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Title	:	Statistical Analysis Plan - 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)
Product name	:	Sintilimab (IBI308)
Protocol number	:	CIBI308C303
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Version History:

Version	Date	Summary of Changes
0.1	2019-02-11	Draft
1.0	2019-11-21	Version 1.0
2.0	2020-4-24	1. Correct the name of dMed Biopharmaceutical Co., Ltd. on cover page 2. Modify the calculation formula of dose intensity in 6.5, as Days of Exposure can better reflect Dose delays. The original formula is as follow: Dose intensity = Cumulative dose / Number of cycles 3. Add two-stage method in 8.1.1 to adjust the effect of crossover on OS. 4. Correct the definition of TEAE in 8.2.1.1. The cut-off day is defined as 90 days after the last dose of study treatment or starting of crossover treatment.

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1. INTRODUCTION

This statistical analysis plan (SAP) provides a comprehensive and detailed description of strategy and statistical methodology to be used to implement the analysis of data based on protocol "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)" (CIBI308C303, version 2.1 dated 24Jan2019). The purpose of the SAP is to ensure the credibility of the study findings by pre-specifying the statistical approaches to the analysis of study data prior to database lock and will be approved before database lock. This SAP does not include analysis plan for population PK which will be described in a separate document.

2. SUMMARY OF STUDY PLAN

2.1. Modifications to the Statistical Section of the Protocol

The changes made in this SAP from protocol version 3.0 are summarized in Table 1.

Table 1. Changes from Protocol

Protocol	Changes made in SAP	Reasons
Definition of TTR: from the date of randomization to the date of the first confirmed response (CR or PR). Subjects who do not meet CR or PR, will be censored at the last date of imaging assessment.	Time to response (TTR): Defined as from the date of randomization to the date of the first confirmed response (CR or PR).	To keep the consistency of the analysis of the same study drug

2.2. Study Objectives and Endpoints

Table 2. Study Obejectives and Definition of Study Endpoint

Study objective	Study endpoint
Primary objective	Primary endpoint

Study objective	**Study endpoint**
• To compare the progression-free survival (PFS) per RECIST v1.1 in the first-line treatment of advanced or metastatic squamous non-small cell lung cancer (NSCLC) treated with sintilimab in combination with gemcitabine and platinum-based chemotherapy versus placebo in combination with gemcitabine and platinum-based chemotherapy	• Progression free survival (PFS) per RECIST v1.1 assessed by independent radiographic review committee (IRRC)
Secondary objective	Secondary endpoint
• To compare the overall survival (OS) between the two treatment arms	• Overall survival (OS)
• To compare the objective response rate (ORR) per RECIST v1.1 between two treatment arms	• Objective response rate (ORR) per RECIST v1.1
• To compare the disease control rate (DCR) per RECIST v1.1 between the two treatment arms	• Disease control rate (DCR) per RECIST v1.1
• To compare the time to objective response (TTR) per RECIST v1.1 between the two treatment arms	• Time to response (TTR) per RECIST v1.1
• To compare the duration of response (DOR) per RECIST v1.1 between the two treatment arms	• Duration of response (DOR) per RECIST v1.1
• To evaluate the safety and tolerability of sintilimab in combination with gemcitabine and platinum-based chemotherapy	• Adverse Events • Clinical laboratory test • Vital Sign • Electrocardiogram • Immunogenicity •
Exploratory objective	Exploratory endpoint
• To explore the biomarkers in tumor tissue that can potentially predict the efficacy of sintilimab	• PD-L1 expression

Study objective	Study endpoint
arm including but not limited to PD-L1 expression	
• To explore the biomarker in peripheral blood that can potentially predict the efficacy of sintilimab arm including but not limited to T cell receptor (TCR) and circulating tumor DNA (ctDNA)	• TCR • ctDNA
• To compare the quality of life of subjects treated with sintilimab in combination with chemotherapy and placebo in combination with chemotherapy using Lung Cancer Symptom Scale (LCSS) and European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30, V3.0 Chinese version)	• Lung cancer symptom scale (LCSS) • EORTC QLQ-C30
• To compare PFS in sintilimab arm receiving subsequent anti-cancer therapy after disease progression versus placebo arm crossing over to receive sintilimab	• PFS 2 after initiation of new anti-cancer therapy • ORR with new anti-cancer therapy after PD • TTR with new anti-cancer therapy after PD • DoR with new anti-cancer therapy after PD
• To explore the population pharmacokinetic (PK) characteristics of sintilimab	• (See separate population PK analysis plan)

2.3. Study 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 (see Figure 1).

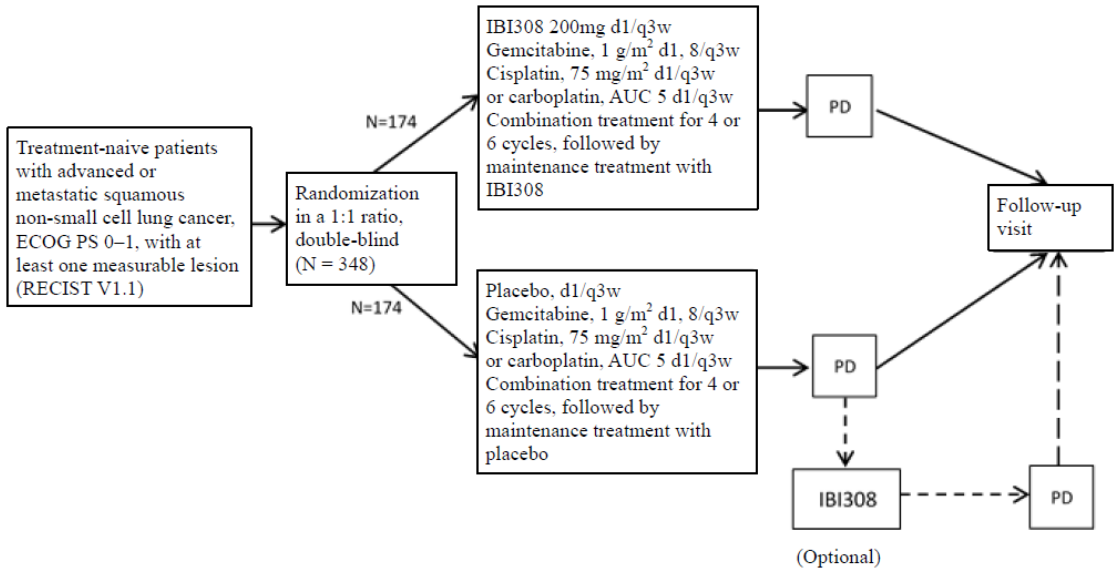

Figure 1. Study Design

Note: 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.

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 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. 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.

Table 3 and Table 4 below show the schedule of study visits.

Table 3. 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

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
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 4. 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.

2.4. Statistical Hypothesis

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)

2.5. 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.

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 α = 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.

2.6. 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 stratification factors of randomization are as follow:

- staging (stage IIIB/IIIC vs. stage IV)
- platinum-based medications (cisplatin vs. carboplatin)
- PD-L1 expression level (< 1% vs. ≥ 1%). Subjects with unevaluable PD-L1 expression level will be classified as < 1%.

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.

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.

3. PLANNED ANALYSES

3.1. Interim Analyses

The primary endpoint PFS will be 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).

The α boundary for the efficacy stopping at the interim analysis is based on O'Brien-Fleming spending function, where 1-sided nominal α=0.0074 (corresponding HR≈0.698). The overall 1-sided type I error is therefore controlled at level of 0.025. If at the interim analysis the actual number of PFS events differs from planned 185, the α boundary will be adjusted based on the actual number of PFS events observed according to O'Brien-Fleming spending function.

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.

3.2. Final Analyses

The final analysis for PFS of this study is expected to occur after approximately 23 months after first subject randomized (which is expected to be approximately 8 months after last subject randomized). However, please note the time might be different than planned as the final analysis time of this study is event driven.

After approximately 263 PFS events occur, the following steps will be completed before performing the final analysis:

1. All subject will complete study or the study is discontinued at the interim analysis.
2. All data are cleaned and database are locked for final analysis.
3. All pre-requisite steps before unblinding are completed, and formal randomization code release for final analysis is performed.

4. ANALYSIS POPULATIONS

Table 5. Definition of Analysis Population

Analysis population	Definition	Scope
Full Analysis Set (FAS)	• Randomized subjects who received at least 1 administration of study medication. • Analysed based on randomization assignment •	• Analysis of medical history, prior and concomitant medication, demographics and baseline characteristics • Efficacy analysis
Safety Set (SS)	• Randomized subjects who received at least 1 administration of study medication • According to actual study drug received. If a subject receives incorrect treatment during the study, this subject's data will be summarized according to the first study drug actually received.	• Safety analysis • Drug exposure analysis

Analysis population	Definition	Scope
Per-protocol Set (PPS)	• Subset of FAS • 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). •	• Sensitivity analyses for primary and key secondary efficacy endpoints
Intent To Treat (ITT)	• All randomized subjects • Analysed based on randomization assignment	• Sensitivity analyses for primary and key secondary efficacy endpoints

ITT, FAS and SS set will be determined by programming. PP set will be determined by blind clinical review committee before database locking.

5. GENERAL RULES AND DATA HANDLING CONVENTIONS

5.1. General Rules

All summaries and statistical analyses will be generated using SAS version 9.2 or higher.

Except for the superiority hypothesis test of the primary efficacy endpoint PFS (one-sided α = 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, all data collected will be summarized and listed. Categorical variables will be summarized with number and percentage of subjects for each category. Unless otherwise specified, number of subjects per each treatment group in the corresponding analysis population will be the default denominator in percentage calculation. For percentage, 1 decimal point will be displayed.

Descriptive summary with n, mean, standard deviation (SD), median, min and max will be provided for continuous variables. Mean and median will be displayed with 1 additional decimal points than the raw values. SD will be displayed with 2 additional decimal points than the raw values. Min and Max will be displayed with the same decimal points as the raw values. Hazard

ratio will be displayed with 3 decimal points and p-value will be displayed with 5 decimal points (or >0.99999, or <0.00001).

5.2. Missing Data Handling

The following approaches are default methods for missing data handling. Imputation is only conducted for summary, and the imputed data will not be presented in listings.

- Missing date for AE and CM will be imputed following rules below:
  - If start date is partial missing, without conflicts with other data (such as end date), Jan will be used to impute missing month and 01 will used to impute missing day. However, if the year or year-month for the partial missing start date is the same as the year or year-month of the first dose date, the event will be considered as starting during treatment period and first dose date will be used to impute the partial missing start date. If the end date is determined to be earlier than the first dose date, aforementioned imputation with Jan/01 is applicable to the partial missing end dates.
  - If start date is completely missing, without conflicts with other data (such as end date), first dose date will be used to impute the missing start date. If the end date is determined to be earlier than the first dose date, then start date will be imputed with end date-1.
  - Partial missing end date will be imputed with Dec (for missing month) and or last date of the month (for missing day). If the result from such imputation gives dates after death date, data cut-off date, end of study date, the earliest date in the above mentioned dates will be used to impute the missing end date.
  - Actual missing value will be displayed in AE or CM listing
- AE with missing CTCAE grade will be counted as grade 3 or above.
- If AE assessment of the relationship with the investigational drug is missing, it will be counted as “related”.
- Other missing values will not be imputed and only non-missing data will be included in the analysis.

5.3. Other Data Handling Rules

If raw value from laboratory tests cannot be included in the calculation directly (e.g. coded with characters), coded values will be converted first as appropriate. Generally, upper and lower limit, such as “<10” or “≤5” will be converted to “10” or “5”, “<100” will be converted to “100” in the summary tables. Original values will be kept in subject listings. BQL data in PK and PD analysis will be imputed with BQL/2 for post baseline samples and 0 for baseline samples.

5.4. General Definition

Age

Age is calculated based on years between informed consent date and birthday:

[integer part of (informed consent date - birthday + 1) / 365.25].

Baseline

Unless otherwise specified, baseline values will be the last non-missing value before first study drug administered.

In analyses for the crossover phase, new baseline will be defined as last non-missing value before crossover if applicable. If appropriate, starting of new anti-cancer therapy will be considered as new baseline for crossover phase.

Change from baseline

Change from baseline at any specific time point is defined as values at this time point - corresponding baseline values.

Relative days in study

Days lapsed since first study drug taken:

If a date is missing, relative days is missing.

If the date is earlier than the date of first study drug taken, relative days = date - date of first study drug taken.

If the date is not earlier than the date of first study drug taken, relative days = date -date of first study drug taken+1.

6. SUBJECT DISPOSITION

6.1. Subject Disposition

Following information will be provided for subject disposition:

- Number and percentage of screened subjects, including screen failure subjects and reason for screen failure
- Number and percentage of subjects randomized by study centres
- Number and percentage of subjects randomized, receiving treatment during double blind phase of the study, completing double blind phase of the study, prematurely discontinuing study treatment during double blind phase of the study and discontinuing study early

- Number of percentage of subjects unblinded during the study, number and percentage of subjects receiving crossover treatment after unblinding, and number and percentage of subjects discontinuing study during crossover phase of the study
- Listing of subjects prematurely discontinuing study and reason for discontinuing during double blind phase and crossover phase according to the e-CRF record
- Number and percentage for each analysis population (FAS population, ITT population, SS population and PPS population)
- Listing of reasons for subjects excluded in each of the analysis population
- Listing of randomization assignment and actual treatment received for each subject

6.2. Protocol Deviation and Code Broken

All critical/major deviations potentially impacting efficacy analyses and other important deviations will be summarized in tables giving numbers and percentages of deviations by treatment group. Listing will also be provided.

Protocol deviation will be monitored, classified and recorded during the study before database lock. Protocol deviation data will be reviewed. Analysis population will be finalized if applicable based on protocol deviation classifications before database lock.

Number and percentage of subjects and the reasons that these subjects have code broken during the study conduct will be summarized. A listing will also be provided.

6.3. Demographics and Disease Characteristics

In general, baseline is defined as the last non-missing evaluable assessment prior to initiation of any of the study treatment unless specified otherwise. Demographic variables as listed below will be summarized by treatment arm:

- Gender
- Age and Age group (≤60 years vs >60 years)
- Race
- Ethnicity
- Height
- Weight
- BMI
- BSA
- Stratification factors
- Smoking history
- ECOG PS

- Duration of disease

Baseline disease characteristics as listed below will be summarized by treatment arm:

- Lung cancer diagnosis (Histological diagnosis, diagnosis method, TNM staging, clinical staging, EGFR status, ALK status, Metastasis status, CNS involvement)
- Baseline target lesion and non-target lesion
- Prior anti-cancer surgery for lung cancer
- Prior anti-cancer medication for lung cancer
- Prior anti-cancer radiation therapy for lung cancer
- Prior surgery other than anti-cancer therapies
- Medical history related to other type of cancer
- Non-oncology related medical history

Medical history data will be coded based on latest Medical Dictionary of Regulatory Activities (MedDRA) version available at the time of analysis. Summary by SOC and PT by treatment group will be provided. Each subject will only be counted once for the same SOC or PT.

Listings will also be provided for demographics and baseline characteristic data.

Other baseline characteristics such as vital sign and etc. are presented along with the post baseline values in corresponding summary tables.

6.4. Concomitant Medication

Prior medications are those the subject used prior to first study treatment intake and discontinued before first dosing.

Concomitant medications are any treatments received by the subject concomitantly to study treatment, from first study treatment intake to the last study treatment + 90 days.

Treatment emergent concomitant medications are any treatments received by the subject concomitantly to study treatment, from first study treatment intake to the last study treatment + 90 days, which are not received before first study treatment intake.

All medications will be coded using the World Health Organization-Drug Dictionary (WHO-DD) using version currently in effect at the time of analysis. Summary of concomitant medication will be provided by ATC 3 and ATC 4. Each subject will be only counted once for each ATC 3/ATC 4 classification.

In addition, radiation therapy during the treatment period and post treatment discontinuation, new anti-cancer therapy or surgery will also be summarized by treatment group.

6.5. Drug Exposure

Duration of drug exposure in days

- last dose date - first dose date + 21 days (except for gemcitabine).
- For gemcitabine, if the last dose date is at D1, duration of drug exposure in days = last dose date – first dose date + 10.5; else duration of drug exposure in days = last dose date – first dose date + 14.

Duration of drug exposure in weeks

- Duration of drug exposure in weeks = duration of drug exposure in days / 7, with 1 decimal point.

Number of cycles administered

- Actual number of cycles during which non-zero dose drug are administered. Cycles with discontinuing or missing of treatment will not be counted.

Number of administered

- Actual number of drug administered. If a planned dose is discontinued or missing, it will not be counted.

Cumulative dose

- the sum of all actual doses. The dosage unit for sintilimab/placebo is mg; the dosage unit for carboplatin is AUC (min•mg/mL); the dosage units for cisplatin and gemcitabine are mg/m^2.

Dose intensity

- Dose intensity = (Cumulative dose / Drug exposure in days) * 21
- Relative dose intensity = 100 * (Actual dose intensity / Planned dose intensity)

Planned dose is calculated according to Table 4 in the study protocol. Extent of exposure will be assessed within the safety population for sintilimab / placebo and chemotherapy. Number of administered, duration of drug exposure (in days and in weeks), and percentage of subjects completing different number of cycles will be summarized for combination treatment period, maintenance period and overall treatment period. The cumulative dose, dose intensity, relative dose intensity, and percentage of subjects in different categories of the relative dose intensity (<80%, 80% - 120%, >120%), dose reduction (occur or not, number of dose reduction during treatment period), dose delay (occur or not, number of dose delay during treatment period) will also be summarized.

Study drug exposure in subjects receiving crossover treatment of sintilimab will also be summarized for their treatment received during the crossover period.

7. STATISTICAL ANAYSIS METHOD

Unless otherwise stated, primary analyses will be conducted in FAS and sensitivity analyses in ITT, PPS will also be provided.

For efficacy endpoints based on tumor assessment according to RECIST v1.1, primary analysis will be based on the assessment result by independent radiographic review committee (IRRC). Assessment result by investigator will be used in sensitivity analysis, unless otherwise specified.

7.1. Primary Efficacy Analysis

7.1.1. Definition of PFS

Progression-free survival (PFS) is defined as the time from the date of randomization to the date of the first radiographic disease progression or the date of death due to any cause, whichever comes first. In the absence of disease progression or death before the study cut-off date, PFS will be censored at the date of the last valid assessment performed before the cut-off date. In the absence of post baseline valid assessment, PFS will be censored at randomization date. Detailed PFS censor rule is described in Table 6.

Table 6. Censoring Rules for Primary and Sensitivity Analyses of PFS

Scenarios	Primary analysis	Sensitivity analysis 1	Sensitivity analysis 2
No post-baseline evaluation nor death	Censored at randomization	Censored at randomization	Censored at randomization
No PD, no death, new anti-cancer therapy not initiated	Censored at last valid tumor assessment	Censored at last valid tumor assessment	Censored at last valid tumor assessment if treatment continues, otherwise PD at the time of treatment discontinuation
No PD, no death, anti-cancer therapy is initiated	Censored at last valid tumor assessment before starting of the new anti-cancer therapy	Censored at last valid tumor assessment before starting of the new anti-cancer therapy	PD at starting of the new anti-cancer therapy

PD or death after 1 missing assessment	Event at the time of PD or death	Event at the time of PD or death	Event at the time of PD or death
PD or death after ≥2 missing assessments	Event at the time of PD or death	Censored at last non-missing assessment before 2 missing assessments	Event at the time of PD or death

7.1.2. Primary Analysis Methods

To comparing PFS between treatment arm, A p-value by stratified log-rank test will be provided, stratified by randomization stratification factors.

The hazard ratio and its 95% confidence interval (CI) will be estimated using the stratified Cox proportional hazards regression model (stratified by randomization stratification factors) with treatment covariate only.

Kaplan-Meier estimates of the median progression-free survival time and the associated 95% CIs will be provided for each treatment group, ignoring the impact of stratification factors. Kaplan-Meier curve will be plotted. The Non-parametric maximum likelihood estimation (NPMLE) method based on EMICM algorithm will also be applied to estimate median PFS and 95% CI.

7.1.3. Covariate Adjustment / Subgroup Analyses

In order to evaluate the effect of other co-variates, study site (fixed or random effect) will also be added to the Cox model to explore whether the effect of study site is significant.

The consistency of the treatment effect on PFS between subgroups will be evaluated with respect to stratification factors, ECOG PS (0 vs 1), age (>60, ≤60), sex (male vs female), smoking status (previous/current use vs never), and hepatic metastasis (Yes vs No) by adding each subgroup factor as interactive covariate into Cox model. Forest plot of HR and 95% CI will also be provided. If the covariate for subgroup analyses is one of the stratification factors, corresponding stratification factor will be excluded from the statistical model.

8. SECONDARY ENDPOINT ANALYSES

8.1. Analyses for Secondary Endpoints

Unless otherwise stated, analyses for secondary endpoints will be conducted in FAS, and sensitivity analyses in ITT, PPS will also be provided.

Analyses based on IRRC assessed ORR, DCR, TTR, DOR will be the primary analyses. Such analyses based on investigator's assessment will also be provided as sensitivity analyses unless otherwise specified.

Summarize the baseline sum of longest diameters of target lesions and the change from baseline (absolute change and relative change) by visit. Waterfall plot will also be provided for best percentage change in sum of longest diameters of target lesions.

8.1.1. Overall Survival (OS)

OS: Defined as the time from the date of randomization to the date of death due to any cause. In the absence of the confirmation of death before the analysis cut-off date, OS will be censored at the last date the subject was known to be alive or at the study cut-off date, whichever is earlier. The determination of a subject's last survival date will be based on all data collected in the database which can verify a subject's last known alive date.

If the test for PFS is significant, a confirmatory test for OS will be conducted.

Same analysis approaches as those for PFS analyses will be applied to OS analyses, including stratified log-rank test, stratified Cox model, estimates of HR and 95% CI, subgroup analysis, estimate of median survival time and 95% CI.

Considering that subject may receive new anti-cancer treatment, and subject in placebo group may crossover to sintilimab monotherapy after PD, widely used methods such as rank preserving structural failure time (RPSFT, Robins & Tsiatis, 1991), and two-stage method (Latimer et al., 2014) will be applied to adjust for crossover effect in OS analysis. The adjusted OS and 95% CI will be provided. This method is an extension of rank preserved accelerated failure time model, which is proposed to adjust the bias caused by noncompliance of protocol treatment. Since the above RPSFT model does not include the effect of disease progression, analysis using RPSFT model considering the effect of PD proposed by Li et al. will also be conducted, according to the actual proportion of crossover after PD. Estimate of survival rate at different time points (e.g. 6 months, when PD and crossover are most likely to occur) will also be provided to evaluate the effect of crossover. Besides, the following sensitivity analysis will be conducted:

- Same approach as specified in primary analysis of OS, except that subjects who crossover to sintilimab monotherapy after PD (for placebo group) or start new anti-cancer therapy will be censored at the first time of starting new anti-cancer therapy or sintilimab monotherapy.

8.1.2. Objective Response Rate (ORR)

ORR: Defined as the proportion of subjects who have achieved confirmed CR or PR per RECIST 1.1 in the analysis population.

$$\text{ORR} = \frac{number\ \ of\ \ subjects\ \ achieving\ \ CR\ \ or\ \ PR}{number\ \ of\ \ all\ \ subjects} \times 100\%$$

The ORRs and 95% CIs will be provided for each group as well as for the difference in ORRs and 95% CI of the difference between sintilimab and placebo group. CIs per treatment group will be calculated using Clopper-Pearson method, ignoring the effect of stratification factors. Treatment group difference and associated 95% CI will be calculated based on Miettinen-Nurminen methods for stratified data.

Subgroup analysis will also be performed to estimate ORR and 95% CI within each treatment group and between treatment groups for each subgroup. Forest plot will also be provided.

8.1.3. Disease Control Rate (DCR)

DCR: the proportion of subjects who have achieved confirmed CR or PR or stable disease (SD) per RECIST 1.1.

$$\text{DCR} = \frac{number\ \ of\ \ subjects\ \ achieving\ \ CR\ \ or\ \ PR\ \ or\ \ SD}{number\ \ of\ \ all\ \ subjects} \times 100\%$$

Same analysis approach as those used for ORR analyses will be applied to DCR except for subgroup analyses.

8.1.4. Time to Response (TTR)

Time to response (TTR): Defined as from the date of randomization to the date of the first confirmed response (CR or PR).

The descriptive statistics including number of subjects, mean, variance, median, minimum and maximum will be provided for TTR by treatment groups for the objective responders only.

8.1.5. Duration of Response (DOR)

Duration of response (DoR): Defined as the time from the date of the first confirmed response (CR or PR) to the date of subsequent PD or death, whichever is earlier. DoR is calculated only for subjects who have had a response. In the absence of subsequent disease progression or death before

the study cut-off date, DoR will be censored at the date of the last valid assessment performed before the cut-off date.

The descriptive statistics such as min and max, and Kaplan-Meier curves will be provided for DoR by treatment groups for the objective responders only.

8.2. Safety Analyses

Safety analysis will be based on the SS population. The primary analysis of safety will be based on the "treatment-emergent" principle defined as from the first dose to last dose of study drug + 90 days. Analysis of safety will include:

- AEs
- Clinical laboratory variables
- Vital signs
- ECG
- Immunogenicity
- Other safety variables, including physical examinations and ECOG performance status

Unscheduled visit will be included in any post-baseline summaries but will not be included in the by-visit summaries. All unscheduled visits will be displayed in the listing.

Separate analyses will be provided for subjects in placebo arm who receives crossover treatment by period before crossover and after crossover. The safety analyses based on safety data before crossover will be the primary safety analyses (i.e. safety data after crossover will not be included in the primary safety analysis for subjects in placebo arm). Safety data after crossover will be summarized separately as exploratory analyses.

8.2.1. Adverse Events

8.2.1.1. Definition

Treatment emergent adverse events are AEs first occurring or worsened in severity from baseline within the time a subject receiving first dose of study treatment to 90 days after the last dose of study treatment or starting of crossover treatment.

8.2.1.2. Analysis of TEAE

Before the clinical database lock, all AEs will be coded using Medical Dictionary for Regulatory Activities (MedDRA) (last version available). Each AE is also graded according to NCI CTCAE

4.03 for its severity. Summary will be provided for double-blind phase, crossover phase, and overall phase.

An overall summary of TEAEs will be provided. The number and percentage of subjects who experienced any:

- TEAE
- Treatment-related TEAE
- Immune-related AE (irAE)
- Infusion reaction
- Serious TEAE
- Treatment-related serious TEAE (TESAE)
- Fatal TEAE leading to death
- TEAE leading to permanent treatment discontinuation
- TEAE leading to study discontinuation

Number and percentage of subjects with AE will also be summarized by SOC, PT and/or CTCAE grade according to the following categories by treatment group:

- TEAE
- Treatment-related TEAE
- irAE
- Infusion reaction
- TESAE
- Treatment-related TESAE
- TEAE leading to permanent treatment discontinuation
- TEAE leading to study discontinuation
- TEAE with CTCAE grade 3 or above
- Treatment-related TEAE with CTCAE grade 3 or above
- Fatal TEAE leading to death
- Important TEAE: refers to any adverse event and obvious abnormality in haematology or other laboratory tests that results in targeted medical measures (such as drug withdrawal, dose reduction and symptomatic treatment) except for serious adverse events. It will be determined in the blind clinical evaluation committee meeting before database locking.

A subject will only be counted once for each unique PT according to the highest grade occurred and most conservative relationship to the study drug determined by the investigators. An AE with CTCAE grade missing will be counted as grade 3 or above. An AE with missing relationship to study drug will be counted as related.

Listings will be provided for all AEs, irAE, infusion reaction, SAE, AE leading to permanent treatment discontinuation, and AE leading to study discontinuation including information on AE start date, end date, CTCAE grade, relationship to study drug, action taken and AE outcomes.

8.2.2. PK and Immunogenicity Analyses

Immunogenicity and pharmacokinetic (PK) data will be collected. The number and percentage of subjects with positive anti-drug antibody (ADA) and neutralizing antibody (NAB) will be summarized by treatment group.

The trough concentration of sintilimab in cycle 1 / 3 / 11 will be summarized descriptively.

8.2.3. Clinical Laboratory Test

Summary of clinical laboratory data will include Haematology, chemistry, urine examination and other laboratory examination including coagulation. Chemistry laboratory test will be further categorized as following table (renal function, liver function, electrolyte and other). In addition, subjects in placebo group receiving crossover treatment will be analysed separately according to different study phases (before or after the crossover) the laboratory tests are taken.

Table 7. Category of Chemistry Laboratory Parameters

Renal function	creatinine, CrCl, BUN/UREA
Liver function	ALT, AST, ALP, direct bilirubin, total bilirubin, albumin, TP, γ-GGT
Electrolyte	Ca, Cl, Mg, P, K, Na
Other	glucose, amylases

Descriptive statistics will be provided for each continuous parameter result and for change from baseline by treatment group, and cycle.

For CTCAE 4.03 gradable laboratory parameters, a shift summary by treatment group of baseline grade versus maximum severity post-baseline grade will be presented.

8.2.4. ECG

Summary statistics with changes from baseline will be provide for ECG. Shift tables on abnormality of ECG test at baseline and post-baseline will also be provided. ECG data will also be listed.

8.2.5. Vital Sign, Physical Exam and other Safety Exams

Vital signs, including systolic and diastolic blood pressure, pulse rate, respiratory rate, body temperature, and weight as well as change from baseline for these measurements, will be summarized by treatment group and cycle for the safety population. Shift table by treatment group of baseline status versus worst post-baseline status will be provided according to the potentially clinically significant abnormality (PCSA) criteria (Table 8). It should be noted that the analysis of increase in diastolic blood pressure from baseline > 20 mmHg is only for subjects with both baseline and post-baseline measurements.

Table 8. PCSA Criteria

Parameters	Criteria	Reference
SBP (mmHg)	Increase from baseline > 20 mmHg*	CTCAE Version 4.03 Grade 2
DBP (mmHg)	≥ 140 mmHg	CTCAE Version 4.03 Grade 2
HR slow	< 60 beats/min	The definition of "Sinus bradycardia" in CTCAE Version 4.03
HR fast	> 120 beats/min	The definition of "Sinus tachycardia", "Supraventricular tachycardia", and "Ventricular tachycardia" in CTCAE Version 4.03

Number and percentage of abnormal physical exam will also be provided. Listing of abnormal physical exam will also be provided.

Shift table will be provided to summarize changes in ECOG PS.

Listing will be provided for all other safety exams.

9. EXPLOATORY ANALYSES

9.1. Biomarkers in tumor tissue and peripheral blood

Summarize the number and percentage of subjects, as well as the corresponding ORR, DOR, PFS in different subgroup based on the baseline level of PD-L1 expression (<1%, 1~49%, >49%), and dynamic change in TCR, and ctDNA.

9.2. Quality of Life Analysis

9.2.1. Lung Cancer Symptom Scale (LCSS)

The Lung Cancer Symptom Scale (LCSS) consists of nine graphical subscales. Additional scores are derived based on methods described below.

- All symptom score: Average of question 1 to 6
- Respiratory symptom score: Average of question 3 to 5
- Global health score: Average of question 1 to 2

In the above score derivation, no imputation will be used for missing questions.

Descriptive statistics will be provided for each item, derived scores and their corresponding changes from baseline at each visit by treatment groups. Baseline values are defined as last non-missing LCSS measurements before first administer of study drug. The descriptive statistics include mean, standard deviation, min, max, quartiles (q1, q3), median and range.

Stratified Wilcoxon test will be performed to compare between group differences at each post-baseline LCSS assessment visit.

In addition, constrained longitudinal data analysis by Liang-Zeger (2000) will be performed to compare between group differences at each LCSS assessment visit and overall study period. Least square estimate (LSE) with 95% CI for each treatment group and between group differences will be provided and plotted.

9.2.2. EORTC QLQ-C30

The EORTC QLQ-C30 is a core questionnaire for all cancer subjects, with a total of 30 items which are divided into 15 dimensions: five functional dimensions (physical, role, cognitive, emotional, and social), three symptom items (fatigue, pain, and nausea/vomiting), global health and quality of life, and six single items. The scoring method is summarized in Table 9.

Table 9. QLQ-30 Scoring Methods

Dimensions	Code	Category	# of Items	Score range (R)	Scoring method
Physical	PF	Functional	5	3	$(Q_1+Q_2+Q_3+Q_4+Q_5)/5$
Role	RF	Functional	2	3	$(Q_6+Q_7)/2$
Emotion	EF	Functional	4	3	$(Q_{21}+Q_{22}+Q_{23}+Q_{24})/4$
Cognition	CF	Functional	2	3	$(Q_{20}+Q_{25})/2$
Sociability	SF	Functional	2	3	$(Q_{26}+Q_{27})/2$
Global health status	QL		2	6	$(Q_{29}+Q_{30})/2$
Fatigue	FA	Symptom	3	3	$(Q_{10}+Q_{12}+Q_{18})/3$
Nausea and vomiting	NV	Symptom	2	3	$(Q_{14}+Q_{15})/2$
Pain	PA	Symptom	2	3	$(Q_9+Q_{19})/2$
Dyspnoea	DY	Symptom	1	3	Q_8
Sleepless	SL	Symptom	1	3	Q_{11}
Appetite loss	AP	Symptom	1	3	Q_{13}
Constipation	CO	Symptom	1	3	Q_{16}
Diarrhoea	DI	Symptom	1	3	Q_{17}
Financial difficulty	FI	Symptom	1	3	Q_{28}

Data collected from questionnaires are considered as raw scores. Analysis variables are derived from raw scores using the formulas below. Missing value will not be included in the calculation.

For functional items, analysis variable is defined as $\left(1-\frac{\text{raw score}-1}{R}\right)\times 100$;

For symptom variables and global health score, analysis variables are defined as $\frac{\text{raw score}-1}{R}\times 100$.

All analyses variables take value between 0-100 after normalization.

Descriptively summarize the analysis variables and provide the p value (Wilcoxon rank test) for group comparison by each assessment visit.

Same approaches as those used for LCSS will be applied for missing data handling, weighted averaging, summary and statistical inference on QLQ-30 data.

9.3. Efficacy Analyses after PD

Placebo subjects after PD confirmation and unblinding may crossover to receive sintilimab monotherapy as agreed by sponsor per protocol allowance. Only investigator assessment per RECIST 1.1 will be available during crossover phase. PFS 2 is defined as time from start of new anti-cancer therapy until subsequent PD based on RECIST 1.1 or death due to any cause, whichever is earlier. In the absence of disease progression or death at the last tumor assessment, PFS will be censored at this time point.

If subject in IBI308 group receive new anti-cancer treatment after disease progression, subsequent information of new treatment and treatment effect should be collected.

PFS 2 analyses are only applied to subjects receiving crossover treatment in FAS set. The analysis methods are the same as those for PFS analysis.

Post disease progression ORR, TTR, and DOR will also be analyzed for subjects receiving sintilimab crossover treatment in FAS set. Analysis methods are similar to those descripted in 8.1.2, 8.1.4 and 8.1.5, but without between-group comparison.

10. REFERENCES

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11. APPENDICES

11.1. Acronym

Abbreviation	Description
ADA	Anti-drug antibody
ADR	Adverse Drug Reaction
AE	Adverse Event
ANC	Absolute Neutrophil Count
ALT	Alanine transaminase
ALK	Anaplastic lymphoma kinase
ALK	Anaplastic lymphoma kinase
AST	Aspartate amino transferase
BOR	Best overall response
CFDA	China Food and Drug Administration
CR	Complete Response
Cr	Creatinine

Abbreviation	Description
CRF	Case Report Form
CTLA-4	Cytotoxic T Lymphocyte Antigen 4
DCR	Disease control rate
DOR	Duration of response
DLT	Dose-limiting toxicity
EC	Ethics Committee
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EGFR	Epidermal growth factor receptor
EORTC QLQ	European organization for research and treatment of cancer quality of life questionnaire
GCP	Good Clinical Practice
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HIV	Human Immunodeficiency Virus
ICF	Informed Consent Form
irAE	Immune-related Adverse Event
IRRC	Independent radiographic review committee
LCSS	The Lung Cancer Symptom Scale
MTD	Maximal tolerated dose
Nab	Neutralizing antibody
NSCLC	Non-Small Cell Lung Cancer
ORR	Overall response rate

Abbreviation	Description
OS	Overall Survival
PBMC	Peripheral blood mononuclear cell
PD	Pharmacodynamics
PD-1	Programmed cell death 1
PFS	Progression Free Survival
PK	Pharmacokinetic
PR	Partial Response
RECIST	Response Evaluation Criteria In Solid Tumors
RP2D	Recommended Phase II dose
SAE	Severe Adverse Event
SD	Stable Disease
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 limits of normal