalities, the examination of other thyroid function parameters should be considered. During study treatment, the study drugs can be administered before the test results are accessible. Tests will be conducted at each study site.
10. This item involves the testing of HIV and HCV antibodies as well as hepatitis B panel (HBsAg, HBsAb, HBcAb, HBeAg, and HBeAb), and should be completed within 28 days before the first dose. The test will be conducted at the study site during screening.
11. Anti-HCV antibodies will be tested at the screening visit. For subjects tested positive for HCV antibodies, HCV-RNA load should be determined during screening, within 3 days before each administration of study drugs from cycle 2 onwards, or at an earlier time if clinically indicated. During study treatment, the study drugs can be administered before the test results are accessible.
12. Hepatitis B panel will be tested at the screening visit. For subjects tested positive for HBsAg and/or HBcAb, HBV-DNA load should be determined during screening, within 3 days before each administration of study drugs from cycle 2 onwards, or at an earlier time if clinically indicated. During study treatment, for patients previously tested negative for HBsAg, the study drugs can be administered before the HBV-DNA load test results are accessible.
13. The blood myocardial enzyme and troponin tests should at least include: creatine phosphokinase (CK), creatine phosphokinase isoenzyme (CK-MB), and troponin (troponin T or troponin I). The tests will be conducted within 7 days before the first dose of study drugs during screening and within 3 days before each administration of study drugs from cycles 2 and 3 onwards. The conduct or not of subsequent tests will be decided by the investigator.
14. AEs and laboratory safety assessments will be performed based on CTCAE V4.03. Refer to Section 8 for definitions, recording, causality determination, severity level, reporting deadlines, and treatment of AEs and SAEs.
15. Quality-of-life questionnaires include LCSS and EORTC QLQ-C30 (V3.0 Chinese version), which will be completed on the day of the first dose (predose), at each imaging evaluation (during the visit), and at the safety follow-up (during the visit). If an unscheduled imaging evaluation is performed, the quality-of-life questionnaires should also be completed.
16. Tumor assessment includes the assessment based on RECIST V1.1. Tumor imaging examinations usually include contrast-enhanced CT or MRI of chest, abdomen, and pelvic cavity. Contrast-enhanced MRI of head should also be performed at baseline for subjects with signs or symptoms of suspected CNS metastasis. The same subject should receive the same type of imaging examination during the study. The baseline evaluation will be performed within 28 days before randomization. Tumor imaging evaluation will be performed at week 6 (± 7 days) and week 12 (± 7 days) since randomization, every 9 weeks

(± 7 days) thereafter until week 48, and every 12 weeks (± 7 days) after week 48. After the first assessment of imaging PD (PD) by the investigator based on RECIST V1.1, if the subject has SD clinically, the current treatment can be continued and the imaging evaluation should be performed again 4–6 weeks later for confirmation (based on RECIST V1.1). If PD is not confirmed, the study treatment should be continued and imaging evaluations should be performed at the protocol-specified time points until imaging-confirmed PD. If a subject discontinues study treatment for a reason other than objective PD, the imaging evaluation should be performed at the end of treatment and then at the protocol-specified time points thereafter until one of the following events occurs: initiation of new anti-tumor therapy, objective PD, loss to follow-up, death, or withdrawal of ICF, whichever occurs first. Unscheduled imaging evaluations can be performed at any time during the study if the patient develops clinically unstable disease. If the subject has clinically unstable disease after the first assessment of imaging PD, the confirmation 4–6 weeks later is not required and the study treatment should be discontinued.

17. Immunogenicity assays will be performed within 1 h prior to IBI308/placebo infusion in cycles 1/2/4/8/12/16, then every 8 cycles (cycle 24, 32, and so on) thereafter, and during the safety visit. If an infusion-related reaction occurs during IBI308 or placebo administration, blood samples should be taken near the start and end of this event and around 30 days after the reaction, for comparative analysis of immunogenicity. Tests will be conducted in the central laboratory.

18. PK samples will be collected at the following time points: within 1 h before and immediately (+ 5 min) after IBI308 or placebo infusion in cycle 1, and within 1 h before IBI308 or placebo infusion in cycles 2/4/12. Tests will be conducted in the central laboratory.

19. Subjects will receive treatment with either IBI308 in combination with gemcitabine and platinum (cisplatin or carboplatin) or placebo in combination with gemcitabine and platinum (cisplatin or carboplatin) for 4 or 6 cycles, followed by maintenance therapy with IBI308 or placebo, respectively. After the first assessment of imaging PD by the investigator based on RECIST V1.1, if the subject has SD clinically, the current treatment can be continued and the imaging evaluation should be performed again 4–6 weeks later for confirmation (based on RECIST V1.1). If PD is confirmed, unblinding should be performed and subjects of IBI308 in combination with chemotherapy group (test group) should end the study treatment, while subjects of placebo in combination with chemotherapy group (control group) can be conditionally crossed over to receive monotherapy of IBI308 based on the judgment of the investigator and the willingness of the subjects; if PD is not confirmed, the study treatment will be continued until imaging-confirmed PD followed by unblinding and other subsequent processing same as above. If the subject has clinically unstable disease after the first assessment of imaging PD, the confirmation 4–6 weeks later is not required and unblinding can be directly performed followed by processing same as above. During the study, the treatment should be discontinued if one of the following occurs: clinically unstable disease, intolerable toxicity, receipt of new anti-tumor therapy, withdrawal of ICF, loss to follow-up, death, or other conditions requiring treatment discontinuation as judged by the investigator, whichever occurs first. The maximum duration of treatment with IBI308 is 24 months in both groups.

20. Each subject is required to provide at least 10 sections of archived or fresh tumor tissue samples meeting test requirements during screening.

21. Each subject is also required to provide 10 mL of whole blood samples for tumor biomarker testing at the following time points: prior to the first dose, every time when imaging evaluation is performed but before the next treatment is started in the treatment period, the time when PD is confirmed, and during safety visit. Tests will be conducted in the central laboratory.

22. A safety follow-up visit will be carried out on day 30 (± 3 days) after the last dose or before initiation of new anti-tumor therapy, whichever occurs first. All AEs that occur prior to the safety follow-up visit should be documented until the events recover to grade 0–1 or the baseline level, 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), whichever occurs first. All SAEs that occur within 90 days after the last dose or before initiation of new anti-tumor therapy (whichever occurs first) should be followed up and documented.
23. Survival follow-ups: once every 90 days (± 7 days) after the safety follow-up. Telephone follow-ups are allowed.

Table 2. Schedule of visits during crossover treatment with IBI308

Stage	Crossover treatment (21 days per cycle)[1]							Safety visit[17]	Survival visits[18]
	C1	C2	C3	C4	C5	C6	C7 and later		
Time window (day)	+3	±3	±3	±3	±3	±3	±3	Day 30 (± 3) after the last dose	Every 90 days (± 7)
Standard study procedures									
Vital signs[2]	X	X	X	X	X	X	X	X	
Weight/height[3]	X							X	
Comprehensive physical examination	X							X	
ECOG PS score	X	X	X	X	X	X	X	X	
12-lead ECG[4]	X	X	X	X	X	X	X	X	
Routine blood test/blood chemistry/urinalysis[5]	X	X	X	X	X	X	X	X	
Coagulation function[6]	X							X	
Pregnancy test[7]	X							X	
Thyroid function[8]	X	X	X	X	X	X	X	X	
Virological antibody test (HIV, HBV, and HCV)[9]	X								
Test HCV-RNA if positive for HCV antibody[10]	X	X	X	X	X	X	X	X	
Test HBV-DNA if positive for HBsAg and/or HBcAb[11]	X	X	X	X	X	X	X	X	
Blood myocardial enzyme and troponin[12]	X	X	X						
AE evaluation[13]	X	X	X	X	X	X	X	X	X
Concomitant medications	X	X	X	X	X	X	X	X	

Stage	Crossover treatment (21 days per cycle)[1]							Safety visit[17]	Survival visits[18]
	C1	C2	C3	C4	C5	C6	C7 and later		
Time window (day)	**+3**	**±3**	**±3**	**±3**	**±3**	**±3**	**±3**	**Day 30 (± 3) after the last dose**	**Every 90 days (± 7)**
Quality-of-life questionnaires[14]	X			X			X	X	
Subsequent anti-tumor therapy								X	X
Survival condition									X
Efficacy evaluation									
Tumor imaging evaluation[15]	X			X			X	X	X
Administration of study drugs									
IBI308, 200 mg i.v. Q3W	X	X	X	X	X	X	X		
PK and immunogenicity									
Immunogenicity[16]									

Note:

1. Only after all patients in the control group have been assessed for overall status by the investigator and confirmed to have PD by the IRRC and meet the requirements for administration of IBI308, can they be crossed over to receive treatment with IBI308. The imaging results obtained at the end of the last dose can be used for the evaluation before crossover treatment. Regardless of the confirmation date of PD, subjects must start the administration of IBI308 at least 21 days after the last chemotherapy.
2. Vital signs include: body temperature, pulse, respiratory rate, and blood pressure.
3. Body height is measured only before the first dose.
4. Time of 12-lead ECG examinations: within 7 days before the first dose of IBI308, within 3 days before each administration from cycle 2 onwards, and during safety follow-up.
5. Routine blood test: red blood cell (RBC), hemoglobin (HGB), hematocrit (HCT), white blood cell (WBC), platelet (PLT), and WBC differential [lymphocyte, neutrophil, monocyte, eosinophil, and basophil]. Blood chemistry: hepatic function [TBIL, DBIL, ALT, AST, γ-GT, ALP, ALB, TP, LDH, and CK], renal function (UREA or BUN, and Cr), blood electrolytes (Na, K, Cl, Mg, Ca, and P), amylase, and fasting blood glucose (FBG). Urinalysis: pH, UWBC, UPRO, URBC, UGLU, and specific gravity. Subjects with ≥ 2+ urine protein in urinalysis during screening should undergo a 24-h urine protein

quantitation test. The tests will be conducted within 7 days before the first dose of IBI308, within 3 days before each administration of study drugs from cycle 2 onwards, and during safety follow-up. Tests will be conducted at each study site.

6. Coagulation function test: PT and INR. The test is conducted within 7 days before the first dose of IBI308 and during safety follow-up. Tests will be conducted at each study site.
7. Women of childbearing age will undergo urine or serum pregnancy test within 3 days before the first dose of IBI308 and during the safety follow-up. 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. The thyroid function test will be conducted within 21 days before the first dose, within 3 days before each administration from cycle 2 onwards, and during the safety follow-up. During study treatment, the study drugs can be administered before the test results are accessible. Tests will be conducted at each study site.
9. This item involves the testing of HCV antibodies and hepatitis B panel (HBsAg, HBsAb, HBcAb, HBeAg, and HBeAb), and should be completed within 21 days before the first dose. Tests will be conducted at each study site.
10. For subjects tested positive for HCV antibodies, HCV-RNA load should be determined within 3 days before administration of study drugs in each cycle, or at an earlier time if clinically indicated. During study treatment, the study drugs can be administered before the test results are accessible.
11. For subjects tested positive for HBsAg and/or HBcAb, HBV-DNA load should be determined within 3 days before administration of study drugs in each cycle, or at an earlier time if clinically indicated. During study treatment, for patients previously tested negative for HBsAg, the study drugs can be administered before the HBV-DNA load test results are accessible.
12. The blood myocardial enzyme and troponin tests should at least include: creatine phosphokinase (CK), creatine phosphokinase isoenzyme (CK-MB), and troponin (troponin T or troponin I). The tests are performed within 7 days before the first dose of IBI308 during crossover treatment and within 3 days before each administration of study drugs from cycles 2 and 3 onwards. The conduct or not of subsequent tests will be decided by the investigator.
13. AEs and laboratory safety assessments will be performed based on CTCAE V4.03. Refer to Section 8 for definitions, recording, causality determination, severity level, reporting deadlines, and treatment of AEs and SAEs.
14. Quality-of-life questionnaires include LCSS and EORTC QLQ-C30 (V3.0 Chinese version), which will be completed on the day of the first dose (predose), at each imaging evaluation (during the visit), and at the safety follow-up (during the visit).
15. Tumor assessment includes the assessment based on RECIST V1.1. Tumor imaging examinations usually include contrast-enhanced CT or MRI of chest, abdomen, and pelvic cavity. Contrast-enhanced MRI of head should also be performed at baseline for subjects with signs or symptoms of suspected CNS metastasis. The same subject should receive the same type of imaging examination during the study. Subjects in the stage of crossover treatment with IBI308 will be assessed every 9 weeks (± 7 days) since the first dose until the occurrence of imaging PD (based on RECIST V1.1). For patients who

discontinue the treatment for reasons other than objective PD, an imaging evaluation should be performed at the end of treatment and then at the protocol-specified time points thereafter until one of the following events occurs: initiation of new anti-tumor therapy, PD, loss to follow-up, death, or withdrawal of ICF, whichever occurs first. Unscheduled imaging evaluations can be performed at any time during the study if the patient develops clinically unstable disease.

16. If an infusion-related reaction occurs during IBI308 infusion, blood samples should be taken near the start and end of this event and around 30 days after the reaction and used for comparative analysis of immunogenicity. Tests will be conducted in the central laboratory.
17. A safety follow-up visit will be carried out on day 30 (± 3 days) after the last dose or before initiation of new anti-tumor therapy, whichever occurs first.
18. Survival follow-ups: once every 90 days (± 7 days) after the safety follow-up. Telephone follow-ups are allowed.

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List of Abbreviations

Abbreviation	Full name (English)
ADA	Anti-drug antibody
ADR	Adverse Drug Reaction
AE	Adverse Event
ANC	Absolute Neutrophil Count
ALT	Alanine Transaminase
ALK	Anaplastic Lymphoma Kinase
AST	Aspartate Amino Transferase
BOR	Best Overall Response
CNS	Central Nervous System
CR	Complete Response
CRA	Clinical Research Associate
CRO	Clinical Research Organization
Cr	Creatinine
CI	Confidence Interval
CRF	Case Report Form
Ecrf	Electronic Case Report Form
CT	Computed Tomography
CTLA-4	Cytotoxic T Lymphocyte Antigen 4
CTCAE	Common Terminology Criteria for Adverse Events
DCR	Disease Control Rate
DOR	Duration of Response
DLT	Dose-Limiting Toxicity
EC	Ethics Committee
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EDC	Electronic Data Capture
EGFR	Epidermal Growth Factor Receptor
EORTC	European Organization for Research and Treatment of Cancer
QLQ	Quality of Life Questionnaire
EMA	European Medicines Agency
MedDRA	Medical Dictionary for Regulatory Activities
MRI	Magnetic Resonance Imaging
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HIV	Human Immunodeficiency Virus

Abbreviation	Full name (English)
HR	Hazard Ratio
ICF	Informed Consent Form
IDMC	Independent Data Monitoring Committee
INR	International Normalized Ratio
irAE	Immune Related Adverse Event
IRRC	Independent Radiographic Review Committee
irRESICT	Immune-Related Response Evaluation Criteria in Solid Tumors
LCSS	Lung Cancer Symptom Scale
MTD	Maximal Tolerated Dose
MDSC	Myeloid-Derived Suppressor Cells
NAb	Neutralizing Antibody
NSCLC	Non-Small Cell Lung Cancer
NCI	National Cancer Institute
ORR	Objective Response Rate
OS	Overall Survival
PBMC	Peripheral Blood Mononuclear Cell
PD	Pharmacodynamics
PD-1	Programmed Cell Death 1
PD-L1	Programmed Cell Death Ligand 1
PFS	Progression Free Survival
PK	Pharmacokinetic
PR	Partial Response
RECIST	Response Evaluation Criteria in Solid Tumors
RP2D	Recommended Phase II Dose
PT	Prothrombin Time
PT	Preferred Term
SAE	Serious Adverse Event
SAP	Statistics Analysis Plan
SD	Stable Disease
SOC	System Organ Classification
TBIL	Total Bilirubin
TCR	T-Cell Receptor
ctDNA	Circulating Tumor DNA
TMB	Tumor Mutation Burden
TTR	Time to Response
UADR	Unexpected Adverse Drug Reaction
ULN	Upper Limit of Normal
VEGF	Vascular Endothelial Growth Factor

1 BACKGROUND

1.1 Disease Background

Cancer has been one of the leading causes of death worldwide, and China is also facing increasing challenges from the cancer. Among all cancer deaths, the leading death cause is lung cancer (25.2%), where non-small cell lung cancer (NSCLC) accounts for about 80–85%. About 70% of patients with NSCLC, at diagnosis, suffers from locally advanced or metastatic disease that is unresectable[1]. In addition, 30–60% of patients with stage I–III NSCLC undergoing radical surgery may eventually develop recurrence or distant metastasis[2].

In the past two decades, the advances of NSCLC drugs mainly focus on non-squamous NSCLC, including pemetrexed maintenance therapy[3], anti-angiogenic anti-vascular endothelial growth factor (VEGF) monoclonal antibody (bevacizumab)[4], and TKI drugs that drive the mutations of epidermal growth factor receptor (EGFR) gene or the rearrangement of anaplastic lymphoma kinase (ALK)[5, 6]. Squamous still accounts for about 30% of new cases, despite the annual decline of its proportion in NSCLC. The research and development of drugs for squamous has been stagnating due to the specific epidemiological, histopathological, and molecular characteristics thereof. Currently, the first-line regimen for patients with advanced squamous NSCLC is still platinum-based doublet chemotherapy (paclitaxel or gemcitabine in combination with platinum), which has a response rate (RR) of about 30%, a progression free survival (PFS) of about 5.5 months, and an overall survival (OS) of about 10.8 months[7, 8]. Therefore new treatment models and drugs are urgently needed for advanced squamous NSCLC to improve the efficacy and survival. Recent years have experienced rapid advancement of studies on inhibiting immune checkpoints to activate the human immune system and enable the effect of attacking the tumor cells. The applying of immune checkpoint inhibitors (such as programmed cell death receptor 1/ligand 1 (PD-1/PD-L1) antibody) provides a new clinical pathway for the treatment of NSCLC, especially for the first-line treatment of advanced or metastatic NSCLC[9]. At present, PD-1 /PD-L1 monoclonal antibodies with marketing approval for advanced NSCLC mainly include nivolumab (trade name: OPDIVO®, from BMS), pembrolizumab (trade name: KEYTRUDA®, from MSD), atezolizumab (trade name: TECENTRIP®, from Roche) and durvalumab (trade name: IMFINZI®, from AstraZeneca) worldwide.

Monotherapy of anti-PD-1 /PD-L1 monoclonal antibodies is more effective and safe than chemotherapy in the second-line treatment of advanced NSCLC. The CheckMate 017 study, a randomized, open, phase III clinical study, compared the efficacy and safety between nivolumab and docetaxel in advanced squamous NSCLC patients who failed platinum-based chemotherapy. The results showed OS of 9.2 and 6 months for nivolumab and docetaxel groups, respectively, death risk decrease of 41% (HR 0.59; $P < 0.001$) for nivolumab treatment, and a PFS of

nivolumab superior to that of docetaxel[10]. In addition, the incidence of adverse reactions of nivolumab treatment was significantly lower than that of docetaxel. Based on this study, nivolumab was approved for second-line treatment of advanced squamous NSCLC on Mar. 4, 2015; and in Oct. 2015, CheckMate 057 study results made nivolumab approved for second-line treatment of advanced non-squamous NSCLC[11]. Moreover, KEYNOTE-010, a phase II/III clinical study, indicated that patients with PD-L1 positive advanced NSCLC experienced better OS benefits from second-line treatment with pembrolizumab compared with docetaxel. Based on the results of POPLAR study and OAK study, both of which were randomized controlled trials comparing atezolizumab and docetaxel in the treatment of second-line and above NSCLC, with OS of 12.6 vs. 9.7 months and 13.8 vs. 9.6 months, respectively, Roche's anti-PD-L1 antibody (atezolizumab) was approved by the Food and Drug Administration (FDA) for second-line treatment of NSCLC in 2016.

The situation is the same for Chinese population that the efficacy and safety of anti-PD-1 monoclonal antibodies in the second-line treatment of advanced NSCLC are better than chemotherapy. CheckMate 078 was a registered clinical study of nivolumab in China. This multicenter, randomized phase III trial compared the efficacy and safety of nivolumab and docetaxel in stage IIIb/IV NSCLC patients who experienced PD after platinum-based doublet chemotherapy. In the Checkmate 078 study, a total of 504 squamous and non-squamous NSCLC patients (451 from China, 45 from Russia, and 8 from Singapore) were enrolled, and then patients were randomized in a 2:1 ratio to receive nivolumab and docetaxel, respectively, until occurrence of PD or unacceptable toxicities. The primary end point was overall survival (OS). Compared with docetaxel, nivolumab significantly prolonged survival, with a hazard ratio (HR) of 0.68 (97.7% CI: 0.52–0.90; P = 0.0006); nivolumab also significantly prolonged PFS of patients; and compared with chemotherapy, nivolumab reduced the PD risk by 23% (HR = 0.77; 95% CI: 0.62–0.95; P = 0.0147). For the secondary end point, nivolumab group had a significantly better ORR compared with the docetaxel group (17% vs. 4%). In the safety, the nivolumab was also superior to docetaxel. Subgroup analysis showed that OS benefits were observed in patients with different PD-L1 expression levels and tumor histological types. Compared with chemotherapy, the HR of OS was 0.61 (95% CI: 0.42–0.89) for squamous NSCLC patients and 0.76 (95% CI: 0.56–1.04) for non-squamous NSCLC patients, more significant benefit for squamous NSCLC patients.

For advanced NSCLC patients with high expression of PD-L1, first-line monotherapy with anti-PD-1 monoclonal antibody is superior to platinum-based doublet chemotherapy. KEYNOTE 024 was a phase III randomized controlled study to evaluate and compare the efficacy and safety of pembrolizumab with that of standard platinum-based chemotherapy in previously untreated patients with advanced NSCLC, who showed no EGFR or ALK variations but high PD-L1

expression (≥ 50% positive PD-L1 expression in tumor cells)[12]. In this study, a total of 305 patients were enrolled and randomized in a 1:1 ratio to pembrolizumab group and platinum-based doublet chemotherapy group, respectively; the patients in the chemotherapy group can cross to the pembrolizumab group in case of PD. The primary endpoint was PFS. The study showed that, compared with chemotherapy, pembrolizumab prolonged PFS by nearly 4 months (10.3 vs. 6.0 months, HR = 0.50, P < 0.001); the secondary endpoint OS was also significantly prolonged (HR = 0.60, P = 0.005); and compared with chemotherapy, pembrolizumab showed an overall RR of 45% (45% vs. 28%, P = 0.0011) and its safety was superior. Subgroup analysis showed that the HR of PFS for squamous cell carcinoma was 0.35 (0.17–0.71) and for non-squamous cell carcinoma was 0.55 (0.39–0.76). In order to further expand the indication population, MSD conducted the KEYNOTE 042 study. KEYNOTE 042 was a randomized, open-label phase III clinical trial and indicated that pembrolizumab was superior to standard platinum-based doublet chemotherapy for PD-L1 positive (TPS > 1%) and EGFR-/ALK-NSCLC (non-squamous or squamous) patients and could significantly prolonged the OS of patients.

Anti-PD-1 monoclonal antibody and combination immunotherapy might be superior to the platinum-based doublet regimen in the first-line treatment of advanced NSCLC with high tumor mutation burden (TMB). Although CheckMate 026 indicated no advance of nivolumab in efficacy even for the patients with PD-L1 expression of > 50%, a retrospective study showed that nivolumab treatment was superior to chemotherapy in ORR (47% vs. 28%) and PFS (9.7 months vs. 5.8 months) in patients with high TMB expression[13]. The CheckMate 227 study showed that, compared with chemotherapy, nivolumab in combination with ipilimumab (anti-cytotoxic T lymphocyte antigen 4 (CTLA-4) monoclonal antibody) significantly improved PFS in advanced NSCLC patients who had high TMB expression (TMB ≥10 mut/mb, regardless of PD-L1 expression) and showed equal benefit for squamous and non-squamous cell carcinoma[14].

For the entire advanced NSCLC population, PD-1 monoclonal antibody in combination with chemotherapy may also be superior to chemotherapy. Chemotherapy has traditionally been regarded as a treatment having immunosuppressive effect, but more and more basic and clinical studies have shown that some chemotherapeutics that induce DNA damage can promote immune effect[15]. Based on the results of KEYNOTE 021G study that pembrolizumab significantly improved ORR and prolonged PFS, on May 10, 2017, FDA accelerated the approval of pembrolizumab in combination with emetaxel and carboplatin for treatment of previously untreated patients with advanced NSCLC (non squamous) and without EGFR-sensitive mutations/ALK rearrangement. Subsequent KEYNOTE 189 further demonstrated its survival benefits[16]. KEYNOTE 189 was a randomized, double-blind, placebo-controlled phase III study to evaluate the efficacy of pembrolizumab in combination with pemetrexed and platinum-based

chemotherapy as the first-line treatment for patients with non-squamous NSCLC (without EGFR-sensitive mutations/ALK rearrangement). A total of 614 patients were randomized in a 2:1 ratio to receive pembrolizumab in combination with pemetrexed and cisplatin/carboplatin as well as placebo in combination with pemetrexed and cisplatin/carboplatin, followed by pembrolizumab or placebo in combination with pemetrexed maintenance, respectively. The OS (HR 0.49, P < 0.00001) and PFS (HR 0.52, P < 0.00001) were significantly improved in the pembrolizumab group compared with the placebo group. Patients in the pembrolizumab group had not yet achieved median OS, compared with 11.3 months for the placebo group, with median PFS of 8.8 and 4.9 months, respectively. Subgroup analysis showed that subgroups with different PD-L1 expression levels could benefit from pembrolizumab treatment. The ORR of the pembrolizumab and placebo groups was 47.6% and 18.9% (P<0.00001), respectively, and the safety was comparable[16]. The KEYNOTE 407 study evaluated the efficacy of pembrolizumab in combination with carboplatin and paclitaxel/albumin paclitaxel as the first-line treatment of metastatic squamous NSCLC compared with carboplatin and paclitaxel/albumin paclitaxel. The first interim analysis achieved the pre-determined secondary end point of ORR (58.4% vs. 35.0%, P = 0.0004), and the second interim analysis achieved the primary study end point of PFS (6.4 vs. 4.8 months, HR 0.56, P < 0.0001) and OS (15.9 vs. 11.3 months, HR 0.64, P < 0.0008).

Currently, the first-line chemotherapy regimen for patients with advanced squamous NSCLC is still doublet regiment of taxol or gemcitabine in combination with platinum (cisplatin or carboplatin), while anti-PD-1 monoclonal antibody in combination with gemcitabine and platinum-based regimen may be one of the preferred regimens. Nonclinical studies have shown that gemcitabine can eliminate immunosuppressive cells such as myeloid-derived suppressor cells (MDSCs)[17], and platinum-based drugs can induce immunogenic tumor cell death[18]. Phase Ib clinical studies have shown that nivolumab in combination with gemcitabine and cisplatin as the first-line treatment of NSCLC has a RR of 50%. InnoventBio CIBI308A101 phase Ib cohort E studied the safety and preliminary efficacy of IBI308 in combination with gemcitabine and cisplatin chemotherapy used as first-line treatment for advanced squamous cell NSCLC, and as of Jun. 11, 2018, 16 subjects had completed at least one efficacy evaluation, of which 10 had achieved partial response (PR), 6 had stable disease (SD), indicating a RR of 62.5%, a disease control rate (DCR) of 100%, and the grade ≥ 3 TRAEs of 36.4% and thus showing good efficacy and safety.

Based on the above clinical study results, squamous NSCLC may be the benefit population of immunotherapy, and PD-1 monoclonal antibody has a definite efficacy in advanced squamous NSCLC patients; the toxicity of first-line treatment in combination with platinum-based chemotherapy was controllable and combination therapy may be synergistic in improving efficacy. Patients with low expression of PD-L1 can also benefit from the combination therapy

of PD-1 monoclonal antibody and platinum-based chemotherapy, and therefore relevant studies in Chinese patients with advanced squamous NSCLC should be encouraged, so as to fill the gap in the first-line treatment of immunoantitumor therapy for lung squamous carcinoma patients in China as soon as possible.

1.2 IBI308

1.2.1 Mechanism of action

Tumor treatment via immune checkpoints has been a research hotspot in recent years, and tremendous breakthroughs have been made in this field. Unlike cytotoxic drugs, monoclonal antibodies or small molecule tyrosine kinase inhibitors that target oncogenes, immune checkpoint therapy of tumors does not directly target tumor cells, but rather improve the function of T cells, remove the tolerance of the immune system to tumor cells, and improve the effective recognition and killing of tumor cells by T cells via blocking the inhibitory signals against T cell proliferation and activation. Currently, the immune checkpoint targets showing significant clinical efficacy in tumor treatment include CTLA-4 and PD-1/PD-L1[19].

So far, five PD-1/PD-L1 monoclonal antibody products have been approved by FDA for marketing, including nivolumab (tread name: OPDIVO®, from BMS), pembrolizumab (KEYTRUDA®, from MSD), atezolizumab (trade name: TECENTRIP®, from Roche), avelumab (BAVENCIO®, from Pfizer/Merck Drugs & Biotechnology), and durvalumab (trade name: IMFINZI®, from AstraZeneca); indications include advanced melanoma, advanced NSCLC, advanced classic Hodgkin's lymphoma, advanced renal cell renal carcinoma, advanced urothelial carcinoma, advanced head and neck tumors, etc[20]. In addition, many indications have been under phase III clinical studies or have been submitted for approval. The marketing of the above drugs confirms the important role of PD-1 /PD-L1 antibody drugs in tumor immunotherapy.

Sintilimab (R&D code: IBI308) is a recombinant fully human IgG_4 PD-1 monoclonal antibody. Multiple nonclinical *in vitro* and *in vivo* trials have shown the blockade function of IBI308 of the PD-1 pathway, and completed nonclinical studies on pharmacodynamics, animal PK and toxicology indicated that IBI308 was characterized by clear targets, reliable source of cell lines, and good stability and activity. Refer to "Investigator's Brochure" for detailed study results.

1.2.2 Phase Ia clinical results of IBI308

A phase Ia dose-escalation trial of IBI308 was initiated in Sep. 2016 (study code CIBI308A101 1a). Subjects with advanced solid tumors who had failed standard treatment was 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. DLT is observed for 28 days after the first dose for each dose group. After completion of DLT observation, subjects are treated with IBI308 Q2W (1 mg/kg, 3 mg/kg, or 10 mg/kg) or Q3W (200 mg) until PD, intolerable toxicity, withdrawal of ICF, or other reasons requiring treatment discontinuation (whichever occurs first).

PK studies of patients with advanced solid tumors in phase Ia showed that the serum drug concentration of IBI308 (administered by intravenous infusion) gradually increased after the start of infusion, reached C_{max} after the end of infusion, and then slowly decreased. Within the dose range of 1–10 mg/kg, the IBI308 exposure *in vivo* had a dose-proportional increase, suggesting linear kinetic characteristics. In subjects with solid tumors, after the single dose of IBI308, the elimination half-life (Geo.Mean (CV%)) was 14.4 (28.9%) days, the clearance rate was 11.5 (42.5%) mL/h, the steady-state distribution volume was 5.43 (34.4%) L, and apparent distribution volume was 5.77 (33.2%) L, showing comparable PK characteristics to similar marketed anti-PD-1 antibodies (nivolumab, pembrolizumab).

In a phase Ia pharmacodynamic study of patients with advanced solid tumors, single dose of IBI308 at 1 mg/kg (N = 3) could achieve rapid (24 h) saturation (mean ≥ 95%) of the PD-1 receptors on the surface of peripheral CD3T cells of solid tumor subjects and could maintain the occupancy level during the study period (28 days) of continuously reducing drug concentrations and in a therapy of multiple doses that were given consecutively. The dose groups of 3 mg/kg (N = 3), 200 mg (N = 3), and 10 mg/kg (N = 3) showed comparable results of PD-1 occupancy to the 1 mg/kg, suggesting no dose and concentration dependences within the range of 1–10 mg/kg for PD-1 receptor occupancy. IBI308 also showed good anti-tumor activity in subjects with multiple advanced solid tumors who had failed standard treatment. The evaluation as per RECIST V1.1 showed the best overall efficacy that 2 subjects achieved PR and 2 achieved SD, and the evaluation as per irRECIST showed that 2 subjects achieved irPR and 3 achieved irSD. A new subject (01002) with hepatocellular carcinoma who received failed treatment with sorafenib achieved irSD. The subject had been receiving IBI308 treatment after PD, and the tumor burden had continued to decrease compared with that at PD. After 3 cycles of continuous treatment, the subject was evaluated as irSD according to irRECIST. As of Oct. 30, 2017, the subject was still receiving IBI308 treatment. Subjects receiving tumor immunotherapy may experience tumor pseudoprogression, which is significantly different from the efficacy characteristics of traditional chemotherapy. One of the 12 subjects receiving IBI308 treatment was observed increased and then decreased tumor burden. In clinical trials after IBI308 study, the efficacy criteria for immune solid tumors have been referenced to further explore the trend of changes in tumor pseudoprogression. As of Oct. 30, 2017, deaths (due to PD) were observed in a total of 3 subjects during follow-up visits.

1.2.3 Phase Ib study results of IBI308 in first-line patients with squamous NSCLC

CIBI308A101 phase Ib cohort E mainly enrolled patients with advanced, recurrent, or metastatic squamous NSCLC who had not received previous systematic anticancer therapy. The patients were treated with IBI308 in combination with gemcitabine and cisplatin, and as of Jun. 11, 2018, 16 subjects completed at least one efficacy evaluation, of which 10 achieved PR, 6 achieved SD, indicating a RR of 62.5%, DCR of 100%, grade ≥3 TRAE of 36.4% and thus showing good efficacy and safety.

1.3 Risk/Benefit Assessment

Considering the mechanism of action of IBI308 and the clinical safety information of drugs with similar mechanism, the AEs during this clinical trial will possibly be immune-mediated inflammatory resulted from the activation of immune system, e.g. pneumonia, thyroiditis, hepatitis, dermatitis/skin lesions, etc. 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 5.2.2 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.

Gemcitabine in combination with platinum is the current standard chemotherapy regimen for first-line treatment of patients with advanced squamous NSCLC in China. This study will apply IBI308 or not on the basis of this regimen to the first-line treatment of patients with advanced squamous NSCLC. Therefore, this study will provide patients with standard effective first-line chemotherapy to ensure the clinical benefit of patients. Phase Ia and Ib clinical data of IBI308 suggested that IBI308 had definite pharmacological activity and good tolerability in patients with advanced tumors, and preliminarily showed ideal anti-tumor activity in previously untreated patients with advanced squamous NSCLC. We intended to conduct further large-scale multicenter, randomized, phase III clinical studies in patients with advanced, recurrent, or metastatic squamous NSCLC who have not received previous systematic anticancer therapy, so as to clarify the efficacy and safety of IBI308 in combination with standard chemotherapy in such population and to provide a data basis for relevant indications for marketing.

2 STUDY OBJECTIVES

2.1 Primary Objectives

Based on RECIST V1.1, to compare the PFS of IBI308 in combination with gemcitabine and platinum-based chemotherapy with that of placebo in combination with gemcitabine and platinum-based chemotherapy in the first-line treatment of patients with advanced or metastatic squamous NSCLC.

2.2 Secondary Objectives

- To compare the OS of the subjects between the two groups;
- Based on RECIST V1.1, to compare the ORR of the subjects between the two groups;
- Based on RECIST V1.1, to compare the DCR of the subjects between the two groups;
- Based on RECIST V1.1, to compare the TTR of the subjects between the two groups;
- Based on RECIST V1.1, to compare the DOR of the subjects between the two groups;
- To evaluate the safety and tolerability characteristics of IBI308 in combination with gemcitabine and platinum-based chemotherapy.

2.3 Exploratory Objectives

- To explore potential biomarkers in tumor tissues that can predict the efficacy of IBI308: including but not limited to immunohistochemistry assay of PD-L1 expression and RNA assay in tumor specimens;
- To explore potential biomarkers in peripheral blood that can predict the efficacy of IBI308 group, including but not limited to TCR and ctDNA assay;
- To compare the quality of life of patients treated with IBI308 in combination with chemotherapy vs. placebo in combination with chemotherapy by using LCSS and EORTC QLQ-C30 questionnaires;
- To explore the PFS of subjects in the control group after crossover treatment with IBI308;
- To explore the population PK characteristics of IBI308.

3 Study design

3.1 Overall Design

This study is a multicenter, randomized, double-blind, phase III study to compare the efficacy and safety of IBI308 in combination with gemcitabine and platinum-based (cisplatin/carboplatin) chemotherapy vs. placebo in combination with gemcitabine and platinum-based (cisplatin/carboplatin) chemotherapy in first-line treatment of previously untreated Chinese subjects with advanced or metastatic squamous NSCLC.

In this study, a total of 348 previously untreated subjects with advanced or metastatic squamous cell NSCLC will be randomized in a 1:1 ratio to the test group and the control group, 174 cases in the test group and 174 cases in the control group (in the actual study, if the actual number of enrolled subjects is different from the number of planned enrollment due to unforeseen reasons, such as the enrollment speed is faster than the requirements of the protocol, the end date of screening should be determined in advance to ensure that the number of actually enrolled subjects does not exceed the number of planned enrollment by 10%, i.e., a maximum of 382 subjects shall be enrolled, 191 in each group). Randomization stratification factors include staging (stage IIIB/IIIC vs. stage IV), platinum-based medications (cisplatin vs. carboplatin), and PD-L1 expression level (< 1% vs. ≥ 1%). In this study, the parallel control is placebo in combination with gemcitabine and platinum-based (cisplatin/carboplatin) chemotherapy and the test group will receive IBI308 in combination with gemcitabine and platinum-based (cisplatin/carboplatin) treatment. Both groups will receive the corresponding treatment for 4 or 6 cycles, followed by IBI308 or placebo maintenance therapy, respectively.

The primary objective of the study is to compare the PFS of IBI308 in combination with gemcitabine and platinum-based (cisplatin/carboplatin) chemotherapy with that of placebo in combination with gemcitabine and platinum-based (cisplatin/carboplatin) chemotherapy in the first-line treatment of patients with advanced or metastatic squamous NSCLC by Independent Imaging Review Board (IRRC) based on RECIST V1.1. Tumor imaging evaluation will be performed at week 6 (±7 days) and week 12 (±7 days) since randomization, every 9 weeks (±7 days) thereafter until week 48, and every 12 weeks (±7 days) after week 48.

After the first assessment of imaging PD by the investigator based on RECIST V1.1, if the subject has SD clinically, the current treatment can be continued and the imaging evaluation should be performed again 4–6 weeks later for confirmation (based on RECIST V1.1). If PD is confirmed, unblinding should be performed and subjects of IBI308 in combination with chemotherapy group (test group) should end the study treatment, while subjects of placebo in combination with chemotherapy group (control group) can be conditionally crossed to monotherapy of IBI308 based on the judgment of the investigator and the willingness of the

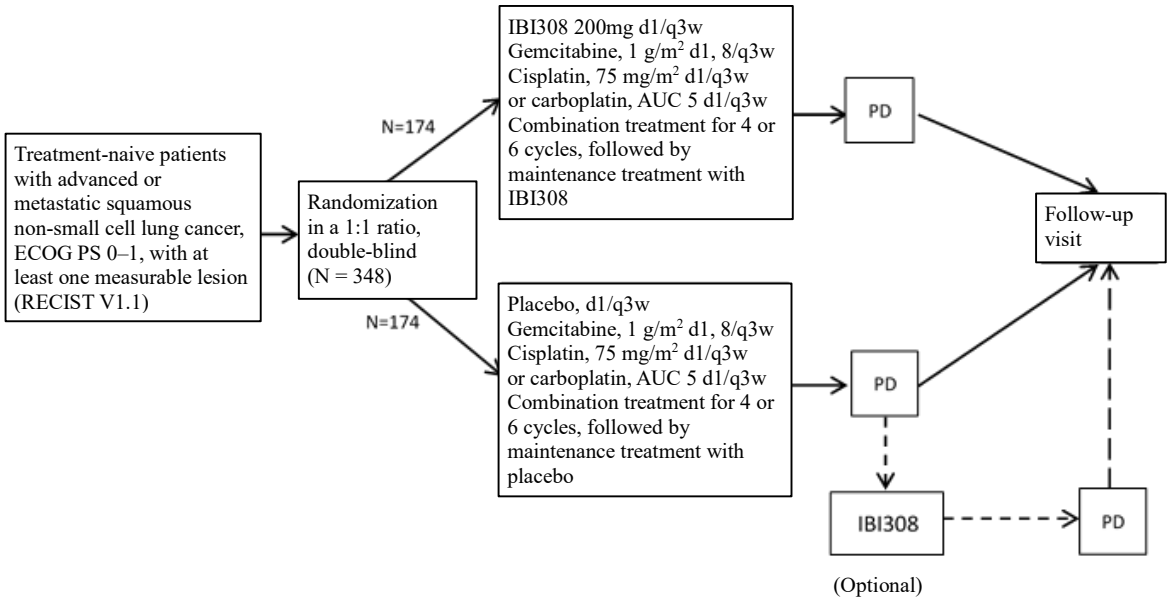
subjects, until PD, toxicity intolerability, receiving new anti-tumor therapy, withdrawal of ICF, loss of follow-up or death, or other reasons requiring termination of study treatment, whichever occurs first; if PD is not confirmed, the study treatment will be continued until imaging-confirmed PD followed by unblinding and other subsequent processing same as above. If the subject has clinically unstable disease (refer to Section 7.1.3) after the first assessment of imaging PD, the confirmation 4–6 weeks later is not required and unblinding can be directly performed followed by processing same as above. During the study, the treatment should be discontinued if one of the following occurs: clinically unstable disease, intolerable toxicity, receipt of new anti-tumor therapy, withdrawal of ICF, loss to follow-up, death, or other conditions requiring treatment discontinuation as judged by the investigator, whichever occurs first. The maximum duration of treatment with IBI308 is 24 months in both groups.

During the study, subjects should receive continual treatment until objective PD, intolerable toxicity, withdrawal of ICF, loss of follow-up or death, withdrawal of the subjects from the trial based on the decision of the investigator or the sponsor, pregnancy of the subjects, poor compliance to the study, management-related reasons, or receiving the study drug for up to 24 months. For patients who discontinue the treatment for reasons other than PD, an imaging evaluation should be performed at the end of treatment, and during follow-up the imaging evaluation should be performed according to imaging examination scheduled time points specified in the protocol until one of the following events occurs: start of new anti-tumor therapy, objective PD, loss of follow-up or death, withdrawal of ICF by the subjects, whichever occurs first.

The investigator will monitor potential AEs throughout the trial and grade the severity level of AEs according to the National Cancer Institute (NCI) General Term Standard for Adverse Events (CTCAE) Guidelines, V4.03. After the end of treatment, a 30-day safety follow-up will be conducted for subjects to monitor AE. If the patient does not receive new anti-tumor therapy within 90 days after the last dose, serious adverse events (SAE) within 90 days after the last dose will be collected; and if the subject has started a new anticancer therapy, SAE before the new anticancer therapy will be collected, whichever occurs first.

This study will be conducted in accordance with the Good Clinical Practice (GCP).

Figure 1. Schematic of study design



Notes: In the actual study, if the actual number of enrolled subjects is different from the number of planned enrollment due to unforeseen reasons, such as the enrollment speed is faster than the requirements of the protocol, the end date of screening should be determined in advance to ensure that the number of actually enrolled subjects does not exceed the number of planned enrollment by 10%, i.e., a maximum of 382 subjects shall be enrolled, 191 in each group.

3.1.1 Trial blinding

IBI308 and placebo will be in the same packages to ensure blindness. The subjects, investigators, and sponsor staff or designee participating in the treatment or clinical evaluation of the subjects should be unknown about the grouping.

Refer to section 6.4.3 for a description of the unblinding method for subjects during the trial (if required).

3.1.2 Sample size estimation

IBI308 is expected to prolong PFS of subjects from 5.5 months to 7.9 months (HR = 0.7), and with the enrollment time of 15 months, the total study time of 23 months, power of 82%, one-sided $\alpha = 0.025$ and considering a monthly dropout rate of 0.5%, a total of 348 subjects (174 in the test group and 174 in the control group) are needed to be randomized to achieve the 264 PFS events required in the trial. In the actual study, if the actual number of enrolled subjects is different from the number of planned enrollment due to unforeseen reasons, such as the enrollment speed is faster than the requirements of the protocol, the end date of screening should be determined in advance to ensure that the number of actually enrolled subjects does not exceed

the number of planned enrollment by 10%, i.e., a maximum of 382 subjects shall be enrolled, 191 in each group.

An interim analysis will be performed in this study when 70% of PFS events (i.e., 185 PFS events) occur. Superiority in efficacy of the test group over the control group will be determined using Lan-deMets spending function and O'Brien-Fleming boundary in the interim analysis. One-sided P value for the interim analysis is 0.0074. If the actual interim analysis time point in the study differs from the planned (185 PFS events), the P value for the interim analysis should be adjusted according to the Lan-deMets spending function and O'Brien-Fleming.

In the interim analysis, with one-sided $\alpha = 0.0074$, if $HR \leq 0.698$ is observed for the test group of IBI308 in combination with gemcitabine and cisplatin or carboplatin chemotherapy vs. the control group of placebo in combination with gemcitabine and cisplatin or carboplatin chemotherapy, it is demonstrated that the superiority has been concluded in the interim analysis.

For the secondary endpoint OS, no formal sample size calculation will be made, and the analysis is expected to be performed 1 year after the last subject is enrolled.

This study is expected to be conducted in 30–40 sites of China.

3.1.3 Study randomization

The randomization method of this study is as follows: Subjects are randomized in a 1:1 ratio to the test group and the control group, receiving IBI308 in combination with chemotherapy and placebo in combination with chemotherapy, respectively. The central randomization method is adopted with competitive enrollment for each center. The central randomization procedure will use an interactive web response system (IWRS), which can generate and dispense a random number to subjects who have completed all of the screening assessment items of the study and meet the inclusion criteria. The random number will connect the subjects into a designed treatment group (IBI308 in combination with chemotherapy group or placebo in combination with chemotherapy group) and can assign investigational drugs to subjects as per required quantity. For subjects withdrew from the study, whatever the reason of withdrawal, their random numbers will be retained. IWRS staff will only write randomized table and will not be involved in any specific trial operation. The assigned study drug must be administered within 48 hours of randomization.

In this trial, the settings of IWRS will be used to fulfill the following requirements in the randomly enrolled patients: patients with PD-L1 expression of < 1% do not exceed 35% of the total randomization population; patients with PD-L1 expression of ≥ 1% are not less than 65% of the total random population.

3.1.4 Stratification

The stratification of randomization is based on the following factors:

- Staging (stage IIIB/IIIC vs. stage IV)
- Platinum-based medications (cisplatin vs. carboplatin)
- The expression level of PD-L1 (< 1% vs. ≥ 1%), the patients whose expression level of PD-L1 cannot be evaluated are classified into the < 1% group.

3.2 Design Principles

3.2.1 Basis for selection of randomized double-blind study design

This study intends to adopt a randomized double-blind design, where blinding can reduce bias due to human error, make the study results more reliable, and improve the compliance of subjects.

3.2.2 Basis for selection of IBI308 administration regimen and dosage

According to current national and international guidelines, platinum-based doublet chemotherapy is still the standard first-line treatment for advanced squamous NSCLC population. The KEYNOTE 407 study evaluated the efficacy of pembrolizumab in combination with carboplatin and paclitaxel/albumin paclitaxel compared with carboplatin and paclitaxel/albumin paclitaxel first-line treatment for metastatic squamous NSCLC. The interim analysis reached the primary study end points of PFS and OS. IBI308 is an anti-PD-1 monoclonal antibody, and multiple immune-functioning mouse models has demonstrated the anti-tumor activity of monotherapy of IBI308 (see the Investigator's Brochure). In the phase Ia clinical study of IBI308 (CIBI308A101 Ia/b), pharmacodynamic results showed that IBI308 had a definite blocking effect on PD-1 receptor in the body, and satisfactory efficacy was achieved after treatment of IBI308 in combination with gemcitabine and cisplatin in the phase Ib cohort E first-line previously untreated population with advanced squamous NSCLC. Therefore, this trail will study the efficacy and safety of IBI308 in combination with gemcitabine and platinum (cisplatin/carboplatin) chemotherapy and placebo in combination with gemcitabine and platinum (cisplatin/carboplatin) chemotherapy in first-line treatment in previously untreated population with advanced or metastatic squamous NSCLC.

In this study, IBI308 is intended to be administered at a dosage of 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 currently completed in the previous study, combined with the nonclinical *in vitro*/*in vivo* pharmacodynamic data and relevant comparison

data to similar drugs. Under the premise that no significant variation occurs in drug clearance characteristics of subjects, IBI308 of 200 mg Q3W is administered continuously for 84 days (4 times) 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 Basis for selection of PFS as primary study end point

For a novel anti-tumor therapy, PFS is a widely accepted indicator of clinical efficacy in randomized phase III clinical studies and is able to demonstrate satisfactory risk-benefit characteristics of new therapies. In recent years, the FDA and the European Medicines Agency (EMA) have also identified it as one of the most important registration end points for clinical studies on NSCLC. PFS can be assessed by IRRC according to RECIST V1.1, thereby minimizing bias as much as possible. Therefore, PFS is intended to serve as primary study end point of this study.

3.2.4 Basis of allowing the control group to cross to IBI308 after progressive disease

Multiple studies have demonstrated the efficacy of anti-PD-1 monoclonal antibody in NSCLC patients who have failed first-line platinum-based chemotherapy, and the benefit and good tolerability in the NSCLC patients who have failed first-line platinum-based chemotherapy after subsequently receiving IBI308 monotherapy have also been demonstrated in the CIBI308A101 Ib cohort E (result has not yet been formally published). Based on the above results, subjects in the control group are allowed to cross to the treatment with IBI308 monotherapy after imaging PD based on the judgment of the investigator.

3.3 Independent Data Monitoring Committee (IDMC)

An independent data monitoring committee (IDMC) is set up to conduct an interim analysis of the primary efficacy endpoint (PFS) and safety. The personnel composition, responsibilities, and procedures of the IDMC are detailed in the IDMC regulations.

4 STUDY POPULATION

4.1 Inclusion Criteria

Subjects shall meet the following criteria:

1) Subjects must sign written ICF prior to the implementation of any procedures related to the trial;

2) Aged ≥ 18 years and ≤ 75 years;

3) With a life expectancy of more than 3 months;

4) With at least one measurable lesion confirmed by the investigator according to RECIST V1.1. Measurable lesions located in the radiation field of previous radiotherapy or subjected to locoregional therapy can be selected as target lesions if PD is confirmed;

5) Patients with histologically or cytologically confirmed locally advanced (stage IIIB/IIIC), metastatic or recurrent (stage IV) squamous NSCLC who cannot receive surgery or radical concurrent chemoradiotherapy, based on the "8th Edition of the TNM Classification for Lung Cancer" issued by the International Association for the Study of Lung Cancer and the American Joint Committee on Cancer Classification;

6) With an Eastern Cooperative Oncology Group Performance Status score (ECOG PS score) of 0 or 1;

7) Have not received any prior systemic anti-tumor therapy for advanced/metastatic disease; for patients who have received prior platinum-based adjuvant chemotherapy/radiotherapy, neoadjuvant chemotherapy/radiotherapy, or radical chemoradiotherapy for PD, they are eligible for the study if PD occurs at > 6 months after the last treatment;

8) With adequate hematologic function, defined as ANC $\geq 1.5 \times 10^9$ /L, platelet count $\geq 100 \times 10^9$ /L, and hemoglobin ≥ 90 g/L (no blood transfusion history within 7 days);

9) Adequate hepatic function, defined as total bilirubin (TBIL) ≤ 1.5 × upper limit of normal (ULN) and AST as well as ALT ≤ 2.5 × ULN for all patients, or AST and ALT ≤ 5 × ULN for patients with liver metastasis;

10) Adequate renal function, defined as clearance of creatinine (CCr) ≥ 50 mL/min (Cockcroft-Gault formula);

11) Adequate coagulation function, defined as international normalized ratio (INR) or prothrombin time (PT) ≤ 1.5 × ULN; for the subject who is receiving anticoagulant therapy, INR or PT within the proposed scope of the anticoagulant medication is acceptable;

12) Female subjects of childbearing age should be tested negative for urine or serum pregnancy within 3 days before the first dose of the study drugs. A blood pregnancy test is required if the urine pregnancy test is inconclusive;

13) For male and female patients at risk of conception, highly effective contraception measures (failure rate < 1% per year) should be taken until at least 180 days after discontinuation of the study treatment;

Note: Abstinence is acceptable as a method of contraception if it is the usual lifestyle and preferred method of contraception for the subject.

4.2 Exclusion criteria

Subjects cannot be enrolled if any of the followings is met:

1) Non-squamous NSCLC in histology. The dominant cell morphology must be identified for mixed cell type (patients with squamous cell carcinoma components > 50% can be enrolled); patients with small cell carcinoma, neuroendocrine carcinoma, and sarcoma components cannot be included;

2) Patients with known EGFR-sensitive mutations or ALK rearrangement;

3) Currently participating in an interventional clinical study, or treated with another study drug or investigational device within 4 weeks before the first dose;

4) Previously received the following therapies: anti-PD-1, anti-PD-L1, or anti-PD-L2 agents or agents targeting another stimulation or synergistically inhibiting T-cell receptor (TCR) (e.g., CTLA-4, OX-40, and CD137);

5) Received proprietary Chinese medicines with anti-tumor indications or immunomodulators (thymosin, interferon, interleukin, etc.) within 2 weeks prior to the first dose, or received a major surgery within 3 weeks prior to the first dose;

6) With active hemoptysis, active diverticulitis, abdominal abscess, gastrointestinal obstruction, and peritoneal metastases requiring clinical intervention;

7) Have undergone solid organ transplantation or hematologic transplantation;

8) With clinically uncontrolled pleural effusion/ascites (patients who do not need effusion drainage or have no significant increase in effusion 3 days after stopping drainage can be enrolled);

9) With a tumor compressing the surrounding important organs (such as esophagus) with relevant symptoms, compressing the superior vena cava, or invading the mediastinal great vessels, heart, etc.;

10) With Class III–IV congestive cardiac failure (based on New York Heart Association Classification) or poorly controlled and clinically significant arrhythmia;

11) With any arterial thrombosis, embolism, or ischemia within 6 months prior to enrollment, such as myocardial infarction, unstable angina, cerebrovascular accident, and transient ischemic attack. With a history of deep venous thrombosis, pulmonary embolism, or any other serious thromboembolic events within 3 months prior to enrollment (implantable port or catheter-related thrombosis, or superficial venous thrombosis is not considered as "serious" thromboembolism);

12) With known allergy to the active ingredients and/or any excipient of IBI308, gemcitabine, cisplatin, or carboplatin;

13) With active autoimmune disease requiring systemic treatment (e.g., use of disease-modifying drugs, corticosteroids, or immunosuppressive agents) within 2 years before the first dose. Replacement therapy (e.g., thyroxine, insulin, or physiologic doses of corticosteroids for adrenal or pituitary insufficiency) is not considered systemic;

14) Patients requiring long-term systemic use of corticosteroids. Patients requiring intermittent use of bronchodilators, inhaled corticosteroids, or local injection of corticosteroids for COPD or asthma can be included in the study;

15) Full recovery (i.e., ≤ grade 1 or reaching the baseline, excluding asthenia or alopecia) from toxicity and/or complications caused by any intervention has not achieved before the start of treatment;

16) Diagnosed with other malignant tumors within 5 years before the first dose, excluding radically cured cutaneous basal cell carcinoma, cutaneous squamous cell carcinoma, and/or radically resected carcinoma *in situ*. For other malignant tumors or lung cancer diagnosed more than 5 years before the first dose, pathological or cytological diagnosis should be performed for recurrent and metastatic lesions;

17) Symptomatic central nervous system (CNS) metastasis. Patients 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 of the following criteria: presence of measurable lesions outside the CNS; absence of metastases in midbrain, pons, cerebellum, meninges, medulla oblongata, or spinal cord; maintain clinical stable condition for at least 2 weeks; discontinue hormone therapy 14 days prior to the first dose of the study drugs;

18) With a history of non-infectious pneumonia requiring corticosteroid therapy within 1 year prior to the first dose or with non-infectious pneumonia at present;

19) With an active infection requiring treatment or have used systemic anti-infective drugs within one week prior to the first dose;

20) With known psychiatric disorder or substance abuse that could affect the compliance with trial requirements;

21) Known history of human immunodeficiency virus (HIV) infection (i.e. HIV 1/2 antibody positive), known syphilis infection (syphilis antibody positive), or active tuberculosis;

22) With untreated active hepatitis B;

Note: Subjects with hepatitis B who meet the following criteria are also eligible for inclusion:

HBV viral load must be less than 1000 copies/mL (200 IU/mL) or below the lower limit of detection (LLD) prior to the first dose, and subjects should receive anti-HBV treatment to avoid virus reactivation throughout the chemotherapeutic period of the study;

For subjects with HBcAb (+), HBsAg (−), HBsAb (−), and HBV load (−), close monitoring is required instead of prophylactic anti-HBV treatment to avoid virus reactivation;

23) Subjects with active HCV infection (HCV antibody positive and HCV-RNA level above the LLD);

24) Have received live vaccines within 30 days prior to the first dose;

Note: Seasonal inactivated influenza virus vaccines for injection are allowed, while live attenuated influenza vaccines for intranasal use are not acceptable;

25) With any medical history, disease, treatment, or laboratory abnormal finding that would interfere with the trial results or prevent the subject from participating in the whole trial, or the investigator believes that participation in this study is not in the best interest of the subject;

26) With local or systemic diseases not attributable to malignancy, or with cancer-related secondary diseases, which would result in a high medical risk and/or uncertainty in survival evaluation.

4.3 Restrictions During the Study

4.3.1 Pregnancy

Since it is known that human IgG_1 and IgG_4 are able to penetrate the placental barrier, administration during pregnancy is not recommended. Pregnant women are not allowed to be included in this study.

4.3.2 Childbearing age

For female subjects of childbearing age who are sexually active with male partners who have not undergone sterilization, and male subjects who have not undergone sterilization and are sexually active with female partners of childbearing age, such subjects and their partners must use one of the acceptable methods of contraception listed in **Table 3** from screening to 180 days after the last dose of study treatment, and then discuss with a responsible physician about the discontinuation of contraception after this time point. Periodic abstinence, calendar-based method, and withdrawal method are not the acceptable forms of contraception. Women of

childbearing age is defined as females who have experienced menarche, have not undergone surgical sterilization (bilateral tubal ligation, bilateral salpingectomy, or panhysterectomy), and are not postmenopausal.

Table 3. Effective contraceptive methods (at least 1 method 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 injection
Diaphragm with spermicide	Levonorgestrel-releasing intrauterine system (e.g. Mirena®)[a]	Combined oral contraceptive pill Low-dose oral contraceptive pill Contraceptive patch

[a] Also considered as a hormonal method.

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

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

4.3.3 During Lactation

IBI308 is unknown for secretion from breast milk. Considering the presence of multiple drugs in breast milk, IBI308 may have potential toxicity for infants. Therefore, lactating women should not be enrolled into this study.

4.4 Criteria for Discontinuation/Withdrawal

4.4.1 Treatment Discontinuation

Treatment discontinuation is not the same as withdrawal from the study. Since data on some clinical events after treatment discontinuation may be important to the study, these information must be collected until the subject's last scheduled visit, even if the treatment has already been discontinued.

The treatment can be discontinued by a subject at any time for any reasons, or determined by the investigator in the case of any AEs. In addition, the investigator or sponsor may discontinue the treatment of a subject if the subject is not suitable for treatment or violates study protocol, or for administrative and/or other safety reasons.

A subject must discontinue the treatment in the case of any one of the followings, but can continue to be monitored during the study:

- Treatment discontinuation required by the subject or his/her legal representative.
- Occurrence of an AE that requires discontinuation due to protocol-specified reasons (refer to Section 5.2).
- Onset of another malignant tumor that requires active treatment.
- Onset of a concurrent disease that interferes further treatment.
- Subject withdrawal determined by the investigator.
- Positive serum pregnancy test results.
- Poor compliance of the subject.
- Unnecessary risks of study drug continuation to the subject determined by the investigator and/or sponsor according to subject's disease status and condition.
- Completion of the 24-month treatment of study drug (a maximum of 24 months for patients in the control group who were cross-treated with IBI308 after objective PD).

For subjects who have discontinued treatment but continue to receive visits in the study, all visits and procedures listed in the schedules of activities (Tables 1 and 2) shall be completed.

4.4.2 Withdrawal

A subject must withdraw from the study if the subject or his/her legal representative withdraws the ICF of participating in the study. A subject will not continue to receive treatment or scheduled visits if he/she withdraws from the study. A subject can receive survival visits after withdrawal from the study with his/her consent. A subject must withdraw from the study if he/she is lost to follow-up.

4.4.3 Clinical criteria for premature discontinuation of study

The study will be discontinued prematurely if the following criteria are met:

- Inaccurate or incomplete of quality and quantity of data records

- Poor compliance to the study protocol and regulatory requirements
- Potential hazard to the subjects' health as suggested by the adverse drug reaction (ADR) incidence or severity level in this or other studies
- Planned changes or discontinuation of study drug development

If the sponsor decides not to continue the supply of the study drugs, sufficient notice will be made to facilitate the appropriate adjustments to the subject's treatment.

5 STUDY DRUG AND OTHER TREATMENTS

Study drugs are defined as IBI308, placebo, gemcitabine, and cisplatin or carboplatin in this study. The first dose of study treatment should be started on the day of randomization (day 1 of cycle 1), and no later than 48 h after the randomization. The sponsor should be notified if the first dose is not administered after 48 h. Every effort should be made to start the study treatment on the day of randomization. As determined by the investigator and for administrative reasons, the study treatment can be administered before the scheduled day 1 of cycles or within 3 days thereafter.

Table 4. Study therapeutic drugs

Study drug	Dose	Frequency	Route of administration	Treatment cycle	Usage
IBI308[1]	200mg	Q3W	Intravenous infusion	Once Q21D, administered on day 1, consecutive cycles	Test group
Placebo[1]	NA	Q3W	Intravenous infusion	Once Q21D, administered on day 1, consecutive cycles	Control group
Gemcitabine[2]	1.0g/m^2	Q3W	Intravenous infusion	Once Q21D, administered on days 1 and 8, a maximum of 6 consecutive cycles	Test/Control group
Cisplatin[2]	75mg/m^2	Q3W	Intravenous infusion	Once Q21D, administered on day 1, a maximum of 6 consecutive cycles	Test/Control group
Carboplatin[2]	AUC 5	Q3W	Intravenous infusion	Once Q21D, administered on day 1, a maximum of 6 consecutive cycles	Test/Control group

1. IBI308 should be administered by infusion prior to the administration of chemotherapeutics.
2. If the weight fluctuation is less than 10% compared to baseline (the day of the first dose), use the baseline weight to calculate the body surface area, and then calculate the chemotherapeutic dose based on the body surface area. Otherwise, use the weight on the scheduled day of administration to calculate the chemotherapeutic dose. The maximum body surface area adopted in the protocol is 2.0 m^2. For subjects with a body surface area of > 2.0 m^2, the staff of the study center 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.

All the study drugs in **Table 4** are provided by the sponsor, and the product/batch numbers of all procured drugs are accessible. The study sites are responsible for recording the batch numbers, manufacturers, and expiry dates.

5.1 Use of Study Drugs

5.1.1 Use of IBI308

The main active ingredient of IBI308 is the recombinant fully human anti-PD-1 monoclonal antibody, with a concentration of 10 mg/mL. IBI308 is a clear, colorless liquid and is free of foreign matters, flocs, and precipitation. The excipients include 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 salt), and 0.2 mg/mL polysorbate 80, pH 6.0.

The smallest packaging unit is one box. Each box contains 2 vials of sintilimab (IBI308) injection. The package contains the drug name, dosage form, strengths, drug code, batch number, expiry date, storage conditions, and sponsor's information. The label on the vial contains the same information as the outer package except for dosage form, precautions, and dosage and administration. The package and vial should be both labeled "use for clinical study only". IBI308 drug product should be stored at 2–8 ℃ away from light. The shelf life is 24 months. If quality issues such as turbidity and precipitation are observed in the injection, seal the vial immediately and notify the sponsor.

The preparation and infusion of IBI308 are as follows:

1. Completely withdraw the contents of 2 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 the uniformity of the contents. No vigorous shaking is allowed to avoid foam. If large amount of foam forms, stand the IV bag until the foam disappears.
3. Administer with a 0.2–1.2 μm in-line filter (suggested infusion time is 30–60 minutes). 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 ℃ in the fridge); avoid mixing with other drugs; do not administer as an IV push.

5.1.2 Use of chemotherapeutics

Standard chemotherapeutics used in combination are prepared according to the description in the approved product specification and the selected dose is as follows:

- Gemcitabine: 1000 mg/m^2 d1, 8/q3w
- Cisplatin: 75 mg/m^2 d1/q3w
- Carboplatin: AUC 5 (calculated by Calvert formula) d1/ q3w, and the dosage of carboplatin shall not exceed 750 mg.

  Calvert formula

  Total dose (mg) = (target AUC) × (CCr + 25)

  The estimated CCr used in the Calvert formula shall not exceed 125 mL/min

  Maximum carboplatin dose (mg) = target AUC 5 (mg·min/mL) × (125 + 25) = 5 × 150 mL/min = 750 mg

Full hydration is required to prevent the renal toxicity of cisplatin: During the use of cisplatin, a hydration of 3 days is required, and potassium chloride, mannitol, and furosemide should be used to maintain the daily urine volume at 2000–3000 mL. Cisplatin is a chemotherapeutic drug which carries high likeliness to induce vomiting, and therefore antiemetic drugs such as 5-HT3 receptor antagonist, dexamethasone (or other glucocorticoids), dopamine receptor blockers (methoxychlor amine), and antihistamines (such as promethazine hydrochloride and diphenhydramine) are recommended, and NK-1 receptor antagonist (aprepitant) are recommended to prevent chemotherapy-associated vomiting when conditions allow.

5.2 Dose adjustments

5.2.1 General principles

The dose adjustment must be based on the most severe drug toxicity occurred in the previous administration cycle. Before the administration of each study drug on day 1, the subjects' hematologic, hepatic and renal function must meet the requirements for administration, and all other toxicities must resolve to CTCAE grade 0–1 or baseline level (excluding alopecia, fatigue, specific stipulations in the protocol, or other circumstances of no clinical significance as determined by the investigator; when chemotherapy-related myelosuppression resolves to grade 2 or below, IBI308 therapy can be resumed).

For chemotherapy, administration requirements for hematologic function were defined as the absolute count of central granulocytes ≥ 1.5 × 10^9/L, platelet count ≥ 100 × 10^9/L, and

hemoglobin ≥ 90 × 10^9/L; for hepatic function were defined as TBIL ≤ 1.5 × ULN, AST and ALT ≤ 2.5 × ULN (all patients) or ≤ 5 × ULN (patients with liver metastasis); for renal function were defined as CCr ≥ 50 mL/min prior to the first dose (Cockcroft-Gault formula) followed by CCr ≥ 45 mL/min in subsequent cycles. For IBI308/placebo administration, chemotherapy-associated myelosuppression should resolve to grade 2 or below, and the administration requirements in case of immune-related hepatic dysfunction and renal insufficiency refer to Section 5.2.2 and **Table 5** in this protocol. In clinical practice, administration may be acceptable based on the judgment of the investigator despite the presence of a deviation from the scope of above requirements. If the subject can tolerate the study drug as determined by the investigator, the administration of study drug can be conducted after the communication with the sponsor by e-mail, while the close follow-up is required to deal with any subsequent changes in a timely manner.

If the subject fails to meet the administration criteria after the scheduled interval of the administration cycle due to drug toxicity, the next administration is allowed to be delayed. The administrations of IBI308 and chemotherapeutics should be kept in synchronization as far as possible by adjusting the window period of ±3 days. If these study drugs need to be interrupted/permanently discontinued due to the toxicity associated with a certain or multiple study drugs, AEs related to therapeutic drugs, or other reasons, the other study drugs (IBI308 or chemotherapy) can be used alone in conditions that corresponding administration criteria are met.

All dose adjustments should be documented, including reasons and processings.

5.2.2 Dose adjustment of IBI308

Does adjustments of IBI308 are not permitted throughout the trial. The principles of interruption and permanent discontinuation of IBI308 are shown in **Table 5**. If the administration delay occurs in a 3-week treatment cycle for IBI308, all the subsequent administration days should be delayed to ensure that a dosing interval of 21 ±3 days. IBI308-related AEs are usually immune related adverse events (irAEs). For suspension due to irAEs, hormone therapy may be used to resolve the AEs to grade 1 or 0 based on their type and severity, and administration can be resumed after 4 weeks or above of reduction of hormone dose.

Table 5. Dose adjustment protocol for irAEs of IBI308

irAEs	Severity level	Dose adjustments
Pneumonia	Grade 2 pneumonia	Interruption[a]
	Recurrent grade 2 pneumonia, grade 3 or 4 pneumonia	Permanent discontinuation
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 of ≥ 50% (reaching the requirement of grade 2) 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	Interrupt or permanently discontinue
Adrenocortical insufficiency	Grade 2 adrenocortical insufficiency	Interruption[b]
	Grade 3 or 4 adrenocortical insufficiency	Interrupt or permanently discontinue
Hyperthyroidism	Grade 3 or 4 hyperthyroidism	Interrupt or permanently discontinue
Hypothyroidism	Grade 2-4 hypothyroidism	Continue
Type I diabetes	Grade 3 hyperglycemia	Interruption[b]
	Grade 4 hyperglycemia	Interrupt or permanently discontinue
Renal insufficiency	Grade 2 or 3 Cr elevation	Interruption[a]
	Grade 4 Cr elevation	Permanent discontinuation
Neurotoxicity	Grade 2 neurotoxicity	Interruption[a]
	Grade 3 or 4 neurotoxicity	Permanent discontinuation
Other irAEs[c, d]	Intolerance/persistent grade 2 AE	Interruption[a]
	Grade 3 AE	Interrupt or permanently discontinue
	Grade 4 AE or recurrent Grade 3 AE	Permanent discontinuation

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

b: Resume the administration if hypophysitis, adrenocortical insufficiency, hypothyroidism/thyroid dysfunction, or type I diabetes is adequately controlled and only physiological hormone replacement therapy is required.

c: Interruption or permanent discontinuation for an abnormal laboratory test result should be determined based on the concomitant clinical symptoms/signs and the investigator's clinical judgment.

d: In case of immune-related blood amylase and lipase elevations (grade 3 or 4), which are simply abnormal results of laboratory tests and have no clinical symptoms/signs, the investigator can resume the administration of IBI308/placebo after the indicators improve. The investigator can determine the subsequent administration based on the comprehensive considerations of the patients' concomitant symptoms/signs, the instructions for IBI308, and the relevant guidelines.

IBI308 is allowed to be interrupted for up to 12 weeks. If the symptoms do not resolve to the level, at which the treatment can be resumed, within 12 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 > 12 weeks due to dose reduction of glucocorticoid that is used to treat irAEs. Consult the sponsor's medical manager prior to resuming IBI308. Imaging examination for efficacy should not be affected by treatment interruption and should be performed as scheduled.
- IBI308 interruption is over 12 weeks due to the treatment of AEs unrelated to IBI308. Consult the sponsor's medical manager prior to resuming IBI308. Imaging examination for efficacy should not be affected by treatment interruption and should be performed as scheduled.

5.2.3 Management of IBI308 infusion-related reactions

IBI308 may cause severe or life-threatening infusion-related reactions, including severe hypersensitivity reactions or allergic reactions. Signs and symptoms usually occur during or after drug infusion and usually resolve within 24 h after the infusion completion. Refer to **Table 6** for the guidelines for management of IBI308 infusion-related reactions.

Table 6. Guidelines for management of IBI308 infusion-related reactions

NCI CTCAE grade	Treatments	Premedications for subsequent infusions
Grade 1 Mild reaction; infusion interruption not indicated; intervention not indicated	According to subject's medical indications, monitor the vital signs closely until the subject is stable as determined by the investigator.	Absent
Grade 2 Therapy or infusion interruption indicated but responds promptly to symptomatic treatment required (e.g., antihistamines, non-steroidal anti-inflammatory drugs (NSAIDs), anesthetics, IV fluids); prophylactic medications indicated for ≤ 24 hours	**Stop the infusion and monitor symptoms.** Other appropriate treatments include but are not limited to: IV fluids Antihistamines NSAIDS Acetaminophen Anesthetics	The following premedications are recommended within 1.5 h (± 30 min) prior to IBI308 infusion: Diphenhydramine 50 mg PO (or equivalent antihistamines).

NCI CTCAE grade	Treatments	Premedications for subsequent infusions
	According to subject's medical indications, monitor the vital signs closely until the subject is stable as determined by the investigator. If symptoms resolve within 1 h after interrupting the infusion, then the infusion will be resumed at 50% of the original infusion rate (e.g. from 100 mL/h to 50 mL/h). Otherwise, interrupt the treatment until symptoms resolve. Premedications should be given before next scheduled administration. **If grade 2 toxicities occur despite of adequate premedications, the study drugs should be permanently discontinued.**	Acetaminophen 500–1000 mg PO (or antipyretics at equivalent effective dose).
Grade 3 or 4 Grade 3: Prolonged (i.e. not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae (e.g. renal impairment, pulmonary infiltration) Grade 4: Life threatening; pressors or ventilatory support indicated	**Discontinue the infusion.** Other appropriate treatments include but are not limited to: Epinephrine** IV fluids Antihistamines NSAIDS Acetaminophen Anesthetics Oxygen Pressors Corticosteroids According to subject's medical indications, monitor the vital signs closely until the subject is stable as determined by the investigator. Hospitalization may be indicated. **Epinephrine should be used immediately for allergic reactions. **The study drugs should be permanently discontinued.**	Not applicable
Appropriate first-aid equipment should be provided in the ward and physicians should be available at all times during the administration. For more information, refer to "Common Terminology Criteria for Adverse Events" (CTCAE) V4.03 (http://ctep.cancer.gov)		

5.2.4 Dose adjustments of chemotherapeutics

If the toxicity is mainly caused by a certain chemotherapeutic drug as confirmed by the investigator, dose reduction of a single medication can be acceptable; if the toxicity is uncertain and may be caused by two or more drugs, dose reductions of all relevant drugs are feasible. If administration delay of chemotherapeutics occurs in a 3-week treatment cycle, all the subsequent administration days should be delayed to ensure a dosing interval between chemotherapy treatments of 21 ±3 days. If the administrat ion of gemcitabine on day 8 is delayed for more than 7 days due to toxicity, skip the administration on day 8 and resume the treatment in the next cycle. The chemotherapy cycle and the IBI308 cycle should be kept in synchronization as far as possible by adjusting the permitted window period. The longest permitted discontinuation time period of chemotherapeutics is 6 weeks from the last chemotherapy. If the drug requirements of chemotherapy cannot be met after 6 weeks, chemotherapy shall be terminated permanently.

Different dose levels of chemotherapeutics are shown below. If dose reduction is still required after reductions of two dose levels, the chemotherapy should be discontinued.

Table 7. Dose adjustments of chemotherapeutics

	Initial dose	Reduction by 1 dose level	Reduction by 2 dose levels
Gemcitabine	1000mg/m^2	750mg/m^2	500mg/m^2
Cisplatin	75mg/m^2	56mg/m^2	38mg/m^2
Carboplatin	AUC 5, maximum dose 750 mg	AUC 3.75, maximum dose 562.5 mg	AUC 2.5, maximum dose 375 mg

Recommended dose adjustments for chemotherapy-related hematotoxicities

Table 8. Dose adjustments based on chemotherapy-related hematological toxicities in previous cycle

		Gemcitabine	Cisplatin/Carboplatin
Platelet	Neutrophil	Adjust the dose level according to **Table 7**	
≥ 50 × 10^9/L and	≥ 0.5×10 ^{9}/L	Initial dose	Initial dose
≥ 50 × 10^9/L and	< 0.5×10 ^{9}/L	Reduction by 1 dose level	Reduction by 1 dose level
< 50 × 10^9/L, without hemorrhage, and	Any	Reduction by 1 dose level	Reduction by 1 dose level
< 50 × 10^9/L, combined with hemorrhage of ≥ grade 2, and	Any	Reduction by 2 dose levels	Reduction by 2 dose levels
Any condition, and	< 1 × 10^9/L, combined with fever ≥ 38.5 °C	Reduction by 1 dose level	Reduction by 1 dose level

Recommended dose adjustments for chemotherapy-related non-hematotoxicities

Table 9. Dose adjustments based on chemotherapy-related non-hematological toxicities in previous cycle

Adverse event	CTCAE grade	Gemcitabine	Cisplatin	Carboplatin
Nausea or emesis	Grade 3 or 4	Initial dose	Initial dose	Initial dose
Diarrhea	Grade 3 or 4	Reduction by 1 dose level	Reduction by 1 dose level	Initial dose
Rash	Grade 3 or 4	Reduction by 1 dose level	Initial dose	Initial dose
Neurotoxicity	Grade 2	Initial dose	Reduction by 2 dose levels	Initial dose
	Grade 3 or 4	Discontinue	Discontinue	Reduction by 1 dose level
Transaminase increased	Grade 3	Reduction by 1 dose level	Reduction by 1 dose level	Reduction by 1 dose level
	grade 4	Discontinue	Discontinue	Discontinue
Other non-hematological toxicity	Grade 3 or 4	Reduction by 1 dose level	Reduction by 1 dose level	Reduction by 1 dose level

Clearance of creatinine (CCr):

CCr is calculated by Cockcroft-Gault formula (Appendix 3), which is based on the standard body weight. The CCr must be ≥ 50 mL/min before the first administration of chemotherapeutics. A maximum of 6 weeks of administration delay of gemcitabine and/or platinum-based drugs is acceptable for waiting for recovery of CCr to required level in the subject; and if the recovery of CCr to a level of ≥ 45 mL/min is unachieved after more than 6 weeks since the last administration, cisplatin or carboplatin and/or gemcitabine must be discontinued.

5.3 Principles of Managing Immune Checkpoint Inhibitor Toxicities

AEs related to IBI308 exposure may be etiologically associated with immunity. These irAEs may occur within a short period after the first dose or within months after the last dose. They may influence more than one systems simultaneously. Therefore, early diagnosis and treatment are critical to reduce complications. Based on the existing clinical trial data, most irAEs are reversible, and can be managed through discontinuation of IBI308, administration of glucocorticoids, and/or other supportive therapies. For suspected irAEs, appropriate evaluations for confirmed pathogenesis or exclusion of other reasons should be ensured. Other procedures or examinations, such as bronchoscopy, endoscopy, or skin biopsy, may be included into this evaluation. Temporary or permanent discontinuation of IBI308 and administration of

glucocorticoids are adopted depending on the severity level of irAEs. Refer to the "Manual for Management of Immune Related Adverse Events" provided by the sponsor for dose adjustments and toxicity management of potential irAEs.

5.4 Concomitant Treatments

5.4.1 Permitted concomitant treatments

- Medications that meet the protocol requirements, as determined by the investigator (e.g. concomitant medication used for disease-related symptoms and TRAEs).
- 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, minimally invasive treatment, or radiotherapy 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.

5.4.2 Prohibited concomitant treatments

The following treatments are prohibited during the study treatment (including the crossover monotherapy of IBI308 for subjects in the control group after objective PD):

- Any systemic chemotherapy or biotherapy (except for cytokine drugs to treat chemotherapeutics-induced AEs), as well as proprietary Chinese medicines, with anti-tumor effects.
- Immunomodulators, including but not limited to non-specific immunomodulators (such as thymosin, interferon, interleukin, immunoglobulin, and gamma globulin) as well as proprietary Chinese medicines with immunomodulating effects, etc.
- Chemotherapeutics not specified in this protocol.
- Any study drug other than IBI308.
- Radiotherapy to control tumors (palliative radiotherapy is allowed if not directed towards the target lesion, such as radiotherapy for relieving pain from bone metastasis and symptoms of brain metastasis).

- Inoculation with live vaccine within 30 days prior to the first dose of study treatment and throughout the trial. Live vaccines include but are not limited to measles, epidemic parotitis, rubella, chicken pox, yellow fever, rabies, Bacillus Calmette Guerin (BCG), and typhoid (oral) vaccines. Seasonal inactivated influenza virus vaccines are permitted, but live attenuated influenza vaccines are not.
- Corticosteroids. Inhaled steroids for subjects with asthma or chronic obstructive pulmonary disease (COPD) are permitted; temporary use of corticosteroids for relieving dyspnea are permitted; corticosteroids are permitted for the treatment of immune-related AEs; corticosteroids of physiologic dose can be approved after consulting the sponsor.
    - Note: Prophylactic corticosteroids to avoid allergic reactions (e.g. pretreatment prior to administration of IV contrast agent or chemotherapeutics) are permitted.

Based on the assessment of the investigator, subjects requiring any one of the treatment methods above must be excluded from the trial. Subjects may receive other medically-necessary medications as determined by the investigator.

It is very important for the investigator to review every drug (prescription and non-prescription) used by the subject prior to the trial and during each visit.

- During each visit, subjects must be asked about any new medications received.
- To minimize the risk of drug-drug interactions, every measure must be taken to limit the number of concomitant medications that are really necessary.
- Drugs of hepatotoxicity (i.e. those with warnings in the prescribing information) should be avoided during the treatment. The investigators are encouraged to review every potential hepatotoxic drug via www.livertox.nih.gov.
- Prohibited drugs listed in the exclusion criteria are not permitted.

5.4.3 Drug-drug interactions

- IBI308: No information on drug-drug interaction of IBI308 is currently available.
- Gemcitabine: No information on drug-drug interaction of gemcitabine is currently available.
- Cisplatin: cisplatin in combination with aminoglycoside antibiotics, amphotericin B, or cefalotin may increase renal toxicity; cisplatin in combination with probenecid may induce hyperuricemia; chloramphenicol, furosemide, or ethacrynate sodium can increase the ototoxicity of cisplatin; antihistamine may cover up tinnitus, vertigo, and other symptoms caused by cisplatin.

- Carboplatin: IBI308 may alter renal function. Although it is still inconclusive whether the nephrotoxicity of carboplatin would be increased when used in combination with aminoglycosides and other nephrotoxic drugs, the combination use with these drugs is recommended to be avoided.

5.5 Drug Management

5.5.1 Drug management

IBI308 should be refrigerated at 2–8 °C in a dry place and away from light. Do not freeze. Cold-chain should be maintained during transport, and the study drugs should be kept and dispensed by a designee.

The study drugs should be stored in a refrigerator only accessible by the authorized personnel. After receiving the study drugs, the investigator should ensure that the temperature during transport is maintained within the specified range, sign for receipt upon verification, and store the study drugs at the specified temperature. If abnormalities of the storage temperature during either the transport or storage at the study site arise, the study drugs should be moved to an environment in the specified temperature as soon as possible and should not be administered. Notify the sponsor timely and follow the advice of the sponsor.

All the investigational drugs provided by the sponsor should only be used for this clinical trial. Any purposes other than those specified in the protocol are not permitted. The investigator must agree not to provide the study drugs to anyone unrelated to this trial.

Used IBI308 should be stored under the same storage conditions until verification by the clinical research associate (CRA), who will then arrange for the return of study drugs.

5.5.2 Dispensation

This trial will use stratified randomization. The randomization list will be generated by statisticians with SAS. After confirming that the subject meets all of the inclusion and exclusion criteria, the study site will log in the IWRS and enter the subject information into it. The IWRS will allocate a random number to the subject and provide a medication number.

5.5.3 Return and destruction

In this trial, the containers of used IBI308 should be returned, and those of chemotherapeutics can be destroyed on-site according to appropriate guidelines and operating procedures established by study sites and local agencies. If some study sites have difficulties in recovering the IBI308 containers, they are allowed to destroy the containers on-site according to the process of chemotherapeutics containers with the consent of the sponsor.

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 study drugs were made by the clinical research associate (CRA) designated by the sponsor.

5.6 Study drug-related records

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

5.7 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 completed the following procedures for product complaints in accordance with applicable requirements of the study:

- A drug complaint form specific for clinical trials was used to document product complaints and relevant description completely.
- The completed product complaint form should be submitted to the sponsor or designee by fax or email within 24 hours.
- If the investigator was asked to return the product for further investigation, the investigator should return the product along with a copy of the complaint form.

6 STUDY PROCEDURE

6.1 Subject Screening and Randomization Procedures

6.1.1 Subject screening and randomization

The investigator enrolled the subjects by the following steps:

1. Subjects should sign the ICF prior to any study-related procedures.
2. Confirmed the subjects' eligibility by the principal investigator or trained designee after reviewing the inclusion/exclusion criteria.
3. Central randomization is adopted, with the stratification factors of staging (stage IIIB/IIIC vs. stage IV), platinum-based medications (cisplatin vs. carboplatin), and PD-L1 expression level (< 1% vs. ≥ 1%).

Subjects who failed to meet the criteria (screen failures) were 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/exclusion criteria must be followed strictly. If an ineligible subject is enrolled, the sponsor's medical manager and the investigator must discuss whether to allow the subject to continue participating in the study. 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, then the subject will continue participating in the study and receive the study drug; If the investigator considers that continued participation in the study is medically appropriate but the sponsor's medical manager disagrees with the decision, the subject cannot continue to participate in the study. The investigator must 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 informed consent form
- Confirming the inclusion/exclusion criteria
- Recording the demographics, medical history, and previous therapies of lung cancer
- Previous and concomitant medications
- Recording the vital signs, height, and body weight
- Physical examination
- ECOG PS score
- 12-lead electrocardiogram (ECG)
- Routine blood test/blood chemistry/urinalysis/myocardial enzyme and troponin (within 7 days prior to the first dose)
- Hemagglutination function tests (within 7 days prior to the first dose)
- Pregnancy test (within 3 days prior to the first dose)

- Thyroid function (within 28 days prior to the first dose)
- HIV antibodies, hepatitis B panel (HBsAg, HBsAb, HBcAb, HBeAg, HBeAb) and HBV-DNA (if applicable), as well as HCV antibodies and HCV-RNA (if applicable) (within 28 days prior to the first dose)
- AE evaluation
- Concomitant medications
- Tumor imaging evaluation (within 28 days prior to the first dose)
- Archived or fresh tumor tissue sample

Refer to Sections 7.1 and 7.2 for details regarding physical examination, tumor imaging evaluation, and safety evaluation.

6.2.1.1 Medical history

The medical history should be collected by the investigator or qualified designee. The medical history shall include all previous diseases and current active diseases. All autoimmune diseases should be documented, regardless of the date of onset. The medical history shall include the diagnosis and treatments for the disease. A detailed previous therapies of lung cancer (including chemotherapy, radiotherapy, and surgery) will be documented separately, which will not be listed in the medical history.

6.2.1.2 Previous medication

The investigator or qualified designee will review the previous medications of subjects (including any washout requirements specified in the protocol) and document the medications (including replacement/supplement drugs) used within 30 days prior to the first dose of investigational drug.

6.2.1.3 Concomitant medications

The investigator or qualified designee will document all concomitant medications used throughout the trial (from signing of the ICF to the safety follow-up visits).

All medications related to SAE should be documented and reported according to the definition in Section 8.4.

6.2.2 Treatment visits

- Recording the vital signs and body weight
- ECOG PS score

- 12-lead electrocardiogram (ECG)
- Routine blood test/blood chemistry/urinalysis/myocardial enzyme and troponin
- Thyroid function
- HBV DNA and/or HCV RNA (if applicable)
- PK and immunogenicity
- AE evaluation
- Concomitant medication
- Tumor imaging evaluation
- Administration of study drugs
- LCSS and EORTC QLQ-C30
- Full blood sampling for biomarkers

Refer to **Table 1** for the schedule of follow-up visits during the study treatment. Refer to Sections 7.1–7.4 for details regarding tumor imaging evaluation, safety evaluation, and blood sampling for PK/immunogenicity.

6.2.3 Safety visits

A safety follow-up should be carried out on day 30 (± 3 days) after the last dose or before the start of a new anti-tumor treatment, whichever occurs first. The following contents should be included:

- Recording the vital signs
- Body weight
- Physical examination
- ECOG PS score
- 12-lead electrocardiogram (ECG)
- Routine blood test/blood chemistry/routine urinalysis
- Hemagglutination function tests
- Thyroid function
- Pregnancy test

- HBV DNA and/or HCV RNA (if applicable)
- AE evaluation
- Immunogenicity
- Concomitant medication
- Subsequent anti-tumor therapy (if applicable)
- Tumor imaging evaluation
- LCSS and EORTC QLQ-C30
- Full blood sampling for biomarkers

All AEs prior to the safety follow-up visits should be documented until the events recover to grade 0–1 or the baseline level, 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), whichever occurs first.

6.2.4 Survival visits

After completing the safety follow-up, the subject shall be contacted every 90 (± 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.

6.2.5 Subsequent anti-tumor therapy

The investigator or qualified designee will review all the new anti-tumor therapies initiated after the last dose. If the subject initiate a new anti-tumor therapy within 30 days after the last dose, the safety follow-up visit must be performed before initiation of the new therapy.

The subject should be followed for survival after initiation of the new anti-tumor therapy. Refer to Section 6.2.4 "Survival visits" for details regarding survival follow-ups.

6.3 Initiation of Crossover Treatment in Subjects of Control Group After Objective Progressive Disease

If confirmed objective PD occurs after treatment and the unblinding is completed, subjects in the control group can receive monotherapy of IBI308 for crossover treatment based on the judgment of the investigator and the consent of the sponsor, on the conditions of SD and meeting the criteria of crossover treatment. Subjects, other than those discontinue the treatment due to objective PD confirmed by imaging, shall not receive crossover treatment with IBI308.

Regardless of the onset date of objective PD, subjects who is about to receive crossover treatment must start the administration of IBI308 at least 21 days after the last chemotherapy.

Criteria for crossover treatment are presented below:

- Evidence for objective PD is confirmed by IRRC according to RECIST V1.1;
- All AEs (except for alopecia and asthenia) must recover to ≤ grade 1 or the baseline level;
- Subjects who are clinically unstable due to new lesions or brain metastases cannot receive crossover treatment;
- An ECOG PS score of 0–1;
- Subjects have not received any systemic anti-tumor treatment other than chemotherapeutics in this study;
- Palliative radiotherapy (≤ 30 Gy) should be completed at least 7 days before the first dose of crossover therapy;

The study plan for the open-label crossover treatment period is as follows.

6.3.1 Evaluation before crossover treatment

The following procedures must be completed prior to crossover treatment to ensure the eligibility of the subjects in this study, and the imaging results obtained at the end of the last dose can be used for the evaluation before crossover treatment:

- Verify whether the subjects meet the criteria for crossover treatment
- Recording the vital signs, height, and body weight
- Physical examination
- ECOG PS score
- 12-Lead ECG (within 7 days before the first dose)
- Routine blood test/blood chemistry/routine urinalysis (within 7 days prior to the first dose)
- Hemagglutination function tests (within 7 days prior to the first dose)
- Pregnancy test (within 3 days prior to the first dose)
- Thyroid function (within 21 days prior to the first dose)

- HIV antibodies, hepatitis B panel (HBsAg, HBsAb, HBcAb, HBeAg, HBeAb) and HBV-DNA (if applicable), HCV antibodies and HCV-RNA (if applicable) (within 21 days prior to the first dose)
- Blood myocardial enzyme and troponin (within 7 days prior to the first dose)
- AE evaluation
- Concomitant medications
- Tumor imaging evaluation

Refer to Sections 7.1 and 7.2 for details regarding tumor imaging evaluation and safety evaluation.

The investigator or qualified designee will document all the concomitant medication used throughout the trial (from the first dose of IBI308 to the safety visit).

6.3.2 Visits during crossover treatment

- Recording the vital signs
- ECOG PS score
- 12-lead electrocardiogram (ECG)
- Routine blood test/blood chemistry/routine urinalysis
- Thyroid function
- HBV DNA and/or HCV RNA (if applicable)
- Blood myocardial enzyme and troponin
- AE evaluation
- Concomitant medication
- Tumor imaging evaluation
- Administration of study drugs
- LCSS and EORTC QLQ-C30

Refer to **Table 2** for the schedule of visits during crossover treatment. Refer to Sections 7.1–7.2 for details regarding tumor imaging evaluation and safety evaluation.

6.3.3 Safety visit after crossover treatment

A safety follow-up will be carried out on day 30 (± 3 days) after the last dose or before initiation of new anti-tumor therapy, whichever occurs first. The following contents should be included:

- Recording the vital signs
- Body weight
- Physical examination
- ECOG PS score
- 12-lead electrocardiogram (ECG)
- Routine blood test/blood chemistry/routine urinalysis
- Hemagglutination function tests
- Pregnancy test
- Thyroid function
- HBV DNA and/or HCV RNA (if applicable)
- AE evaluation
- Concomitant medication
- Subsequent anti-tumor therapy (if applicable)
- Tumor imaging evaluation
- Survival condition
- LCSS and EORTC QLQ-C30

All AEs prior to the safety follow-up visits should be documented until the events recover to grade 0–1 or the baseline level, 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), whichever occurs first. All SAEs that occur within 90 days after the last dose or before initiation of new anti-tumor therapy (whichever occurs first) should be followed up and documented.

6.3.4 Survival visits after crossover treatment

After completing the safety follow-up, the subject shall be contacted every 90 (± 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.

Note: If the safety visit on day 30 is not performed for a subject, then the date should be calculated from the end of treatment.

6.3.5 Subsequent anti-tumor therapy after crossover treatment

The investigator or qualified designee will review all the new anti-tumor therapies initiated after the last dose. If the subject initiates a new anti-tumor therapy within 30 days after the last dose, the safety follow-up visit must be performed before initiation of the new therapy.

The subject should be followed for survival after initiation of the new anti-tumor therapy. Refer to Section 6.3.4 "Survival visits" for details regarding survival follow-ups.

6.4 Other Procedures

6.4.1 Treatment discontinuation/withdrawal from study

A subject who discontinues the treatment/withdraws from the study before the completion of the treatment should be encouraged to continue follow-up visits and complete all remaining study visits.

When a subject discontinues the treatment/withdraws from the study, all procedures applicable to the end-of-treatment visit should be performed. All adverse events (AEs) present at the time of treatment discontinuation/withdrawal from the study should be followed up according to the safety requirements outlined in Section 8.4 (Documentation of Adverse Events). If a patient discontinues treatment/withdraws from the study for a reason other than objective PD, the patient should receive an imaging evaluation at the end of treatment. For a subject who has completed 24 months of treatment with IBI308, the treatment can be discontinued. The subject who discontinues the treatment after receiving IBI308 for 24 months should return to the study site for a safety follow-up visit and then enter the follow-up phase of this study.

6.4.2 Loss to follow-up

If a subject fails to return to the clinic for required study visits and/or the study site is unable to reach a subject, the following procedures will be performed:

- The study site must attempt to contact the subject and reschedule the missed visit. If the subject is contacted, he/she should be informed of the importance of maintaining the protocol-defined visit schedule.
- At each missed visit, the investigator or designee must make every effort to resume contact with the subject (e.g., by telephone and/or registered letter to the last known subject's mailing address or equivalent local method). These attempts to contact the subject should be documented in the subject's medical records.

  Note: A subject is not considered lost to follow-up until the last scheduled visit for the individual subject has been reached. The quantity of missing data for a subject should be managed according to pre-specified data processing and analysis guidelines.

6.4.3 Unblinding

Generally, the investigator will perform the first imaging evaluation for PD according to RECIST V1.1. After confirmation of PD 4–6 weeks later, individual unblinding can be performed with the permission of the sponsor; if the subject develops clinically unstable disease after the first assessment of imaging PD, the confirmation 4–6 weeks later is not required and unblinding can be directly performed. In case the investigator or sub-investigator needs to determine the drug and dose administered to a subject in an emergency (e.g., in case of an SAE), he/she will contact the sponsor and the Clinical Research Organization (CRO) by telephone and request emergency unblinding. Before unblinding, the investigator or sub-investigator must record the severity level/toxicity grade, relationship with study drugs, and causes of observed AEs in the medical records. Subjects whose treatment assignment has been unblinded must discontinue the administration of study drugs.

In addition, the investigator must log into the IWRS system and perform unblinding in the IWRS system to update the medication assignment. If necessary for the safety of a subject, the emergency unblinding must be performed using IWRS. Subjects whose treatment assignment has been unblinded must discontinue the administration of study drugs.

Once blinding is performed, the blinding-related information (such as date, cause, and personnel responsible for unblinding) must be recorded immediately, and the sponsor's medical manager must be informed as soon as possible. The unblinded information regarding corresponding subject code should be revealed to the principal investigator or designee only, but not to the staff of the study site or the sponsor who directly participate in this trial. Subjects whose treatment assignment has been unblinded must discontinue the administration of study drugs.

The interim analysis will be performed by an independent statistician and the results will be submitted to the IDMC. The investigator, subjects, and the sponsor will remain blinded.

7 STUDY EVALUATIONS

7.1 Efficacy evaluation

7.1.1 Tumor imaging and disease evaluation

Tumor imaging examinations usually include contrast-enhanced computed tomography (CT) or magnetic resonance imaging (MRI) of chest, abdomen, and pelvic cavity. Head MRI should be performed at baseline for subjects with signs or symptoms of suspected CNS metastasis. The same subject should receive the same type of imaging examination during the study.

During the screening, the investigator of the study site will confirm the presence of measurable lesions based on RECIST V1.1 to determine the eligibility of the subject. As defined in the RECIST V1.1, there are a total of up to 5 target lesions and 2 target lesions per organ.

All planned imaging data of all subjects at the study site should be submitted to the IRRC service provider. Besides, additional imaging data (including other devices) obtained at unscheduled time points to determine PD and imaging data obtained for purposes other than recording the imaging PD should also be submitted to the IRRC service provider.

7.1.2 Tumor imaging evaluation at baseline

During screening, the first tumor imaging examination must be performed within 28 days before randomization. Before randomization, the investigator of the study site should confirm the subjects have measurable lesions based on the RECIST V1.1.

As a clinical routine test, the imaging examination performed within 28 days prior to randomization, whose quality meets the diagnosis requirements, may be evaluated by the investigator for oncology assessment in the screening period.

The method used for evaluation of tumor burden during each subsequent follow-up should be the same as the one used at the baseline (CT/MRI). Imaging examinations may be performed on other suspected involved sites (e.g., head) according to the clinical symptoms and signs of the subject.

7.1.3 Tumor imaging evaluation during trial

The imaging evaluations should be carried out at the time points specified in the protocol as far as possible throughout the study. Since randomization, the tumor imaging evaluation should be performed in week 6 (± 7 days) and week 12 (± 7 days), respectively. Afterwards, one tumor imaging evaluation should be performed every 9 weeks (± 7 days) until week 48, and then performed once every 12 weeks (± 7 days). After the first assessment of imaging PD by the investigator based on RECIST V1.1, if the subject has SD clinically, the current treatment can be

continued and the imaging evaluation should be performed again 4–6 weeks later for confirmation (based on RECIST V1.1). If PD is confirmed, unblinding should be performed and subjects of IBI308 in combination with chemotherapy group (test group) should end the study treatment, while subjects of placebo in combination with chemotherapy group (control group) can be conditionally crossed over to receive monotherapy of IBI308 based on the judgment of the investigator and the willingness of the subjects, until PD, intolerable toxicity, receipt of new anti-tumor therapy, withdrawal of ICF, loss to follow-up, death, or other reasons requiring discontinuation of study treatment, whichever occurs first; if PD is not confirmed, the study treatment will be continued until imaging-confirmed PD followed by unblinding and other subsequent processing same as above. If the subject has clinically unstable disease after the first assessment of imaging PD, the confirmation 4–6 weeks later is not required and unblinding can be directly performed followed by processing same as above.

Unscheduled imaging evaluations can be performed at any time during the study if the patient develops clinically unstable disease.

Clinically unstable disease is defined as follows:

- Clinically significant signs and symptoms suggesting PD (including worsening laboratory test values)
- ECOG PS decreased (score increased)
- Rapid PD
- Tumor progression at important anatomical sites that requires other urgent medical interventions (e.g., spinal cord compression)

For patients discontinuing the treatment for reasons other than imaging PD, imaging evaluation should be performed at the end of treatment and at time points specified in the protocol until one of the following events occurs: initiation of new anti-tumor therapy, objective PD, withdrawal of ICF, loss to follow-up, or death.

Head CT/MRI examinations should be performed at baseline before the start of study treatment for subjects with known or suspected brain metastases during the screening. Throughout the study, these subjects should also receive head CT/MRI examinations to evaluate brain metastases as non-target lesions.

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 PD is confirmed, the date of PD should be the date of initial discovery.

The tumor imaging evaluation in this study is based on IRRC following the RECIST V1.1. See Appendix 4 for evaluation methods.

7.1.4 Tumor imaging evaluation at the end of treatment and in follow-up period

For subjects who have completed treatment or who have discontinued treatment for reasons other than objective PD, a tumor imaging evaluation should be performed when the treatment is completed/discontinued. Subsequent imaging evaluations should be carried out at time points specified in the protocol until one of the following events occurs: initiation of new anti-tumor therapy, objective PD, death, or end of the study, whichever occurs first.

7.2 Safety evaluation

The investigator or qualified designee will evaluate the AEs of each subject throughout the study and follow-up period as required by the study schedule. AEs are graded and documented according to NCI CTCAE (V4.03). AEs are characterized by severity level, causality, toxicity level, and measures taken for study treatment.

All AEs of unknown causes during the treatment should be evaluated to determine whether the events are irAEs.

Refer to Sections 8 for details regarding AE evaluation and documentation.

7.2.1 Physical examination

7.2.1.1 Comprehensive physical examination

A comprehensive physical examination will be performed by the investigator or qualified designee during the screening, and abnormalities with clinical significance will be documented. In addition, the comprehensive physical examination should be performed at time points specified in the study schedule. After the first dose of the study drugs, any new clinically significant abnormalities indicated by physical examination should be documented as AEs.

7.2.1.2 Targeted physical examination

In cycles where a comprehensive physical examination is not required by the study schedule, targeted physical examination should be performed by the investigator or qualified designee if clinically indicated, scheduled prior to administration on day 1 of each treatment cycle. New clinically significant abnormalities should be documented as AEs.

7.2.1.3 Body height, body weight, and vital signs

The investigator or qualified designee will document vital signs during screening, prior to each administration of the study drugs, and at the end of treatment in accordance with the instructions in the study schedule. Weight must be measured before every planned dose during the study. If the body weight of a subject fluctuates by less than 10% from the baseline (the day when the first dose of study drugs is given), the baseline body weight will be used to calculate the chemotherapeutic dose. Otherwise, the actual dose will be calculated based on the weight of scheduled dosing days.

Height will be measured at baseline only. Vital signs include body temperature, pulse, respiratory rate, and blood pressure.

7.2.1.4 12-lead electrocardiogram (ECG)

A standard 12-lead electrocardiogram (ECG) will be recorded according to local standard procedures during screening. Abnormalities with clinical significance should be documented. ECG examinations can be performed at other time points as clinical indicated.

7.2.1.5 Eastern Cooperative Oncology Group (ECOG) performance status scoring

The investigator or qualified designee will evaluate the ECOG performance status during screening, prior to administration on day 1 of each treatment cycle, at the end of treatment, and in safety follow-up period in accordance with the instructions in the study schedule.

7.2.2 Laboratory test and evaluation

The items of laboratory test are presented below. Refer to the study procedure manual for the operation procedures of body fluid sample collection. Refer to the section of laboratory evaluation in the study schedule for the time of test.

7.2.2.1 Laboratory safety evaluation (routine blood test, coagulation test, urinalysis, blood chemistry, etc.)

Refer to **Table 10** for laboratory test items including routine blood test, coagulation test, urinalysis, blood chemistry, etc.

Table 10. Laboratory test

Routine blood test and coagulation test	Blood chemistry	Urinalysis	Others
Hemoglobin	Albumin	PH	Pregnancy test (blood or urine)[a]
Platelet count	Alkaline phosphatase	Glucose	Total triiodothyronine (T3) or FT3, FT4, and TSH[b]
WBC (total and differential)[c]	Alanine aminotransferase	Protein[d]	Anti-HCV antibody
RBC	Aspartate amino transferase	Specific gravity	HCV-RNA
Hematocrit	Calcium	Urinary white blood cell	HBsAg
INR	Chloride	Urine red blood cell	HBV-DNA
PT	Cr		Anti-HBc
	Blood glucose		HBeAg
	Phosphorus		HBsAb
	Magnesium		HBeAb
	Potassium		Anti-HIV antibody
	Sodium		Creatine phosphokinase (CK)
	TBIL		Creatine phosphokinase isoenzyme (CK-MB)
	Direct bilirubin		Troponin T or troponin I
	Total protein		
	Blood urea or blood urea nitrogen		
	Amylase		
	Lactate dehydrogenase		
	γ-GT		
	Creatine kinase		

FT4 = free thyroxine; HBc = hepatitis B core antigen; HBeAg = hepatitis B e antigen; HBeAb = hepatitis B e antibody; HBV = hepatitis B virus; HBsAb = hepatitis B surface antibody; HbsAg = hepatitis B surface antigen; HCV = hepatitis C virus; INR = international normalized ratio; PT = prothrombin time; RBC = red blood cell; T3 = total triiodothyronine; TSH = thyroid stimulating hormone; WBC = white blood cell.

a Applicable for women with child-bearing potential only, perform at 3 days before the first dose and during the safety follow-up period.

b T3 is preferred. Free T3 can be detected in case T3 is not applicable.

c WBC differential includes lymphocytes, neutrophils, monocytes, basophils, and eosinophils.

d The 24-h urine protein quantitation test should be performed for subjects with urine protein of ≥ 2+

The laboratory test during screening should be performed within 7 days before the first dose of study drugs. Exceptions include hepatitis and thyroid serology examinations, which can be performed within 28 days (close-label stage) or 21 days (IBI308 crossover treatment stage) before the first dose. After cycle 1, the pre-dose laboratory safety inspections can be performed within 3 days before administration, unless otherwise stated in the study schedule.

The laboratory test results must be reviewed and confirmed to be acceptable by the investigator or qualified designee before each administration of study drugs, unless otherwise stated in the study schedule. The unresolved laboratory abnormalities that are classified as drug-related AEs should be followed up until remission. After the end of treatment, there is no need to repeat the laboratory test if the results are within the normal range.

7.2.2.2 Pregnancy test

All women considering participating in the trial who have not undergone surgical sterilization or who have not reached menopause must receive a pregnancy test within 3 days before the first dose of the study drugs. A serum test is required if the urine test is inconclusive. Subjects must be excluded/discontinued from the trial if test results are positive or critically positive.

7.2.2.3 Samples tested by central laboratory

Refer to the study procedure manual for details regarding the collection time, storage, and transportation of the samples to be tested by central laboratory.

7.3 Pharmacokinetics:

PK samples will be collected at the following time points: within 1 h before the infusion of IBI308/placebo in cycle 1, immediately (+ 5 min) after the infusion of IBI308/placebo in cycle 1, and within 1 h before the infusion of IBI308/placebo in cycles 2/4/12.

For PK analysis, 3.5 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.

7.4 Immunogenicity

Immunogenicity samples will be collected within 1 h prior to IBI308/placebo infusion in cycles 1/2/4/8/12/16, then every 8 cycles (cycles 24, 32, and so on) thereafter, and during the safety follow-up. If an infusion-related reaction occurs during IBI308 infusion, blood samples should be taken near the start and end of this event and around 30 days after the reaction and used for comparative analysis of immunogenicity. For subjects in the control group crossed over to receive monotherapy of IBI308, blood samples will be collected only in the presence of IBI308

infusion-related reactions. The blood samples collected near the start and end of the event and about 30 days after the event will be reserved for comparative analysis of immunogenicity. The collected blood samples will be analyzed for immunogenicity in the central laboratory.

ADA titer should be tested for each subject. ADA-positive samples should be further tested for neutralizing antibodies (NAbs). For ADA and NAb assays, 5 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.

7.5 Quality-of-Life Evaluation

The evaluation of quality of life will be performed based on the LCSS and EORTC QLQ-C30. Quality-of-life questionnaires should be completed on the day of the first dose, at the time of each imaging evaluation, during the first safety follow-up visit, and at the time when any unscheduled imaging evaluation is performed.

The Lung Cancer Symptom Scale (LCSS) consists of 9 graphical subscales that measure the quality of life of patients over the last 24 h. This scale is divided into two parts that are filled by patients and physicians respectively. The patient part consists of 9 items, and the answer of each item is marked on a line segment. The physician part mainly evaluates the number and severity level of symptoms, which are presented by grading. The 9 subscales of the LCSS include six major symptoms of lung cancer patients: decreased appetite, fatigue, cough, dyspnea, hemoptysis, and pain. The remaining 3 subscales include patients' self-assessment regarding the grading of lung cancer symptoms and the impacts of the disease on daily activities.

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

7.6 Biomarker analysis

7.6.1 Tissue biomarkers

All eligible subjects should provide tumor tissue samples meeting requirements (tissue blocks or unstained sections) for analyses of PD-L1 immunohistochemical expression level, RNA detection, etc. The following two tissues are acceptable:

1. Archived tumor tissues: Wax blocks should be kept for less than 1 year, and sections should be prepared within 6 months;
2. Fresh tumor tissues collected during screening.

At least 10 unstained sections are needed, with the thickness of 4–5 μm. If the tissue sample size is too small to provide 10 archived or fresh tumor tissue sample sections meeting the test requirements during screening, please communicate with the sponsor timely, and explain and record the reasons clearly to obtain the consent of the sponsor. The sponsor may accept the situation where 10 sections are not available due to limited samples in clinical practice, but at least sufficient sections (5 sections) should be provided for the central laboratory to detect the expression of PD-L1.

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

The detection result of PD-L1 expression level is used for randomization stratification. The result will not be provided to the investigator or subjects but directly submitted to the randomization system so as to ensure the study compliance.

7.6.2 Blood biomarkers

Each subject needs to provide 10 mL of whole blood samples at the following time points: prior to the first dose, every time when efficacy evaluation is performed but before the next treatment is started in the treatment period, the time when PD is confirmed, and during safety visit. Biomarker studies include but are not limited to TCR and ctDNA detection.

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

7.7 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.

8 Safety Reports and AE Management

8.1 Definition of AEs

An adverse event (AE) is defined as any unfavorable and unexpected medical event that is observed in the clinical study subject since the signing of ICF, regardless of the causality to the study drugs. AEs include but are not limited to the followings:

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

8.2 Definition of Serious Adverse Events

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

- Death, except for the cases caused by PD;
- Life-threatening (a life-threatening event is defined as an AE that exposes the subject to the risk of death, but does not include the AE that may lead to death only if the event exacerbates).
- 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 due to worsening of an AE are not considered as SAEs. E.g., hospitalization due to pre-existing diseases, without new AEs or exacerbation of pre-existing diseases (e.g., hospitalization to examine laboratory abnormalities that have been persistent before the study starts); hospitalization for other reasons (e.g., annual routine physical examinations); hospitalization during the study as specified in the protocol (e.g., procedure as required by the study protocol); elective hospitalization unrelated to exacerbation of AEs (e.g., elective surgery); scheduled treatment or surgical procedures, which should be documented in the study protocol and/or individual subject's baseline information; hospitalization merely due to the use of blood products.

- Resulting in permanent or severe disability/incapacity.
- Resulting in congenital abnormalities/birth defects.
- Other important medical events: defined as events that may jeopardize the subjects and require medical or surgical interventions to prevent one of the other outcomes listed in the definition above.

8.3 Evaluation of Adverse Events

The investigator will evaluate all AEs according to the NCI "Common Terminology Criteria for Adverse Events" (CTCAE) V4.03. AEs with altered CTCAE grade will be documented in the AE case report form (CRF)/worksheet.

All AEs, regardless of the CTCAE grade, must be assessed for whether they are SAEs or not.

Table 11. Detailed rules for AE evaluation

V4.03 CTCAE Grade	**Grade 1**	**Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated**
	Grade 2	**Moderate; minimal, local, or noninvasive intervention indicated; limiting age-appropriate instrumental ADL**
	Grade 3	**Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self care ADL**
	grade 4	**Life-threatening consequences; urgent intervention indicated**
	Grade 5	**Death related to AE**
Seriousness	An SAE refers to any one of the following events at any dose or during the use of study drugs:	
	†**Leading to death**;	
	†**Life-threatening**; or as determined by the investigator, the subject is at immediate risk of death at the time of the event (Note: this does not include an AE that may lead to death if the event worsens);	
	†**Leading to permanent or serious disability/insufficiency**; (substantial disruption of the subject's ability to conduct normal life);	
	†**Hospitalization or prolonged hospitalization**; (defined as an inpatient admission, regardless of the length of stay, even if the hospitalization is a prophylactic measure for continuous observation. Note: Hospitalization due to pre-existing disease that does not worsen during the trial [including elective surgery] is not considered as an SAE. A pre-existing disease refers to clinical conditions diagnosed prior to the treatment with study drugs and documented in the subject's medical history);	
	†**Congenital anomalies/birth defects**; (for the offspring of the subject using the product, regardless of the time of diagnosis);	
	Other important medical events; events that are not fatal or life-threatening, and does not require hospitalization, but may jeopardize the subject and may require medical or surgical interventions to prevent one of the above outcomes (marked with †) based on appropriate medical judgment.	
Duration	The start and end dates of AEs should be documented. Indicate the appropriate length of time and units if the duration is less than 1 day.	
Measures taken	Does the AE lead to discontinuation of the study drugs?	
Relationship with the investigational drug	Is the AE caused by the study drugs? A medically qualified investigator is required to assess the causality relationship between the study drugs and AEs. To ensure that causality is assessed by a medically qualified investigator, the investigator must sign/date (initials) the source document or worksheet to support the causality assessment on the AE form. This signed document must be retained within the period required by the regulations. The following criteria serve as a reference guide to assist the investigator in assessing the relationship between the investigational drug and AEs based on available information. **The following factors are used to assess the relationship between the study drugs and AEs;** if the correlation between each criterion and the corresponding factor increases (in terms of quantity and/or intensity), the likelihood that the AE is caused by the study drugs increases;	

	Exposure	Is there any evidence that the subject is exposed to the investigational drug, e.g. a credible medical history, an acceptable compliance evaluation (drug count, daily log, etc.), expected pharmacological effect, and *in vivo* drug/metabolite measurement samples?
	Time course	Does the AE have a reasonable time relationship with the administration of the investigational drug? Is the time of AE consistent with the criteria for drug-induced AEs?
	Possible causes	Is the AE not be explained by other pathogenies, such as underlying disease, other drugs/vaccines, or other hosts or environmental factors?
	Dechallenge	Is the study drugs discontinued or dose/exposure/frequency reduced? If yes, can the AE resolve or improve? If yes, then it is a positive dechallenge. If no, then it is a negative dechallenge. Note: The above is not applicable if the followings occur: (1) the AE results in death or permanent disability; (2) the AE resolves/improves despite continuing treatment with the study drugs; (3) the study is single-dose; (4) only one dose of the study drugs is administered.
	Rechallenge	Is the subject re-exposed to the study drugs? If yes, does the AE reoccur or worsen? If yes, then it is a positive rechallenge. If no, then it is a negative rechallenge. Note: The above is not applicable if the followings occur: (1) the initial AE results in death or permanent disability, or (2) the study is single-dose, or (3) only one dose of the study drugs is administered. Note: A rechallenge is not recommended for an SAE that is possibly caused by the investigational drug or if re-exposure to the investigational drug may result in potentially serious risks to the subject. However, if continuing study treatment is beneficial to the subject and no replacement treatment is available, a rechallenge can be performed after the approval is obtained from the sponsor's clinical director.
	Consistency with the characteristics of investigational drug	Is the clinical/pathological manifestation of the AE consistent with pharmacological or toxicological data of the study drugs or other similar drugs?
Based on his/her best clinical judgment, the medically qualified investigator will consider the above factors and report the results of the causality assessment in the CRF/worksheet.		
Causality documentation		**The following table can be used to assess the causality (not all the criteria are required to be met)**
Related		Evidence of exposure to study drugs. A reasonable time relationship between the occurrence of the AE and administration of the investigational drug. The AE is more likely to be attributed to the study drugs, rather than other causes.
Unrelated		The subject does not receive the study drugs, or the time relationship between the occurrence of the AE and the administration of the study drug is unreasonable, or other explanations are more likely to be attributed to (still applicable to overdosed subjects without relevant AEs).

8.4 Documentation of Adverse Events

The investigator should document AEs and SAEs using medical terms and concepts. Avoid colloquialisms/abbreviations. All AEs (including SAEs) should be documented in the AE forms of the electronic case report forms (eCRFs).

8.4.1 Collection and time of adverse events

The investigators learned about AEs by asking the subjects non-leading questions.

All the AEs, including SAEs, that occurred from the signing of the ICF to 30 days after the last dose were collected, regardless of whether it was observed by the investigator or self-reported by the subject.

The investigator needs to report all SAEs and the AEs related to the study drugs or study procedures from 30 days after the last dose to 90 days after the last dose.

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

If the subject initiates new anti-tumor therapy within 90 days after the last dose, then only SAEs related to the study drugs are required to be documented thereafter.

8.4.2 Follow-up of adverse events

The AE should be followed until the events return to the baseline values or grade 0–1, or until the investigator believes that no further follow-up is required for reasonable reasons (if the event cannot be resolved or has already been improved). If the event cannot be resolved, a reasonable explanation 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 study drugs.

8.4.3 Contents of AE documentation

The investigator should document the complete information of any AE, including diagnosis (in the absence of diagnosis, symptoms and signs including laboratory test abnormalities should be documented), time and date of occurrence (if applicable), CTCAE severity grade and alteration (for events ≥ grade 3), whether it is an SAE, measures taken for the study drugs, treatment for the AE, outcome of the event, and causality between the event and study drugs.

For an SAE, the investigator shall also provide the date when the AE meets the criteria for an SAE, the date when the investigator is informed of the SAE, the reason of being an SAE, date of hospitalization, date of hospital discharge, possible cause of death, date of death, whether an autopsy has been performed, causality assessment of the study procedures, causality assessment

of other drugs, and other possible causes of the SAE. The investigator shall provide the rationales of the causality and a description of the SAE. In the SAE description, the followings shall also be included: the subject number, age, gender, height, and weight; indication for receiving the investigational drug, cancer staging, and overall condition; SAE occurrence, development, outcome, and result; laboratory results related to the SAE (the time of the examination, units, and normal ranges must be provided); medical history, onset and duration of concurrent diseases related to the SAE; medication history and initiation, duration, and dosage of concomitant medications related to the SAE; initiation, duration, and dosage of the study drug.

Descriptions of the AE are as follows:

Diagnosis, signs, and symptoms

In the presence of diagnosis, instead of individual symptoms and signs (including laboratory test results), the definite diagnosis should be documented in the eCRF. 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, included the signs and symptoms. The record of signs and symptoms shall then be deleted. A follow-up SAE report shall be submitted.

AEs secondary to other events

Generally, AEs secondary to other events (such as result of another event or clinical sequelae) 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 assessment time points.

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

Laboratory test abnormalities

All clinically significant laboratory test abnormalities were reported as AEs. The investigators had responsibilities to review all the laboratory test abnormalities and determine whether the abnormalities should be reported as AEs.

Death

During the entire course of the study, all the deaths that occurred within 90 days after the last dose were documented in the Death Report Form in the eCRFs and reported to the sponsor timely, regardless of the causality with the study 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.

Pre-existing medical conditions

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

Progressive disease

A PD 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. Expected PD should not be reported as an AE. Any deaths, life-threatening events, hospitalization or prolonged hospitalization, permanent or significant disability/incapacity, congenital anomaly/birth defects, or other important medical events caused by PD should not be reported as an SAE.

New anti-tumor therapy

If the subject initiates new anti-tumor therapy within 90 days after the last dose, then only SAEs considered related to the study drugs are required to be documented and reported.

8.5 Expedited Reporting of SAEs and Pregnancy

SAE reporting:

All SAEs that occur from the signing of ICF to 90 days (inclusive) after the last dose must be reported. The investigator must fill the "SAE Report Form" provided by the sponsor, regardless of whether it is the initial report or a follow-up report. The report should be sent to the sponsor (drugsafety@innoventbio.com) within 24 hours of noticing the event, as well as to national

regulatory authorities and EC in accordance with the laws and regulations of China.

For SAEs occurring outside of the above period, those considered related to the study drugs should also be reported.

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. The investigator should also report the events to the national regulatory authorities and EC in accordance with 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 exposed to the study drugs 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 exposed to the study drugs becomes pregnant, the subject will continue in the study. The investigator must report to the sponsor within 24 hours of noticing the event and submit the "Innovent Clinical Study Pregnancy Report/Follow-Up Form".

The investigator must continuously monitor and visit 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 event should be reported according to SAE procedures.

8.6 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 12. 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 TBIL ≥ 2 × ULN, ALP ≤ 2 × ULN, and no hemolysis	AST or ALT ≥ 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 assessment must include the laboratory tests, detailed medical history, and physical assessment, and the possibility of hepatic tumor (primary or secondary) shall be considered.

Other than repeated AST and ALT tests, albumin, creatine kinase, TBIL, direct bilirubin, gamma-glutamyltransferase (γ-GT), PT/INR, and ALP should also be tested. Detailed medical history include history of alcohol, acetaminophen, soft drugs, various supplements, traditional Chinese medicine, chemical drug exposure, family diseases, occupational exposure, sexual behavior, travel, contact with patients with jaundice, surgery, blood transfusion, hepatic diseases or allergies, cardiac diseases, and immune diseases. Further tests may include the detection of acute hepatitis A, B, C and E, hepatic imaging (such as biliary tract), autoantibodies, and echocardiography. If a retest shows consistency with the criteria outlined in **Table 12** 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, and the "Abnormal Hepatic Function Monitoring and Follow-Up Report" should be submitted to the sponsor.

8.7 Management of Drug-Related Toxicities

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

8.7.1 Immune related adverse events

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. Signs and symptoms of irAEs were monitored. If there are no definite alternative causes (e.g. infections), signs or symptoms of the subjects during the study may be related to the immune system.

Refer to Sections 5.2 and 5.3 for dose adjustments of IBI308 and principles of AE management.

8.8 Emergency Unblinding

During the study, if there is a need for unblinding (e.g., occurrence of an SAE), the responsible investigator of the study site will submit a request, and the sponsor's medical director and principal investigator will decide together whether to carry out unblinding. If emergency unblinding is required, the investigator can discuss with the sponsor and submit a request to unblind. After approval, the subject's treatment allocation will be known through the IWRS. In case of emergency unblinding, relevant information must be documented in the eCRF and reported to the IWRS provider and the sponsor promptly. Upon unblinding, the subject should discontinue current study drugs while being followed up until tumor progression or death.

9 STATISTICAL ANALYSIS

9.1 Statistics analysis plan

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 and unblinding. The SAP will contain details and result expression regarding the planned analyses.

9.2 Statistical Hypothesis and Sample Size

This study mainly aims to confirm that IBI308 in combination with chemotherapy can prolong the progression free survival (PFS) of treatment-naive patients with advanced or metastatic squamous NSCLC compared with chemotherapy alone. The following statistical hypothesis tests will be performed in this study for the primary endpoint PFS:

Null hypothesis H_0: PFS (test group) ≠ PFS (control group)

Alternative hypothesis H_1: PFS (test group) > PFS (control group)

IBI308 is expected to prolong PFS of subjects from 5.5 months to 7.9 months (HR = 0.7). Calculated with the enrollment time of 15 months and the total study time of 23 months, power = 82% and one-sided $\alpha = 0.025$. Besides, an interim analysis (Lan-deMets spending function combined with O'Brien-Fleming) will be performed when 70% of PFS events are observed. Considering a monthly dropout rate of 0.5%, a total of 348 subjects (174 in the test group and 174 in the control group) are needed to be randomized to achieve the 264 PFS events required in the trial. In the actual study, if the actual number of enrolled subjects is different from the number of planned enrollment due to unforeseen reasons, such as the enrollment speed faster than the requirements of the protocol, the end date of screening should be determined in advance to ensure that the number of actually enrolled subjects does not exceed the number of planned enrollment by 10%, i.e., a maximum of 382 subjects should be enrolled, 191 in each group.

For the secondary endpoint OS, no formal sample size calculation will be made, and the analysis is expected to be performed 1 year after the last subject is enrolled.

9.3 Definition of Analysis Sets

Full analysis set (FAS): The FAS consists of all randomized subjects based on an intend to treat (ITT) principle. The analysis of this population will be performed based on treatment groups to which subjects are randomized. The FAS is a main analysis set, which is applicable to the analyses regarding efficacy, subject distribution, protocol deviation, medical history, previous and concomitant medications, demographics, and baseline characteristics.

Safety analysis set (SS): The SS consists of the randomized subjects who have received at least 1 study treatment. In the analysis of this population, subjects will be grouped based on the treatment they actually received during the study. If a patient receives incorrect medication in one cycle while receiving correct medications in other cycles, the patient will be grouped based on the correct treatment. The SS is used to investigate drug exposure and used for all safety analyses.

Per protocol set (PPS): The PPS is a subset of the FAS, which consists of randomized subjects who do not have major protocol deviations affecting efficacy evaluation and have completed at least 1 cycle of administration with available imaging evaluation results (or have failed to completed at least 1 cycle of administration due to PD and have clear evidence of imaging PD). The PPS is used for the sensitivity analyses of primary efficacy endpoints and key secondary efficacy endpoints.

9.4 Statistical Analysis Methods

The statistical analysis endpoints of this study include

Primary endpoints:

- Progression free survival (PFS) assessed by IRRC based on RECIST V1.1

Secondary endpoints:

- Overall survival (OS) of subjects in the two groups;
- Objective response rate (ORR) of subjects in the two groups assessed based on RECIST V1.1;
- Disease control rate (DCR) of subjects in the two groups assessed based on RECIST V1.1;
- Time to response (TTR) of subjects in the two groups assessed based on RECIST V1.1;

- Duration of response (DOR) of subjects in the two groups assessed based on RECIST V1.1;
- Safety and tolerability characteristics of IBI308 in combination with gemcitabine and platinum (cisplatin/carboplatin) chemotherapy.

Exploratory endpoints

- To explore potential biomarkers in tumor tissues that can predict the efficacy of IBI308: including but not limited to immunohistochemistry assay of PD-L1 expression in tumor specimens;
- To explore potential biomarkers in peripheral blood that can predict the efficacy of IBI308 group, including but not limited to TCR and ctDNA assay;
- To compare the quality of life of patients treated with IBI308 in combination with chemotherapy vs. standard chemotherapy by using LCSS and EORTC QLQ-C30 questionnaires;
- To explore the PFS of subjects in the control group after crossover treatment with IBI308;
- To explore the population PK characteristics of IBI308.

9.4.1 General statistical analysis

All statistical analyses should be performed by programming calculation using the SAS 9.2 (or later version) statistical analysis software.

Except for the superiority hypothesis test of the primary efficacy endpoint PFS (one-sided $\alpha = 0.0074$) in interim analysis and PFS (one-sided $\alpha = 0.0228$) in final analysis, 95% CIs and nominal P values will be provided for other between-group comparisons (unless otherwise specified). If the one-sided P value ≤ 0.025, the difference between groups can be considered statistically significant.

Unless otherwise specified, quantitative data will be descriptively summarized using mean ± standard deviation or median (maximum, minimum), while count data will be descriptively summarized using frequency (percentage).

All statistical analyses, unless otherwise specified, will include treatment and randomization stratification factors in the analysis model.

9.4.2 Efficacy analysis

9.4.2.1 Analysis of primary study endpoint

- PFS: time from randomization to the first objective tumor progression or death of the subject. 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 or have no death record will be censored on the date of randomization.

The stratified log-rank test will be used to compare the PFS between groups. The between-group HR and corresponding 95% CI will be estimated with a stratified COX proportional hazards model, with the randomization stratification factor as the stratification factor. The COX proportional hazards model will also be used to assess the effects of various covariates possibly related to prognosis and efficacy prediction on the estimated HR. The covariates may include randomization stratification factor, ECOG PS (0 vs. 1), age (> 60 vs. ≤ 60), sex (male vs. female), smoking history (previous/present vs. never), and liver metastases (yes vs. no). Before much more complicated models are adopted, an initial model only containing treatment and randomization stratification factors will be constructed to ensure that the conclusion obtained from the COX model is consistent with that obtained from the stratified log-rank test. Furthermore, the median PFS and corresponding 95% CI will be estimated by using the Kaplan-Meier method, and the survival curves will be plotted.

Considering the possible influence of tumor evaluation interval on PFS analysis, the interval-censored non-parametric method will also be used to estimate the median PFS and corresponding 95% CI.

9.4.2.2 Analysis of secondary study endpoints

- 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.

A stratified log-rank test will be used to compare the OS between groups. The between-group HR and corresponding 95% CI will be estimated with a stratified COX proportional hazards model, with the randomization stratification factor as the stratification factor. The COX proportional hazards model will also be used to assess the effects of various covariates possibly related to prognosis and efficacy prediction on the estimated HR. The covariates may include randomization stratification factor, ECOG PS (0 vs. 1), age (> 60 vs. ≤ 60), sex (male vs. female), smoking history (previous/present vs. never), and liver metastases (yes vs. no). Before much more complicated models are adopted, an initial model only containing treatment and randomization stratification factors will be constructed to ensure that the conclusion obtained

from the COX model is consistent with that obtained from the stratified log-rank test. Furthermore, the median OS and corresponding 95% CI will be estimated by using the Kaplan-Meier method, and the survival curves will be plotted.

Given the fact that patients receiving standard chemotherapy may be crossed over to receive treatment with IBI308 after PD, a recognized statistical method will be used to adjust the effect of crossover treatment on OS. For example, the two-stage method or the rank-preserving structural failure time (RPSFT) model proposed by Robin and Tsiatis is adopted after checking method assumptions/applicability based on the obtained data.

- ORR: the proportion of subjects achieving complete response (CR) or partial response (PR) as per RECIST V1.1 in the analysis population (the formula is as follows).

$$ORR = \frac{CR + \text{Number of subjects achieving PR}}{\text{Number of all subjects}} * 100\%$$

The ORRs and corresponding 95% CIs of treatment group and control group as well as the between-group difference and corresponding 95% CI will be estimated by using binomial distribution.

- DCR: the proportion of subjects achieving CR, PR or stable disease (SD) as per RECIST V1.1 in the analysis population (the formula is as follows).

$$DCR = \frac{CR + PR + \text{Number of subjects achieving SD}}{\text{Number of all subjects}} * 100\%$$

The ORRs and corresponding 95% CIs of treatment group and control group as well as the between-group difference and corresponding 95% CI will be estimated by using binomial distribution.

- TTR: time from randomization to the first objective tumor response (CR or PR) of the subject. Subjects achieving neither CR nor PR will be censored on the date of their last imaging evaluation.

The median TTR will be estimated via the Kaplan-Meier method and survival curves will be plotted.

- DOR: the time from the first documented objective tumor response (CR or PR) to objective PD or death for subjects achieving CR or PR. Subjects who do not have PD or die will be censored on the date of their last imaging evaluation.

The median DOR will be estimated via the Kaplan-Meier method and survival curves will be plotted.

9.4.3 Safety analysis

The safety analysis will be performed based on SS. Safety parameters include AEs, laboratory tests, vital signs, ECG, and immunogenicity. Data will be summarized by group, and AEs will be aggregated and summarized. For patients receiving placebo in combination with chemotherapy followed by crossover treatment with IBI308, the primary safety analysis will only be performed on the data obtained before crossover treatment (e.g., for the placebo in combination with chemotherapy group, AEs during treatment with IBI308 will not be analyzed). Exploratory analyses will be performed on the safety data obtained since the first crossover treatment with IBI308.

9.4.3.1 Drug exposure

The drug exposure, duration of treatment (number of treatment cycles), dose adjustments during treatment, and accumulative number of dose adjustments during treatment will be summarized.

9.4.3.2 Adverse events

All adverse events (AEs) will be coded and categorized according to MedDRA, and graded by severity level according to CTCAE V4.03.

The distributions of incidences (frequency) and severity levels of AEs, adverse drug reactions (ADRs), immune related adverse events (irAEs), AEs leading to treatment discontinuation, AEs leading to study termination, AEs leading to death, grade 3 or greater AEs, serious adverse events (SAEs), etc. will be summarized respectively according to SOC and PT in MedDRA.

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

9.4.3.3 Pharmacokinetic and immunogenicity analyses

The immunogenicity and PK data are collected in this study, and the number and percentage of subjects who develop ADAs and NAbs during the study will be summarized by group. The PK analysis will include, but is not limited to, descriptive statistical analysis of IBI308 trough concentrations in cycles 1/3/11.

9.4.3.4 Laboratory test

Measured values and changes from baseline of laboratory tests will be analyzed using descriptive statistics. Baseline results and worst results during the study will be presented in cross tabulation.

9.4.3.5 ECG

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

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

Measured values and changes from baseline of vital signs, physical examination, and other safety-related examinations will be analyzed using descriptive statistics. Baseline results and worst results during the study will be presented in cross tabulation.

9.4.4 Compliance analysis

The proportion and frequency of subjects who violate the expected administration regimen, the proportion of subjects receiving drugs at 80–120% of the dose prescribed in the protocol, the proportion of subjects who complete the study, and the proportion of subjects who complete different treatment cycles will be summarized by group.

9.4.5 Subjects' baseline characteristics

Subjects' demographic characteristics (sex and age), diagnosis and treatment information of indication (tumor types, pathological diagnosis, clinical staging, and 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, ECOG PS scores, laboratory tests, past/concomitant/new combined medications) will be analyzed using descriptive statistics.

9.4.6 Interim Analysis

The primary endpoint PFS is analyzed at approximately 23 months after the start of the trial (i.e., at the end of the study, expected to be at approximately 8 months after randomization of the last subject). Besides, an interim analysis will be carried out during the study.

Time of interim analysis: The analysis will be performed when 70% of PFS events (185 cases) occur (at approximately 16 months after the start of the trial).

Objective of interim analysis: to demonstrate that IBI308 in combination with chemotherapy is superior to placebo in combination with chemotherapy regarding the primary study endpoint PFS

In the interim analysis, with one-sided $\alpha = 0.0074$, if $HR \leq 0.698$ is observed for the test group of IBI308 in combination with gemcitabine and cisplatin or carboplatin chemotherapy vs. the control group of placebo in combination with gemcitabine and cisplatin or carboplatin chemotherapy, it is demonstrated that the superiority has been concluded in the interim analysis.

The analysis results and reports will be submitted to the IDMC, which will judge whether the trial is valid according to the estimated valid cut-off value and give advice to the sponsor on whether the study data can be submitted in advance. The IDMC charter will be finalized and approved by IDMC and sponsor prior to the interim analysis. If the study proceeds, the IDMC will continue performing regular evaluation and monitoring on safety data until the final analysis.

If the IDMC suggests the sponsor to submit the trial data in advance based on the estimated valid cut-off value and the sponsor decides to follow the advice, the investigator, subjects, the independent imaging evaluation, and the sponsor staff who directly participate in the study implementation should remain blinded. Some sponsor staff not directly involved in the study implementation will be unblinded for the submission based on interim analysis data.

9.4.7 Subgroup analysis

In order to confirm the consistency of efficacy in various subgroup populations, subgroup analyses will be performed regarding randomization stratification factors, ECOG PS (0 vs. 1), age (> 60 vs. ≤ 60), sex (male vs. female), smoking history (previous/present vs. never), liver metastases (yes vs. no), etc., and the HRs and corresponding 95% CIs of efficacy endpoints (PFS, OS, and ORR) of different subgroups will be estimated, and forest plots will be constructed.

9.4.8 Multiple comparisons and adjustments

The only primary endpoint of this study is PFS (assessed by blinded independent central review). The interim analysis will be performed when 70% of PFS events occur. In order to strictly control the overall type I error rate of this study at the one-sided level of 0.025, the interim test of PFS will be carried out at the one-sided level of 0.0074 (corresponding HR cut-off value is 0.698). If the interim analysis result is not significant, PFS will be tested at the one-sided level of 0.0228 at the end of the study.

Final PFS analysis is expected to be performed about 8 months after enrollment of the last subject. If the interim analysis results fail to reach statistical significance, and the PFS events at the final analysis are significantly more than the estimated, the P value of the final analysis will be recalculated using the Flexible spending function according to the α value actually spent in the interim analysis, so as to ensure that the overall type I error is controlled at a one-sided level of 0.025.

For other analyses, 95% CIs and nominal P values will be provided unless otherwise specified. If the one-sided P value ≤ 0.025, the difference between groups can be considered statistically significant.

9.4.9 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.

9.4.10 Exploratory analyses

Descriptive statistics will be given for baseline PD-L1 expression (< 1%, 1–49%, > 49%) and dynamic changes in TCR and ctDNA of overall subjects, as well as proportion of subjects with different expression or distribution levels and corresponding ORR and DOR.

Scores based on LCSS and EORTC QLQ-C30 (V3.0 Chinese version) will be converted from raw scores into standardized scores ranging between 0–100. The results will be subjected to descriptive statistics and Wilcoxon test to analyze the quality of life of patients in the two groups. Besides, the ECOG PS will also be analyzed using descriptive statistics and Wilcoxon test.

The PFS (time from the first dose of IBI308 to objective PD or death from any cause) of the subjects in the control group receiving crossover treatment with IBI308 should be investigated based on the RECIST V1.1.

The PK analysis will include but is not limited to descriptive statistical analysis of IBI308 trough concentrations in cycles 1/3/11.

10 Quality assurance and quality control

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

10.1 Clinical monitoring

The sponsor or its authorized contract research organization (CRO) will conduct clinical monitoring of this study. The CRA shall 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 CRA should maintain regular communication with the investigator and the sponsor.

Before the start of the study, the CRA assesses the qualifications of each study site, and reports issues related to facilities, technical equipment, or medical staff to the sponsor. During the course of the study, the CRA is responsible for the monitoring of whether the written ICF from all

subjects has been obtained and whether the data records are correct and complete. Also, the CRA will compare the data entered into the eCRF with the source data, and inform the investigator of any errors or omissions. Besides, the CRA will also monitor the protocol compliance of the study site, arrange for the supply of the study drugs, and ensure that the drugs are kept under proper 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 investigator, the CRA should submit a written report to the sponsor.

10.2 Data Management/Coding

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

Data entry into the eCRFs should be completed as soon as possible during or after visiting. The eCRFs should be updated at any time to ensure that they reflect the latest developments of the subjects. To avoid the differences in evaluations by different evaluators, it is recommended that the baseline and all the subsequent efficacy and safety evaluations of a given subject shall be performed by the same individual. The investigators are required to review the data to ensure the accuracy and correctness of all the data entered into the eCRFs. 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 eCRF, and assess the completeness and consistency. The CRA will also compare the eCRF with the source documents to ensure the consistency of critical data. Data entry, corrections, and modifications should be performed by the investigator or his/her designee. The data in the eCRFs is submitted to the data server and any modifications in the data should be recorded in the audit trail, including reasons, operator names, time, and dates of modification. The roles and permission levels of the personnel responsible for data entry in the study site will be determined in advance. The CRA or data manager will submit data queries in the electronic data capture (EDC) system, and study personnel should 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 used by the investigators or hospital, including all records related to the subjects, which are able to demonstrate the presence,

inclusion criteria, and participation of subjects (laboratory records, ECGs, pharmaceutical records, and subject folders etc.).

The investigators are required to maintain all source documents and to offer the documents to the CRA for review during each visit. In addition, the investigator must submit a complete eCRF for each enrolled subject, regardless of the duration of participation. The protocol number and subject numbers of all supporting documents (such as laboratory records or hospital records) submitted with the eCRFs 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 investigators 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 could 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).

10.3 Quality Control Audit

During the course of the study, the sponsor or the representative authorized by the sponsor may perform quality control audit on the study sites, database, and relevant study documents. At the same time, the corresponding regulatory authorities may also audit the study sites, database, and relevant study documents at their own discretion. The investigator must inform the sponsor promptly upon receipt of the inspection notice from the regulatory authorities.

The quality control department of the sponsor may also conduct an audit on the clinical study sites. which 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 receiving the notice, the investigator should allow auditors commissioned by the sponsor to conduct trial-related audits and audits conducted by the regulatory authorities. The main objective of an audit is to ensure that the rights and health of the subjects are protected, the ICF is signed, the trial procedures are implemented correctly, and all data processing and reporting related to the evaluation of the study drugs are in line with the requirements of the plan, protocol, implementation, ethical standard operation procedures, GCP, and applicable regulations. The investigator should provide all trial files, source records, and source data.

11 Ethics

11.1 Ethics committee

The sponsor or the representative authorized by the sponsor will provide relevant documents to the corresponding ethics committee (EC) of the study site for approval, including the trial protocol, ICF, Investigator's Brochure, subject recruitment materials or advertising, and other documents required by regulations. Prior to the start of the study, the investigator must obtain written approval from the EC and submit it to the sponsor. The written approval from the EC must specify the title, number, and version number of the study protocol, as well as the version number of 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. The modified study protocol, ICF, and subject recruitment materials should be submitted to the EC for approval. Report and update regularly, and submit the final report according to the safety reporting requirements stipulated by EC. All the above documents and EC approvals must be provided to the sponsor or designee.

11.2 Ethics

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

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 consent from the sponsor. Any protocol deviations must be reported to the EC, the sponsor, or regulatory authorities.

11.3 Informed Consent of Subjects

Before the start of any study procedure, the ICF should be used to explain the possible risks and benefits of this study to potential participants, and the expression used in the ICF should be straightforward. The ICF statement should clarify that the ICF is voluntarily signed and the risks and benefits of participating in this study should be clearly outlined. The subject can withdraw

from the study at any time. Can a subject be enrolled to the clinical trial only when the investigator has fully explained the details of this study, the subject's questions have been satisfactorily answered, the subject has been given sufficient time for consideration, and the written consent from the subject or his/her legal representative has been obtained. 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.

11.4 Data Protection of Subjects

Information about data and privacy protection will be included in the ICF. Precautions should be taken to ensure the confidentiality of the documents and prevent the disclosure of information on 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 identification code and the genetic data of the subject. In addition, relevant regulatory authorities may also request access to relevant documents.

12 STUDY MANAGEMENT

12.1 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.

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. Can the investigator/study site transfer the study documents to other parties that comply with the record-keeping requirements or to another locations that meet record-keeping requirements only after notifying the sponsor and obtaining the written consent.

12.2 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.

12.3 Protocol Revisions

All protocol revisions during the course of the study period must 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 changes 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 the regulatory authorities for approval and only implemented after being approved by the EC and regulatory authorities (if applicable) (with the exception of changes to the protocol that eliminate direct hazards to the trial subjects).

12.4 Responsibilities of the Investigator

The investigator will conduct this study in accordance with the protocol, ethical principles of the Declaration of Helsinki, Chinese GCP, and applicable regulations.

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

12.5 Publishing Policy

All the data generated in this study are confidential information owned by 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 conclusion derived from this trial may be of commercial value to the sponsor. The investigator should 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 data or conclusions. In order to protect the rights and interests, the sponsor may request the investigator not to publish relevant trial data 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. The sponsor must obtain consent of the investigator if the name of the investigator will be included in the content of the announcement, publication, or advertising.

12.6 Financing and Insurance

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

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14 APPENDIX

Appendix 1: Signature Page for Investigator

Protocol Title:

A Randomized, Double-Blind, Phase III Study to Compare the Efficacy and Safety of IBI308 in Combination with Gemcitabine and Platinum-Based Chemotherapy Vs. Placebo in Combination with Gemcitabine and Platinum-Based Chemotherapy in the First-Line Treatment for Patients with Advanced or Metastatic Squamous Non-Small Cell Lung Cancer (ORIENT-12)

Protocol No.: CIBI308C303

This protocol is a trade secret owned by Innovent Biologics (Suzhou) Co., Ltd. I have read and fully understood this protocol, and agree to conduct this study in accordance with the requirements found in this protocol and the 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:

Investigator's signature: _____ Date: _____

Name (Print): _____

Job Title: _____

Name and Address of Study Site: _____

_____

_____

Appendix 2: Performance Status Scoring Criteria (ECOG PS)

Activity score	Description
0	Asymptomatic, fully active, able to carry on all performance without restrictions.
1	Symptomatic, restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light housework, office work.
2	Symptomatic, ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours (confined to bed < 50% during the day).
3	Symptomatic, capable of only limited selfcare. Confined to bed or chair > 50% of waking hours, while not bedridden yet.
4	Completely disabled, cannot carry out any selfcare. Totally confined to bed or chair.
5	Dead.

Appendix 3: Calculation of Clearance of Creatinine and Body Surface Area

Clearance of creatinine (CCr) is calculated based on Cockcroft-Gault formula

Calculation of serum creatinine (SCr) concentration (mg/dL):

$$\text{Male CCr (mL/min)} = \frac{(140 - \text{age}) \times (\text{body weight})^{a}}{72 \times \text{SCr}}$$

$$\text{Female CCr (mL/min)} = \frac{0.85 \times (140 - \text{age}) \times (\text{body weight})^{a}}{72 \times \text{SCr}}$$

Calculation of serum creatinine (SCr) (μmol/L):

$$\text{Male CCr (mL/min)} = \frac{(140 - \text{age}) \times (\text{body weight})^{a}}{0.81 \times \text{SCr}}$$

$$\text{Female CCr (mL/min)} = \frac{0.85 \times (140 - \text{age}) \times (\text{body weight})^{a}}{0.81 \times \text{SCr}}$$

a: The unit of age is year and the unit of body weight is kg.

Calculation of body surface area

Body surface area (m^2) = 0.00616 × height (cm) + 0.01286 × body weight (kg) – 0.1529

Appendix 4: Response Evaluation Criteria in Solid Tumors (RECIST), V1.1 (Excerpts)

1 MEASURABILITY OF TUMOR AT BASELINE

1.1 Definitions

At baseline, tumor lesions/lymph nodes will be categorized measurable or non-measurable as follows:

1.1.1 Measurable

Tumor lesions: Must be accurately measured in at least one dimension (longest diameter in the plane of measurement is to be recorded) with a minimum size of:

10 mm by CT scan (CT scan slice thickness no greater 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 short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). At baseline and in follow-up, only the short axis will be measured and followed.

1.1.2 Non-measurable lesion

All other lesions, including small lesions (longest diameter < 10 mm or pathological lymph nodes with ≥ 10 to < 15 mm short axis) as well as truly non-measurable lesions. Lesions considered truly non-measurable include: leptomeningeal disease, ascites, pleural or pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung, abdominal masses/abdominal organomegaly identified by physical exam that is not measurable by reproducible imaging techniques.

1.1.3 Special considerations regarding lesion measurability

Bone lesions, cystic lesions, and lesions with previous local therapy require particular comment:

Bone lesions:

1) Bone scan, PET scan, or plain films are not considered adequate imaging techniques to measure lesions. However, these techniques can be used to confirm the presence or disappearance of bone lesions;

2) Lytic bone lesions or mixed lytic/blastic lesions, with identifiable soft tissue components, that can be evaluated by cross sectional imaging techniques such as CT or MRI can be considered as measurable lesions if the soft tissue component meets the definition of measurability described above;

3) Blastic bone lesions are non-measurable.

Cystic lesions:

1) Lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts;

2) 'Cystic lesions' thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. 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 therapy, are usually not considered measurable unless there has been demonstrated progression in the lesion. Study protocols should detail the conditions under which such lesions would be considered measurable.

1.2 Specifications by Methods of Measurements

1.2.1 Measurement of lesions

All measurements should be recorded in metric notation, using calipers if clinically assessed. All baseline evaluations regarding the size of tumor lesions should be performed as close as possible to the treatment start. In this study, the baseline evaluations must be completed within 28 days before the beginning of the treatment.

1.2.2 Method of assessment

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging based evaluation should always be done rather than clinical examination unless the lesion(s) being followed cannot be imaged but are assessable by clinical exam.

Clinical lesions: Clinical lesions will only be considered measurable when they are superficial and ≥ 10 mm diameter as assessed using calipers (e.g. skin nodules). For the case of skin lesions, documentation by color photography including a ruler to estimate the size of the lesion is suggested. As noted above, when lesions can be evaluated by both clinical exam and imaging,

imaging evaluation should be undertaken 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, particularly when progression is an important endpoint, since CT is more sensitive than X-ray, particularly in identifying new lesions. However, lesions on chest X-ray may be considered measurable if they are clearly defined and surrounded by aerated lung.

CT, MRI: CT is the best currently available and reproducible method to measure lesions selected for response assessment. This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm or less. 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 is not useful in assessment of lesion size and should not be used as a method of measurement. Ultrasound examinations cannot be reproduced in their entirety for independent review at a later date and, because they are operator dependent, it cannot be guaranteed 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 study, confirmation by CT or MRI is advised. If there is concern about radiation exposure at CT, MRI may be used instead of CT in selected instances.

Endoscopy, laparoscopy: The utilization of these techniques for objective tumor evaluation is not advised. However, they can be useful to confirm CR when biopsies are obtained or to determine relapse in trials where recurrence following CR or surgical resection is an endpoint.

2 TUMOR RESPONSE EVALUATION

2.1 Evaluation of Target Lesions

Complete response (CR): Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to < 10 mm.

Partial response (PR): At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters.

Progressive disease (PD): At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progression).

Stable disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.

2.2 Special Notes on the Assessment of Target Lesions

Lymph nodes: Lymph nodes identified as target lesions should always have the actual short axis measurement recorded (measured in the same anatomical plane as the baseline examination), even if the nodes regress to below 10 mm on study. 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. Case report forms (CRF) or other data collection methods may therefore be designed to have target nodal lesions recorded in a separate section where, in order to qualify for CR, each node must achieve a short axis < 10 mm. For PR, SD, and PD, the actual short axis measurement of the nodes is to be included in the sum of target lesions.

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 evaluations, 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 longest diameter of the entire combined lesion.

2.3 Evaluation of Non-Target Lesions

This section defines the response criteria for non-target lesions. While some non-target lesions may actually be measurable, they need not be measured and instead should be assessed only qualitatively at the time points specified in the protocol.

Complete response (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-PD: At least 1 non-target lesion is found with/without persistent tumor marker levels that exceed normal levels.

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

2.4 Special Notes on the Assessment of Progression of Non-Target Lesions

The concept of progression of disease requires additional explanation as follows: When the patient also has measurable non-target disease, in this setting, to achieve 'unequivocal progression' on the basis of the non-target disease, there must be an overall level of substantial worsening in non-target disease such that, even in presence of SD or PR in target disease, the overall tumor burden has increased sufficiently to merit discontinuation of therapy. 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 is stable or partially resolved, it is very rare that the change of non-target lesions alone can define the overall tumor progression.

When the patient has only non-measurable non-target disease: This circumstance arises in some phase III trials when it is not a criterion of study entry to have measurable disease. However, the overall evaluation 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 evaluation 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 'unequivocal progression' is seen, the

patient should be considered to have had overall PD at that point. It is best to have objective criteria applicable to the assessment of non-measurable lesions. Notably, the additional criteria must be reliable.

2.5 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. An example of this is the patient who has visceral disease at baseline and while on study has a CT or MRI brain ordered which reveals metastases. The patient's brain metastases are considered to be evidence of PD even if he/she did not have brain imaging at baseline.

If a new lesion is not definitive due to its 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 (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.

2.6 Missing Assessments and Inevaluable Designation

When no imaging/measurement is done at a particular time point, the patient is not evaluable (NE) 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.

2.7 Special Notes on Response Assessment

When nodal disease is included in the sum of target lesions and the nodes decrease to 'normal' size (< 10 mm), they may still have a measurement reported on scans. 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 with CR will not be recorded as 0 on the eCRF.

If the efficacy confirmation is required during the study, the optimal overall efficacy 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 global exacerbation 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 a descriptor of an objective response: it is a reason for stopping study therapy. The objective response status of such patients is to be determined by evaluation of target and non-target disease as shown in Attached Tables 1–3.

Conditions that define 'early progression, early death, and inevaluability' are study specific and should be clearly described in each protocol (depending on treatment duration, treatment periodicity).

Sometimes, it may be difficult to distinguish local lesions from normal tissues. When such definition is the basis for the assessment of CRs, 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 literature. 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).

Attached Table 1. Time point response: patients with target (+/– non-target) disease

Target lesion	Non-target lesion	New lesion	Overall response
CR	CR	Absent	CR
CR	Non-CR/non-PD	Absent	PR
CR	NE	Absent	PR
PR	Non-progressive or not completely evaluable	Absent	PR
SD	Non-progressive or not completely evaluable	Absent	SD
Not completely evaluable	Non-progressive	Absent	NE
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

Note: CR = complete response, PR = partial response, SD = stable disease, PD = progressive disease, NE = not evaluable.

Attached Table 2. Time point response: patients with non-target disease only

Non-target lesion	New lesion	Overall response
CR	Absent	CR
Non-CR/non-PD	Absent	Non-CR/non-PD
Not completely evaluable	Absent	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 endpoint for assessment of efficacy in some trials so to assign this category when no lesions can be measured is not advised.

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.

Attached Table 3. Best overall response when confirmation of CR and PR required

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 = not evaluable. [a]: If a CR is truly met at first time point, then any disease seen at a subsequent time point, even disease meeting PR criteria relative to baseline, makes the disease PD at that point (since disease must have reappeared after CR). 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.

2.8 Confirmatory Measurement/Duration of Response

2.8.1 Confirmation

In non-randomized trials where response is the primary endpoint, confirmation of PR and CR is required to ensure responses identified are not the result of measurement error. In studies where SD or PD are the primary endpoints, confirmation of response is not required since it will not add value to the interpretation of trial results. In the case of SD, measurements must have met the SD criteria at least once after study entry at a minimum interval (in general not less than 6–8 weeks) that is defined in the study protocol.

2.8.2 Duration of overall response

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.

2.8.3 Duration of stable disease

SD is measured from the start of the treatment (in randomized trials, from date of randomization) until the criteria for progression are met, taking as reference the smallest sum on study (if the baseline sum is the smallest, this is the reference for calculation of PD). The clinical relativity of SD period varies with different studies and diseases. For a specific trial using the proportion of patients 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.

Appendix 5: EORTC QLQ-C30 V3.0

We are interested in some things about you and your health. Please answer all of the questions yourself by circling the number that best applies to you. There are no "right" or "wrong" answers, so please circle whichever best applies to you. The information you provide will remain strictly confidential.

Please fill in your name: _____

Your birthdate: _____MM/DD/YYYY

Today's date: _____MM/DD/YYYY

	Not at all	A little	Quite a bit	Very much
1. Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase?	1	2	3	4
2. Do you have any trouble taking a long walk?	1	2	3	4
3. Do you have any trouble taking a short walk outside of the house?	1	2	3	4
4. Do you need to stay in bed or a chair during the day?	1	2	3	4
5. Do you need help with eating, dressing, washing yourself or using the toilet?	1	2	3	4
During the last week	**Not at all**	**A little**	**Quite a bit**	**Very much**
6. Were you limited to doing either your work or other daily activities?	1	2	3	4
7. Were you limited in pursuing your hobbies or other leisure time activities?	1	2	3	4
8. Were you short of breath?	1	2	3	4
9. Have you had pain?	1	2	3	4
10. Did you need to rest?	1	2	3	4
11. Have you had trouble sleeping?	1	2	3	4
12. Have you felt weak?	1	2	3	4
13. Have you lacked appetite?	1	2	3	4
14. Have you felt nauseated?	1	2	3	4

15. Have you vomited?	1	2	3	4
16. Have you been constipated?	1	2	3	4
17. Have you had diarrhea?	1	2	3	4
18. Were you tired?	1	2	3	4
19. Did pain interfere with your daily activities?	1	2	3	4
20. Have you had difficulty in concentrating on things, such as reading a newspaper or watching television?	1	2	3	4
21. Did you feel nervous?	1	2	3	4
22. Did you worry?	1	2	3	4
23. Did you feel irritable?	1	2	3	4
24. Did you feel depressed?	1	2	3	4
25. Have you had difficulty remembering things?	1	2	3	4
26. Has your physical condition or medical treatment interfered with your family life?	1	2	3	4
27. Has your physical condition or medical treatment interfered with your social activities?	1	2	3	4
28. Has your physical condition or medical treatment caused you financial difficulties?	1	2	3	4

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

29. How would you rate your overall health during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

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

1	2	3	4	5	6	7
Very poor						Excellent

1. Description of quality of life scoring:

The EORTC QLQ-C30 (V3.0) is a core questionnaire for patients with cancer consisting of 30 items. Items 29 and 30 are divided into 7 grades and are scored 1 to 7 points based on the exact answers; other items are divided into 4 grades (not at all, a little, quite a bit, and very much) and are directly scored 1 to 4 points.

2. Calculation of scores (raw scores) of EORTC QLQ-C30 domain (dimension):

For the convenience of statistical analysis and application, the scale is often divided into certain domains, each of which composed of an aspect of the quality of life component, also known as a

dimension, and serves as an independent variable in analyses. The EORTC QLQ-C30 (V3.0) are composed of 30 items which are divided into 15 domains: 5 functional domains (physical, role, cognitive, emotional, and social functions), 3 symptom domains (fatigue, pain, nausea and vomiting), 1 domain of global health status/quality of life, and 6 single items (each item serves as one domain). The classification is shown in the table below.

The score of the domain (raw score, RS) is obtained by adding up the score of each item in the domain and divided by the number of items included, that is, RS = (Q1 + Q2 + ... + Qn)/n.

Classification of domains of EORTC QLQ-C30

	Item	Item no.
Physical functioning	5	1~5
Role functioning	2	6~7
Emotional functioning	4	21~24
Cognitive functioning	2	20~25
Social functioning	2	26~27
Global health status	2	29~30
Fatigue	3	10、12、18
Nausea and vomiting	2	14~15
Pain	2	9、19
Dyspnoea	1	8
Insomnia	1	11
Appetite loss	1	13
Constipation	1	16
Diarrhea	1	17
Financial difficulties	1	28

3. Calculation of standardized scores of EORTC QLQ-C30

In order to make the scores of all domains comparable, linear transformation is performed by using the range method to transform the raw scores into standardized scores within the range from 0 to 100. Besides, another purpose of the transformation is to change the direction of the score. In the QLQ-C30 questionnaire, all items other than items 29 and 30 are reverse scoring (the higher scores suggesting the worse quality of life). Scoring rules specify: for functional and global health status domains, the higher scores indicate better functional status and quality of life; however, for symptom domain, the higher scores indicate the more symptoms and healthy issues (the worse quality of life). Therefore, the standardized scores of the functional domain needs to change the direction, and more specifically, are calculated by the following formula (where R is the score range for each domain or item).

Functional domain: SS = [1 – (RS – 1)/R] × 100

Symptom and global health status domains: SS = [(RS – 1)/R] × 100