Clinical Study Protocol

Study Title:	A Randomized, Double-blind, Phase III Study Evaluating the Efficacy and Safety of Sintilimab or Placebo in Combination with Pemetrexed and Platinum-based Chemotherapy in the First-line Treatment of Advanced or Recurrent Non-squamous Non-small Cell Lung Cancer (ORIENT-11)
Protocol Number:	CIBI308C302
Version Date and Version Number:	Aug 09, 2019/Version 3.0
Product Name:	Sintilimab (Recombinant Fully Human Anti-Programmed Death Receptor-1 Monoclonal Antibody, R&D code: IBI308)
Study Phase:	Phase III
Sponsor:	Innovent Biologics (Suzhou) Co., Ltd. No. 168 Dongping Street, Suzhou Industry Park Jiangsu Province, China
Sponsor Contact:	Hui Zhou Vice President, Medical Science and Strategy Oncology 021-31652896 hui.zhou@innoventbio.com

Sponsor Signature Page

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Project Number: CIBI308C302

Position	**Name (Print)**	**Signature**	**Date**
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Protocol Synopsis

Protocol Number	CIBI308C302
Sponsor	Innovent Biologics (Suzhou) Co., Ltd.
Study drug	Sintilimab (R&D Code: IBI308)
Active Ingredients	Recombinant Fully Human Anti-Programmed Death Receptor-1 (PD-1) Monoclonal Antibody
Study Title	A Randomized, Double-blind, Phase III Study Evaluating the Efficacy and Safety of Sintilimab or Placebo in Combination with Pemetrexed and Platinum-based Chemotherapy in the First-line Treatment of Advanced or Recurrent Non-squamous Non-small Cell Lung Cancer (ORIENT-11)
Study Phase	Phase III
Estimated Duration of Study	Expected to be about 23 months (from first subject enrollment to primary statistical analysis)
Study Objectives	Primary Objective: ● To compare the progression-free survival (PFS) per RECIST v1.1 in the first-line treatment of advanced or recurrent non-squamous non-small cell lung cancer (NSCLC) treated with sintilimab in combination with pemetrexed and platinum-based chemotherapy versus placebo in combination with pemetrexed and platinum-based chemotherapy. Secondary Objectives: ● To compare the overall survival (OS) between the two treatment arms; ● To compare the objective response rate (ORR) per RECIST v1.1 between the two treatment arms; ● To compare the disease control rate (DCR) per RECIST v1.1 between the two treatment arms; ● To compare the time to objective response (TTR) per RECIST v1.1 between the two treatment arms; ● To compare the duration of response (DOR) per RECIST v1.1 between the two treatment arms; ● To evaluate the safety and tolerability of sintilimab in combination with pemetrexed and platinum-based chemotherapy.

	Exploratory Objectives: ● To evaluate the efficacy of sintilimab per the immune Response Evaluation Criteria in Solid Tumors (iRECIST); ● To explore the population pharmacokinetic (PK) characteristics of sintilimab; ● To explore the biomarkers that can potentially predict the efficacy of sintilimab arm including but not limited to, PD-L1 expression, and RNA in tumor specimens, circulating tumor DNA (ctDNA) and T cell receptor (TCR) in peripheral blood; ● To compare the quality of life of subjects treated with sintilimab combined with chemotherapy and placebo combined 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); ● To compare PFS in the sintilimab arm receiving subsequent antineoplastic therapy after disease progression versus placebo arm crossing over to receive sintilimab.
Study Design	This study is a randomized, double-blind, multicenter, phase III study of sintilimab in combination with pemetrexed and platinum-based chemotherapy or placebo in combination with pemetrexed and platinum-based chemotherapy in the first-line treatment of subjects with advanced or recurrent non-squamous NSCLC in China. Subjects in this study will receive 4 cycles of sintilimab or placebo in combination with pemetrexed and platinum (cisplatin or carboplatin) followed by maintenance therapy with sintilimab or placebo in combination with pemetrexed until disease progression, intolerable toxicity, withdrawal of consent, death, or other protocol-specified circumstances in which treatment should be discontinued, whichever occurs first. Approximately 378 subjects with advanced or recurrent non-squamous NSCLC who have not previously received systemic therapy for advanced disease will be randomized at a 2:1 ratio to the sintilimab group (experimental group) and the placebo group (control group), with 252 subjects in the sintilimab group and 126 subjects in the placebo group. The actual number of subjects enrolled may differ from the planned number due to unforeseen reasons, such as faster enrollment speed than expected. The final screening end date will be estimated before the enrollment of 378 subjects and best effort will be made to ensure that the

	total number of subjects enrolled do not exceed 110% of the planned number, i.e., 414 subjects, of which 276 subjects are expected in the experimental group and 138 subjects are expected in the control group. The primary efficacy endpoint of the study is PFS per RECIST v1.1 assessed by independent radiographic review committee (IRRC). Subjects in the control group whose disease progression are confirmed may crossover to receive sintilimab monotherapy at the discretion of the investigator and subjects. The sintilimab monotherapy may continue until disease progression, intolerable toxicity, withdrawal of consent, death or other protocol-specified circumstances, whichever occurs first. The maximum treatment duration of sintilimab is 24 months. Interim analysis will be conducted during the study when 70% PFS events occur. The results and report of the analysis will be provided to the independent data monitoring committee (IDMC). The IDMC will make recommendation on whether the study result can be submitted for application in advance based on whether the interim result of this study meets the pre-specified efficacy boundary. IDMC charter will be finalized and approved before the interim analysis. Responsibilities of IDMC members and associated procedures will be defined in the IDMC charter.
Estimation of Sample Size	It is assumed that the median PFS of subjects receiving sintilimab treatment will be improved from 6 months to 9.2 months [with a hazard ratio (HR) = 0.65]. With a projected enrollment time of 15 months, follow-up time of 8 months and an estimated dropout rate of 0.5% per month, to provide approximately 90% power under a two-sided α of 0.05, a total of 378 subjects need to be randomized to obtain the required 263 PFS events in this study. The actual number of subjects enrolled may differ from the planned number due to unforeseen reasons, such as faster enrollment speed than expected. The final screening end date will be estimated before the enrollment of 378 subjects and best effort will be made to ensure that the total number of subjects enrolled do not exceed 110% of the planned number, i.e., 414 subjects, of which 276 subjects are expected in the experimental group and 138 subjects are expected in the control group. An interim analysis will be conducted during the study when 70% PFS events (i.e. 184 events) occur, and the primary interim analysis will be based on PFS. This study is expected to be conducted in 30 ~ 40 sites in China.

Inclusion Criteria	1) Has signed written informed consent before any study-related procedure; 2) Is ≥ 18 and ≤ 75 years old; 3) Has a life expectancy of at least 3 months; 4) Has at least one measurable lesion based on RECIST v1.1 assessed by the investigator; Measurable lesions in a previously irradiated or locally treated area can be selected as target lesions if progression has been demonstrated in such lesions; 5) Has a histologically or cytologically confirmed diagnosis of locally advanced (stage IIIB/IIIC), metastatic, or recurrent (stage IV) non-squamous NSCLC according to the 8th edition of the TNM classification in the International Association for the Study of Lung Cancer and the American Joint Committee on Cancer. Meanwhile, subjects with stage IIIB/IIIC non-squamous NSCLC should not be eligible for radical surgery or radical radiochemotherapy; 6) Ineligible for EGFR or ALK target therapy (documented evidence of absence of sensitizing EGFR mutations and ALK gene rearrangements is required); 7) Eastern Cooperative Oncology Group performance status (ECOG PS) of 0 or 1; 8) Has not received prior systemic antineoplastic therapy for advanced/recurrent non-squamous NSCLC; Subjects who have received prior adjuvant chemotherapy are eligible if the adjuvant chemotherapy is completed at least 6 months prior to the recurrence of disease; 9) Has adequate hematopoietic function as defined by an absolute neutrophil count ≥ 1.5 × 10^9/L, platelet count ≥ 100 × 10^9 /L, hemoglobin ≥ 90 g/L [without transfusion in 7 days and without dependence on erythropoietin (EPO)]; 10) Has adequate hepatic function, defined as a total bilirubin level≤1.5 × upper limit of normal (ULN); aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels ≤2.5 × ULN in subjects without liver metastases, AST and ALT levels ≤5 × ULN in subjects with documented liver metastases; 11) Has adequate renal function, defined as serum creatinine (Cr) ≤ 1.5 × ULN or calculated creatinine clearance ≥ 60ml/min (Cockcroft-Gault formula);

	Urine protein < 2 +, or 24-hour urine protein < 1g; 12) Has adequate coagulation function, defined as international normalized ratio (INR) or prothrombin time (PT) ≤ 1.5 ×ULN ; if the subject is receiving anticoagulant therapy, as long as the PT is within the proposed range for the anticoagulant, the subject is eligible; 13) Female subjects of childbearing potential should have a negative urine or serum pregnancy test within 3 days prior to receiving the first dose of study drug (Cycle 1, Day 1). If the urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required; 14) If there is a risk of conception, male and female subjects must use highly effective contraception (i.e., a method with a failure rate of less than 1% per year) for at least 180 days after end of treatment.
Exclusion Criteria	1) Has predominantly squamous histology NSCLC; Mixed cell types must be primarily (≥90%) adenocarcinoma cells; if small cell elements are present, the subject cannot be enrolled; 2) Is currently participating in an interventional clinical study or received other investigational drugs or device within 4 weeks prior to the first dose of drug treatment; 3) Has previously received the following therapies: anti-PD-1, anti-PD-L1, or anti-PD-L2 agents or agents directed at another stimulatory or co-inhibitory T-cell receptor (e.g., CTLA-4, OX-40, CD137); 4) Has received Chinese medicines with anti-lung cancer indications or immunomodulatory drugs (including thymosin, interferon, interleukin, except for local use to control pleural effusion) within 2 weeks prior to first dose of drug treatment, or has undergone major surgery within 3 weeks prior to first dose of drug treatment; 5) Has received radiotherapy in lung with a dose > 30 Gy within 6 months prior to the first dose of study treatment; 6) Has completed palliative radiotherapy within 7 days prior to the first dose of study treatment; 7) Has clinically active diverticulitis, intra-abdominal abscess, gastrointestinal obstruction; 8) Has received solid organ or blood system transplantation; 9) Has clinically uncontrollable pleural effusion or ascites (subjects who doesn't need drainage of effusion or has no significant increase in effusion 3 days after stopping drainage can be enrolled); 10) Has a known severe allergic reaction (≥grade 3) to any component of sintilimab, pemetrexed, cisplatin, or carboplatin or to any excipients;

	11) Has active autoimmune disease that has required systemic therapy (e.g., use of disease modifying agents, corticosteroids, or immunosuppressive drugs) within 2 years prior to the first dose of study treatment. Replacement therapy (e.g., thyroxine, insulin, or physiologic corticosteroids replacement therapy for adrenal or pituitary insufficiency) is not considered a form of systemic therapy; 12) Diagnosed with immunodeficiency or receiving systemic glucocorticoid therapy or any other form of immunosuppressive therapy within 7 days prior to the first dose of study treatment; Physiological doses of glucocorticoids (≤10 mg/day of prednisone or equivalent glucocorticoid) is allowed; 13) Has not adequately recovered from toxicity and/or complications caused by any intervention prior to starting study treatment (i.e. ≤Grade 1 or to baseline, excluding asthenia or alopecia); 14) Has other malignancies diagnosed within 5 years prior to the first dose of study treatment, with the exception of radically treated basal cell carcinoma of the skin, squamous cell carcinoma of the skin, and/or radically resected carcinoma in situ; 15) Has symptomatic central nervous metastases. Subjects with asymptomatic metastases or stable metastases after treatment may participate in the study as long as all of the following criteria are met: measurable lesion outside the central nervous system; no meningeal, midbrain, pontine, medullary, or spinal metastases; clinically stable for at least 2 weeks; and discontinuation of hormonal therapy 14 days prior to the first dose of study treatment; 16) Has a known history of non-infectious pneumonitis requiring corticosteroid therapy within 1 year prior to the first dose of study treatment or has current interstitial lung disease; 17) Has active infection requiring systemic therapy; 18) Is unable or unwilling to take folic acid or vitamin B_{12} supplementation; 19) Has psychiatric or substance abuse disorder that would interfere with compliance with the requirements of the study; 20) Has a known history of Human Immunodeficiency Virus (HIV) infection (i.e., HIV 1/2 antibodies positive), known active syphilis infection, active pulmonary tuberculosis; 21) Has known untreated active hepatitis B; Note: Subjects with hepatitis B who meet the following criteria are also eligible:

	HBV viral load must be < 1000 copies/ml (200 IU/ml) or below the lower limit of detection before the first dose of study treatment. Subjects with active hepatitis B should receive anti-HBV therapy to avoid viral reactivation throughout the study treatment; For subjects with anti-HBc (+), HBsAg (-), anti-HBs (-) and HBV viral load (-), prophylactic anti-HBV treatment is not required, but viral reactivation should be closely monitored; 22) Has active HCV infection (HCV antibody positive and HCV-RNA level above the lower limit of detection); 23) Has received a live vaccine within 30 days prior to the first dose (Cycle 1, Day 1); Note: Inactivated viral vaccines for seasonal influenza within 30 days prior to the first dose of study treatment are allowed; live attenuated influenza vaccines administered intranasally are not allowed; 24) Has uncontrolled concurrent medical conditions, such as: a) Esophageal or gastric varices requiring immediate intervention (e.g., band ligation or sclerotherapy) or with a high risk of bleeding in the opinion of the investigator or in consultation with a gastroenterologist or hepatologist. Subjects who have portal hypertension (including splenomegaly with the evidence of imaging evaluation) or has a history of variceal bleeding should receive endoscopic examination within 3 months prior to enrollment to evaluate whether the subjects are eligible; b) Hepatic encephalopathy, hepatorenal syndrome, or Child-Pugh B or worse cirrhosis; c) Significant malnutrition (e.g. need intravenous nutrition supplements). Subjects with malnutrition remedied more than 4 weeks prior to the first dose of study treatment are eligible; d) The tumor compresses the surrounding vital organs (such as esophagus) accompanied with relevant symptoms, or compresses the superior vena cava or invades the major mediastinal blood vessels, heart, etc.; e) Class II-IV congestive heart failure (New York Heart Association classification), poorly controlled and clinically significant arrhythmia; f) Uncontrolled arterial hypertension even after receiving standard treatment (systolic blood pressure≥160 mmHg or diastolic blood pressure≥100 mmHg);

	g) Any arterial thrombosis, embolism, or ischemia such as myocardial infarction, unstable angina, cerebrovascular accident, or transient ischemic attack within 6 months prior to enrollment. With a history of deep vein thrombosis, pulmonary embolism, or any other serious thromboembolism within 3 months prior to enrollment (thrombosis caused by implantable venous port or catheter, or superficial venous thrombosis is not considered "serious" thromboembolism); 25) Has a history or current evidence of any disease, treatment, or laboratory abnormality that may interfere with the results of the study, prevent the subject from fully participating in the study, or other condition that the subject is ineligible for enrollment, in the opinion of the investigator; 26) Is breast-feeding.
Study Drug and Mode of Administration	1. Sintilimab: 200 mg, administer intravenous infusion on the first day of each cycle, Q3W. 2. Placebo: 2 vials, administer intravenous infusion on the first day of each cycle, Q3W. 3. Pemetrexed: 500 mg/m^2 , administer intravenous infusion on the first day of each cycle, Q3W. 4. Cisplatin: 75 mg/m^2 , administer intravenous infusion on the first day of each cycle, Q3W or Carboplatin: AUC 5 mg* min/ml, administer intravenous infusion on the first day of each cycle, Q3W.
Evaluation Criteria	**Efficacy Evaluation:** ● Evaluate PFS, OS, ORR, DOR, DCR, and TTR per RECIST v1.1; ● Evaluate iORR, iTTR, iDCR, iPFS, and iDOR per iRECIST. **Safety evaluation:** ● Incidence, severity and relationship with the study drug of all adverse events (AEs), treatment emergent adverse events (TEAEs), immune related adverse events (irAEs) and serious adverse events (SAEs); ● Number of subjects who discontinued treatment due to the above adverse events; ● Positive rate of anti-drug antibody (ADA) and neutralizing antibody (NAb); ● Changes in vital signs, physical examination, and laboratory results before, during, and after study treatment.

Statistical Methods	The primary analysis of this study is to confirm that sintilimab in combination with chemotherapy prolongs PFS compared to placebo in combination with chemotherapy. Efficacy evaluation Stratified log-rank test will be used to compare PFS between groups and stratified Cox proportional hazards model will be used to estimate HR and its 95% confidence interval (CI) between groups. Stratification factors (gender, PD-L1 expression level, platinum), age (>60, ≤ 60), smoking status (former/current smoker, non-smoker), number of organs with metastatic lesions (> 2, ≤2), and other significant covariates will be considered in the model, and their HR and 95% CI will be estimated. Median PFS and its 95% CI will be estimated using the Kaplan-Meier method, and survival curves will be plotted. Stratified log-rank test will be used to compare OS between groups, and stratified Cox proportional hazards model will be used to estimate HR and its 95% CI between groups. Stratification factors (gender, PD-L1 expression level, platinum), age (>60, ≤60), smoking status (former/current smoker, non-smoker), number of organs with metastatic lesions (> 2, ≤2), and other significant covariates will be considered in the model, and their HR and 95% CI will be estimated. Median OS and its 95% CI will be estimated using the Kaplan-Meier method, and survival curves will be plotted. The two groups' ORR and DCR of tumor efficacy evaluation per imaging assessment and 95% CI will be evaluated respectively. The difference between the rates and 95% CI will be calculated. Quality of life scores will be linearly transformed using the range method, and the crude scores will be transformed into standardized scores with values within 0 ~ 100. Descriptive statistics and Wilcoxon test will be performed for the results, and descriptive statistics and Wilcoxon test will be used for the performance status score (ECOG PS). Safety evaluation The exposure of subjects to the study drug will be summarized, including treatment cycles, dose adjustment, cumulative number of dose adjustments of both groups. The cumulative incidence of adverse events, adverse events leading to withdrawal from the study, adverse events leading to death and serious adverse events will be summarized. The incidence (the occurrence number is calculated as the subjects who have experienced a certain adverse event at least once) by systems/ organ classification and preffered term will be

	calculated. The severity of adverse events: if the same subject has experienced the same adverse event many times, the most serious one will be counted for analysis; if the same subject has experienced different adverse events, the most serious adverse event will be counted for analysis. Laboratory parameters: descriptive summaries of laboratory values will be primarily for abnormal values. Laboratory abnormalities will be summarized according to the worst grade in NCI CTCAE Version 4.03. Immunogenicity data will be analyzed using descriptive statistics. Vital signs: use mean±standard deviation, maximum, minimum, and median describe measurements and changes by visit. Physical examination, ECG (including QTcF), blood pressure monitoring, etc. The population PK profile of sintilimab in the advanced non-squamous NSCLC population will be analyzed using nonlinear mixed effects modeling.

Table 1. Study Flow Chart

Phase	Screening Phase	Combination treatment period (1 cycle every 21 days)				Maintenance therapy (1 treatment cycle every 21 days)	End of Treatment Visit [22]	Safety Follow-up[22]	Survival Follow-up [23]
		1	2	3	4				
Scheduling Window	- 28 ~ -1	Day 1 (± 3 days)				Day 1 (± 3 days)	Within 7 days after the end of treatment	30 (± 3) days after the last dose	Every 90 days (± 7 days)
General Study Procedures									
Written informed consent [1]	X								
Inclusion/Exclusion Criteria	X								
Demographics/Past Medical History/Prior Therapies [2]	X								
Vital signs [3]	X	X	X	X	X	X	X	X	
Weight/Height [4]	X	X	X	X	X	X	X	X	
Physical Examination	X						X	X	
ECOG PS score	X	X	X	X	X	X	X	X	
12-lead ECG [5]	X	X	X	X	X	X	X	X	
Hematology/Blood biochemistry/Urinalysis [6]	X		X	X	X	X	X	X	
Coagulation function [7]	X						X	X	
Pregnancy test [8]	X								
Thyroid function [9]	X		X	X	X	X	X	X	

Phase	Screening Phase	Combination treatment period (1 cycle every 21 days)				Maintenance therapy (1 treatment cycle every 21 days)	End of Treatment Visit [22]	Safety Follow-up[22]	Survival Follow-up [23]
		1	2	3	4				
Scheduling Window	- 28 ~ -1	Day 1 (± 3 days)				Day 1 (± 3 days)	Within 7 days after the end of treatment	30 (± 3) days after the last dose	Every 90 days (± 7 days)
Virological antibody tests (HIV, HBV, HCV and Treponema pallidum specific antibodies) [10]	X								
HCV-RNA if HCV antibody positive [11]	X		X	X	X	X	X	X	
HBV-DNA if positive for HBsAg and/or HBcAb [12]	X		X	X	X	X	X	X	
Blood cardiac enzymes and troponin [13]	X		X	X					
Review Adverse Events [14]	X	X	X	X	X	X	X	X	X
Concomitant medications	X	X	X	X	X	X	X	X	
Quality of Life Questionnaire [15]		X	X		X	X	X		
Subsequent antineoplastic therapy							X	X	X
Efficacy Measurements									
Tumor Imaging [16]	X		X		X	X			

Phase	Screening Phase	Combination treatment period (1 cycle every 21 days)				Maintenance therapy (1 treatment cycle every 21 days)	End of Treatment Visit [22]	Safety Follow-up[22]	Survival Follow-up [23]
		1	2	3	4				
Scheduling Window	- 28 ~ -1	Day 1 (± 3 days)				Day 1 (± 3 days)	Within 7 days after the end of treatment	30 (± 3) days after the last dose	Every 90 days (± 7 days)
PK and Immunogenicity									
Immunogenicity [17]		X	X		X	X	X		
PK [18]		X	X		X	X			
Study Drug Administration [19]									
Sintilimab or placebo		X	X	X	X	X			
Pemetrexed		X	X	X	X	X			
Cisplatin or carboplatin		X	X	X	X				
Exploration of Biomarkers									
Archived or fresh tumor tissue sample [20]	X								
Whole blood [21]		X	X		X	X			

Notes:

1. The signing of the informed consent form (ICF) should precede any study procedures.
2. Prior therapies include: therapies for the initial diagnosis, including chemotherapy, radiation therapy, and surgery, as well as therapies for prior concurrent conditions within the last 30 days.
3. Vital signs included: temperature, pulse, respiratory rate, and blood pressure.

4. Height will be measured only at screening. Weight will be measured prior to each dose, at the end of treatment visit, and at the safety follow-up visit. If a subject's body weight fluctuated less than 10% from baseline (the day of the first dose of study treatment), the baseline body weight will be used to calculate the amount of chemotherapy administered. Otherwise, the actual dose will be calculated based on the body weight on the scheduled day of dosing or the day before it. The actual dose can also be calculated based on the body weight on the day of dosing or the day before it according to clinical practice regardless of the baseline weight.

5. Time point of 12-lead ECG examination: during screening period, before administration of each cycle, at the end of treatment visit and at the safety follow-up visit.

6. Hematology includes: red blood cell count (RBC), hemoglobin (HGB), hematocrit (HCT), white blood cell count (WBC), platelet count (PLT), white blood cell differential (lymphocytes, neutrophils, monocytes, eosinophils, basophils). Blood biochemistry includes: liver function (TBIL, DBIL, ALT, AST, γ-GT, ALP, ALB, TP, LDH), renal function (UREA or BUN, Cr), blood electrolytes (Na, K, Cl, Mg, Ca, P), amylase, and glucose. Urinalysis includes: PH, specific gravity, UWBC, UPRO, URBC, UGLU. Subjects whose urinalysis results showed urine protein ≥2+ during screening period should undergo a 24-hour urine protein quantification. Hematology, blood biochemistry, urinalysis are to be performed within 7 days prior to the first dose of study drug in the screening period, within 3 days prior to the start of each cycle of study drug starting from Cycle 2, at the end of treatment visit and at the safety follow-up visit. Tests will be conducted in each local lab. Subjects with hemoglobin≥90 g/L 3 days prior to the start of the second cycle can receive drug.

7. Coagulation tests include: PT and INR are to be performed within 7 days prior to the first dose of study treatment in the screening period, at the end of treatment visit and at the safety follow-up visit. Tests will be conducted in each local lab.

8. Women of childbearing potential will have a urine or serum pregnancy test performed within 3 days prior to the first dose in the screening period. If the result of urine pregnancy test cannot be confirmed as negative, serum pregnancy test will be performed, and the result of serum pregnancy will prevail. Tests will be conducted in each local lab.

9. To be performed within 28 days prior to the first dose, within 3 days prior to the start of each cycle of study medication in Cycle 2, at the end of treatment visit and at the safety follow-up visit. T3/FT3, FT4 and TSH will be tested at screening period. Only TSH will be tested at the beginning of Cycle 2. If there are any abnormalities, other thyroid function tests will be considered. Tests will be conducted in each local lab.
10. Tests for HIV, specific antibodies to Treponema pallidum and HCV, and tests for hepatitis B (HBsAg, HBsAb, HBcAb, HBeAg, HBeAb) should be completed within 28 days prior to the first dose. A screening examination will be conducted in each local lab.
11. To test for anti-HCV antibodies at the screening visit. For HCV antibody-positive subjects, HCV-RNA load are to be measured once during screening, within 3 days prior to the start of study drug administration in each cycle starting from Cycle 2, at the end of treatment visit and at the safety follow-up visit, or sooner if clinically indicated. During the course of study treatment, it is not necessary to wait for the test result to be administered first with the study drug.
12. Five items of hepatitis B are to tested at the screening visit, and for HBsAg and/or HBcAb positive subjects, HBV-DNA load are to be measured once during the screening period, within 3 days before the start of study drug administration in each cycle starting from Cycle 2, at the end of treatment visit and at the safety follow-up visit, or earlier if clinically indicated. During the course of study treatment, it may be unnecessary to wait for the test results and the study drug can be used first.
13. Cardiac biomarker testings and troponin test include at least: creatine kinase (CK), creatine kinase myocardial band (CK-MB), troponin (troponin T or troponin I). Subsequent examinations will be performed at the discretion of the investigator within 7 days prior to the first dose of study drug in the screening period and within 3 days prior to each cycle of study drug in Cycles 2 and 3.
14. Safety assessments of AEs and laboratory tests will be performed according to CTCAE v4.03. For the definition, recording, relevance judgment, severity judgment, reporting time limit and handling of AEs and SAEs, refer to the description in Section 8 of the protocol.
15. Quality of life questionnaires include EORTC QLQ-C30 assessments will be performed prior to the first dose, at each imaging evaluation, and at the end of treatment visit.
16. Tumor response evaluation will be based on RECIST v1.1 and iRECIST. Tumor imaging usually includes contrast-enhanced CT or MRI. The examination parts must include brain, chest, abdomen and pelvis. For subjects without brain metastases at baseline, routine brain imaging is not required thereafter. The same imaging technique should be used for the same subject during the study. Baseline evaluations will be performed within 28 days prior to study entry, and the investigator may

collect imaging results for assessment within 28 days prior to study entry. Tumor imaging evaluation will be performed once respectively at Week 6 (±7 days) and Week 12 (±7 days) from the time of first dosing, and then every 9 weeks (± 7 days); tumor imaging evaluation will be performed every 12 weeks (± 7 days) after Week 48. Subjects with initial documented radiographic disease progression must undergo imaging evaluation at least 4 weeks after the date of the first tumor imaging indicating progressive disease and no later than 8 weeks to confirm disease progression if clinically stable. Subjects who discontinue treatment for reasons other than radiographic disease progression should continue to undergo imaging assessments at protocol-specified imaging intervals until any of the following events occur: initiation of new antineoplastic therapy, disease progression, subject withdrawal of ICF, and death, whichever occurs first. Tumor imaging evaluation should be performed at the end of treatment if the end of treatment is more than 4 weeks since the last imaging examination for tumor assessment. The evaluation will be completed after the occurrence of PD confirmed by central imaging and investigator in RECIST v1.1; the evaluation of iRECIST will start from the first PD visit in RECIST v1.1 until the end of efficacy assessment.

17. Immunogenicity testing will be performed during Cycles 1/2/4/8/12/16, and every 8 cycles thereafter (Cycles 24, 32, etc.) within 1 hour prior to the start of sintilimab/placebo infusion and safety follow up. If an infusion-related reaction occurs during sintilimab/placebo infusion, blood samples should be taken near the start of the event, end of event, and around 30 days after the reaction for immunogenicity analysis. Tests should be conducted at the central lab.

18. PK sampling will be performed at the following time points: within 1 hour before the start of sintilimab/placebo infusion in Cycle 1, immediately (+ 5 min) after the end of sintilimab/placebo infusion in Cycle 1, and within 1 hour before the start of sintilimab/placebo infusion in Cycle 2/4/12. Tests will be conducted at the cental lab.

19. The subjects in the test group will be given sintilimab 200 mg combined with pemetrexed + cisplatin or carboplatin via intravenous infusion once every 3 weeks; the subjects in the control group will be given placebo combined with pemetrexed + cisplatin or carboplatin via intravenous infusion once every 3 weeks. After completion of 4 cycles of treatment with sintilimab or placebo in combination with pemetrexed plus cisplatin or carboplatin, proceed to the maintenance phase with sintilimab or placebo in combination with pemetrexed until disease progression, intolerability of toxicity, withdrawal of ICF, death, or other protocol-specified circumstances in which treatment should be discontinued, whichever occurs first. Subjects in the control arm who have centrally confirmed and/or confirmed radiographic PD may crossover to receive sintilimab monotherapy at the discretion of the investigator. Treatment should be discontinued until disease progression,

intolerable toxicity, withdrawal of consent, death, or other protocol-specified condition, whichever occurs first. The maximum duration of treatment with sintilimab is 24 months. See Table 2 for details of the specific procedures for crossover treatment with sintilimab after imaging PD confirmed and/or confirmed by central imaging.

20. The subjects should provide 5 ~ 10 sections of archived or fresh tumor tissue samples which meet the test requirements during the screening period.

21. Subjects will be required to provide a 10ml whole blood specimen for tumor biomarker testing at the following time points: prior to the first dose, at each imaging evaluation during the treatment period, and prior to the next treatment and confirmation of disease progression. Tests will be conducted in each local lab.

22. End of treatment visit: within 7 days after the end of treatment. Safety follow-up visit: 30±3 days after last dose, or prior to initiation of new antineoplastic therapy. If the end of treatment visit and safety follow-up visit are within 7 days, only the end of treatment visit will be performed. If the safety follow-up visit is prior to the end of treatment visit, only the end of treatment visit will be performed. Refer to Section 6.2.4 for details.

23. Survival follow-up visit: every 90 days (±7 days) after the safety follow-up visit, phone call is acceptable. Refer to Section 6.2.5 for details.

Table 2. Flow Chart of Crossover Phase to Sintilimab Monotherapy

Phase	Crossover Treatment Cycles with Sintilimab (Every 21 days per 1 cycle) [1]							End of Treatment Visit [13]	Safety Follow-up [13]	Survival Follow-up [14]
	1	2	3	4	5	6	7 and above			
Scheduling Window (days)	- 28 ~ -1	± 3	± 3	± 3	± 3	± 3	± 3	Within 7 days after the end of treatment	30 (± 3) days after the last dose	Every 90 days (± 7)
General Study Procedures										
Vital signs [2]	X	X	X	X	X	X	X	X	X	
Weight/Height [3]	X									
Physical Examination	X							X	X	
ECOG PS score	X	X	X	X	X	X	X	X	X	
12-lead ECG [4]	X	X	X	X	X	X	X	X	X	
Hematology/Blood Biochemistry/Urinalysis [5]	X	X	X	X	X	X	X	X	X	
Coagulation function [6]	X							X	X	
Pregnancy test [7]	X									
Thyroid function [8]	X	X	X	X	X	X	X	X	X	
Virological testing (HIV, HBV, HCV and Treponema pallidum specific antibodies) [9]	X									

Phase	Crossover Treatment Cycles with Sintilimab (Every 21 days per 1 cycle) [1]							End of Treatment Visit [13]	Safety Follow-up [13]	Survival Follow-up [14]
	1	2	3	4	5	6	7 and above			
HCV-RNA if HCV antibody positive [9]		X	X	X	X	X	X	X	X	
HBV-DNA if positive for HBsAg and/or HBcAb [9]		X	X	X	X	X	X	X	X	
Blood cardiac enzymes and troponin [10]	X	X	X							
Review Adverse Events [11]	X	X	X	X	X	X	X	X	X	X
Concomitant medications	X	X	X	X	X	X	X	X	X	
Subsequent antineoplastic therapy								X	X	X
Efficacy Measurements										
Tumor Imaging [12]	X			X			X			
Study Drug Administration										
Sintilimab 200mg IV Q3W	X	X	X	X	X	X	X			

Notes:

1. All subjects who enter the crossover treatment phase of sintilimab must have their overall status assessed by the investigator and meet the requirements before continuing to receive sintilimab; Examination after the last dose may be used as a pre-crossover assessment. Subjects must be at least 21 days after completion of the last dose of chemotherapy to be treated with sintilimab, regardless of confirmed disease progression.
2. Vital signs include: temperature, pulse, respiratory rate, and blood pressure.

3. Weight/height will only be measured prior to the first dose.

4. Time point of 12-lead ECG: prior to administration of each cycle of sintilimab, at the End of Treatment visit and at the safety follow-up visit.

5. Hematology includes: RBC, HGB, HCT, WBC, PLT, white blood cell differential [lymphocytes, neutrophils, monocytes, eosinophils, basophils]. Blood biochemistry includes: liver function [TBIL, DBIL, ALT, AST, γ-GT, ALP, ALB, TP, LDH], renal function [UREA or BUN, Cr], blood electrolytes (Na, K, Cl, Mg, Ca, P), amylase, and glucose. Urinalysis includes: PH, specific gravity, UWBC, UPRO, URBC and UGLU. Hematology, blood biochemistry, urinalysis are to be performed within 7 days prior to the first dose, within 3 days prior to the start of each cycle starting from Cycle 2, at the End of Treatment visit and at the safety follow-up visit. Tests will be conducted in each local lab. Subjects with hemoglobin≥90 g/L 3 days prior to the start of the second cycle can receive drug.

6. Coagulation tests include: PT and INR are to be performed within 7 days prior to the first dose of treatment, at the End of Treatment visit and at the safety follow-up visit. Tests will be conducted in each local lab.

7. Women of childbearing potential will have a urine or serum pregnancy test performed within 3 days prior to the first dose. If the result of urine pregnancy test cannot be confirmed as negative, serum pregnancy test will be performed, and the result of serum pregnancy will prevail. Tests will be conducted in each local lab.

8. Thyroid function tests will be performed within 14 days before the first dose, within 3 days before the start of each cycle in Cycle 2, at the end of treatment visit and at the safety follow-up visit. Tests will be conducted in each local lab.

9. Includes HIV, Treponema pallidum specific antibody and HCV antibody tests, and hepatitis B test should be completed within 14 days before the first dose. For HCV antibody-positive subjects, HCV-RNA load may be measured once within 14 days prior to the first dose, within 3 days prior to the start of study drug administration starting from Cycle 2, at the end of treatment visit and safety follow-up visit, or sooner if clinically indicated; it may be unnecessary to wait for the test result to be taken prior to study drug administration during the course of study treatment. For HBsAg and/or HBcAb positive subjects, HBV-DNA load will be measured once within 14 days prior to the first dose, within 3 days prior to the start of study drug administration starting from Cycle 2, at the end of treatment visit and safety follow-up visit, or earlier if clinically indicated; during the course of study treatment, it is not necessary to wait for the test result to be administered first with the study drug. Tests will be conducted in each local lab.

10. The cardiac biomarker and troponin testing shall at least include: creatine kinase (CK), creatine kinase myocardial band (CK-MB), troponin (troponin T or

troponin I). Subsequent examinations will be performed at the discretion of the investigator within 7 days prior to the first dose of study medication and within 3 days prior to the start of each cycle of study medication for Cycles 2 and 3.

11. AEs and laboratory safety evaluations will be assessed according to CTCAE v4.03. For the definition, recording, relevance judgment, severity judgment, reporting time limit and treatment of AEs and SAEs, refer to the description in Section 8 of the protocol.

12. Tumor response evaluations will be based on RECIST v1.1 and iRECIST. Tumor imaging usually includes contrast-enhanced CT or MRI of the brain, chest, abdomen, and pelvis. For subjects without brain metastases prior to the first dose, routine brain imaging is not required thereafter. The same imaging technique should be used for the same subject during the study. The investigator may collect imaging results 28 days prior to the first dose for assessment. Tumor imaging evaluations will be performed every 9 weeks (±7 days) from the time of first dose. Subjects with initial documented radiographic disease progression must undergo imaging evaluation at least 4 weeks after the date of the first tumor imaging indicating progressive disease and no later than 8 weeks to confirm disease progression if clinically stable. For subjects who discontinue treatment for reasons other than radiographic disease progression, imaging evaluations should continue to be performed every 9 weeks (±7 days) as specified in the protocol until any of the following events occur: initiation of new antineoplastic therapy, disease progression, subject withdrawal of ICF, and death, whichever occurs first. Tumor evaluation should be performed at the end of treatment if the end of treatment is more than 4 weeks since the last imaging examination for tumor assessment. The evaluation will be completed after the occurrence of investigator-confirmed PD in RECIST v1.1; the evaluation of iRECIST will start from the first PD visit in RECIST v1.1 until the end of efficacy assessment.

13. End of treatment visit: within 7 days after the end of treatment. Safety follow-up visit: will be performed 30±3 days after the last dose, or before starting a new anti-tumor treatment. If the end of treatment visit and safety follow-up visit are within 7 days, only the end of treatment visit will be performed. If the safety follow-up visit is prior to the end of treatment visit, only the end of treatment visit will be performed. Refer to Section 6.3.4 for details.

14. Survival visit: every 90 days (±7 days) after the safety visit, phone call is acceptable. Refer to Section 6.3.5 for details.

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List of Abbreviations

Abbreviations	Full Name
ADA	Anti drug antibody
ADR	Adverse drug reaction
AE	Adverse event
ALT	Alanine transaminase
ALK	Anaplastic lymphoma kinase
AST	Aspartate aminotransferase
BOR	Best overall response
CI	Confidence interval
CR	Complete Response
Cr	Creatinine
CRF	Case Report Form
CTLA-4	Cytotoxic T Lymphocyte Antigen 4
ct-DNA	Circulating tumor DNA
DCR	Disease control rate
DOR	Duration of response
DLT	Dose-limited toxicity
EC	Ethics Committee
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EGFR	Epidermal growth factor receptor
EMA	European medicines agency
EORTC QLQ	European organization for research and treatment of cancer quality of life questionnaire
FAS	Full Analysis Set
FDA	Food and drug administration
GCP	Good Clinical Practice
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HIV	Human Immunodeficiency Virus
HR	Hazard ratio
ICF	Informed consent form
ir-AE	Immune-related Adverse Event
IRRC	Independent Radiographic Review Committee
iRECIST	Immune Response Evaluation Criteria In Solid Tumors
irRECIST	Immune-related Response Evaluation Criteria In Solid Tumors

Abbreviations	Full Name
ITT	Intention to treat
LCSS	The Lung Cancer Symptom Scale
NAb	Neutralizing antibody
NSAIDS	Nonsteroidal Anti-inflammatory Drugs
NSCLC	Non Small Cell Lung Cancer
ORR	Objective Response Rate
OS	Overall Survival
PD	Progressive Disease
PD-1	Programmed Cell Death 1
PD-L1	Programmed Death-Ligand 1
PFS	Progression-Free Survival
PK	Pharmacokinetic
PPS	Per-Protocol Set
PR	Partial Response
RECIST	Response Evaluation Criteria In Solid Tumors
SAE	Serious Adverse Event
SD	Stable Disease
SS	Safety Analysis Set
TBIL	Total Bilirubin
TEAE	Treatment Emergent Adverse Event
TSH	Thyroid Stimulating Hormone
TTR	Time to Response
ULN	Upper Limit of Normal

1. Study Background

1.1 Disease Background

Cancer has been one of the leading causes of death in the world and has become a major disease that seriously endangers human life and health and restricts social and economic development. Nowadays, the incidence of cancer and the number of deaths are still rising rapidly. In 2012, it was estimated that 14.1 million new cancer cases and 8.2 million new cancer deaths occurred worldwide[1]. China also faces an increasingly serious challenge from cancer. According to the data released by the National Cancer Center in February 2017, there are 4.29 million new cancer cases and 2.81 million cancer deaths in China every year, equivalent to 12,000 cancer cases and 7,500 cancer deaths every day. However, with the further development of the aging population in China, cancer incidence and mortality will continue to rise[2]. Among all cancer deaths, lung cancer (25.2%) is ranked number one, followed by liver cancer (14.4%), gastric cancer (14.3%), and esophageal cancer (9.3%). These four types of cancer have poor prognosis, accounting for 63.2% of all cancer deaths[2].

Non-small cell lung cancer (NSCLC) accounts for approximately 80% to 85% of all lung cancer cases, and approximately 70% of NSCLC subjects are diagnosed with locally advanced or metastatic disease that is ineligible for surgical resection. Moreover, a significant proportion of subjects with early-stage NSCLC who undergo surgery still have a chance of recurrence or distant metastasis, and will progress to death eventually. Approximately 60% of NSCLC in China are non-squamous NSCLC. The treatment modality for subjects with advanced non-squamous NSCLC is based on chemotherapy, and target therapy can be used in a subset of subjects. Epidermal growth factor receptor (EGFR) mutation rate is approximately 40% in Chinese non-squamous NSCLC. EGFR inhibitors (gefitinib, erlotinib or icotinib) are recommended for first-line treatment of advanced NSCLC subjects with sensitizing EGFR mutation. The ALK rearrangement rate in China is about 3%, and the ALK inhibitor crizotinib is recommended as the first-line treatment for advanced NSCLC subjects with ALK rearrangement. The first-line standard treatment for advanced non-squamous NSCLC without sensitive EGFR mutation and ALK rearrangement is platinum-based doublet chemotherapy, with a survival of only 6-9 months after failure of first-line chemotherapy [3] . New drug development for advanced non-squamous NSCLC is an important task that is still a long way off. In recent years, there has been rapid research progress in activating the body's

own immune system by inhibiting immune checkpoints and attacking tumor cells. The use of immune checkpoint inhibitors (such as anti-PD-1/PD-L1 antibody) provides a new clinical approach for the first-line treatment of NSCLC, especially recurrent or metastatic NSCLC.

KEYNOTE-021G was a randomized, open-label, multicenter cohort study of subjects with advanced non-squamous NSCLC who had not received prior chemotherapy and had no EGFR sensitivity mutations/ALK rearrangement. Subjects were randomized to receive pembrolizumab in combination with pemetrexed plus carboplatin or pemetrexed plus carboplatin alone. Subjects in the chemotherapy arm may crossover to receive pembrolizumab monotherapy at the discretion of the investigator after documented disease progression. The primary endpoint of the study was objective response rate assessed by RECIST v1.1 criteria. One hundred and twenty-three subjects participated in the study, in which 60 subjects received pembrolizumab in combination with chemotherapy and 63 subjects received standard first-line chemotherapy with a median follow-up of 10.6 months. The objective response rate of the experimental group was significantly better than that of the control group (55% vs 29%, p = 0.016). The PFS rate of the experimental group was also significantly better than that of the control group (HR = 0.53, p = 0.01). There were 20 subjects in the control group who crossed over to receive pembrolizumab. The incidence of adverse events was similar between the two groups, and subjects were tolerable [4]. KEYNOTE-189, an efficacy validation study for KEYNOTE-021G, enrolled subjects with metastatic non-squamous NSCLC who had not received prior antineoplastic therapy and had no EGFR sensitivity mutation/ALK rearrangement. The study was blinded and the subjects enrolled were randomized at a 2:1 ratio to receive either pembrolizumab plus platinum-based standard chemotherapy (n = 410) or placebo plus platinum-based standard chemotherapy (n = 206). Subjects in the chemotherapy group could crossover to receive pembrolizumab monotherapy after confirmation of disease progression at the discretion of the investigator. The primary endpoint of the study was PFS assessed by IRRC according to RECIST v1.1 and OS. The median follow-up of the study was 10.5 months, and the overall survival rate at 12 months was significantly better in the experimental group than in the control group (69.2% vs 49.4%, HR = 0.49, P<0.001), median PFS was also significantly better in the experimental group than in the control group (8.8 months vs 4.9 months, HR = 0.52, p < 0.001) and safety data was similar between two groups [5] .

Based on the results of the above two clinical studies, anti-PD-1 monoclonal antibody in first-line treatment of advanced non-squamous NSCLC subjects has a positive efficacy and tolerable toxicity. It is worthy to actively conduct relevant studies in advanced non-squamous NSCLC subjects in China as soon as possible to fill the gap in first-line treatment of immune anti-tumor therapy in Chinese subjects.

1.2 Sintilimab

1.2.1 Mechanism of Action

Immune checkpoint therapy is a research and development hotspot in recent years, and continues to make great breakthroughs. Unlike cytotoxic drugs, monoclonal antibodies or small molecule tyrosine kinase inhibitors that target tumor driver genes, immune checkpoint therapy does not act directly on tumor cells, but improves the function of T cells by blocking the inhibitory signals of T cell proliferation and activation, relieves the tolerance of the immune system to tumor cells, and improves the effective recognition and killing of tumor cells by T cells. Immune checkpoint targets that have shown significant clinical efficacy include cytotoxic T lymphocyte-associated antigen-4 (CTLA-4) and programmed cell death receptor 1/ligand 1 (PD-1/PD-L1) [6].

Currently, FDA has approved 5 anti-PD-1/PD-L1 monoclonal antibody, including anti-PD-1 monoclonal antibody nivolumab (trade name: Opdivo) from Bristol-Myers Squibb Company (BMS), anti-PD-1 monoclonal antibody pembrolizumab (trade name: Keytruda) from Merck & Co Inc, and anti-PD-L1 monoclonal antibody atezolizumab (trade name: Tecentriq) from Roche, anti-PD-L1 monoclonal antibody avelumab (trade name: Bavravio) from Pfizer/ Merck KGaA, and anti-PD-L1 monoclonal antibody durvalizumab (trade name: Imfinzi) from AstraZeneca. The approved indications include advanced melanoma, advanced NSCLC, advanced classic Hodgkin's lymphoma, advanced tumour of head and neck, advanced renal cell carcinoma and others [6]. In addition, many promising indications are currently in phase III clinical studies or in the application phase. The approval of the above drugs has confirmed the important position of anti-PD-1/PD-L1 antibody drugs in cancer immunotherapy. At present, there is no anti-PD-1/PD-L1 antibody drug approved in China. It is of great significance to actively develop such inhibitors to provide better treatment options for Chinese subjects with advanced cancer.

Sintilimab (R&D Code: IBI308) is a recombinant fully human IgG_4 anti-PD-1 monoclonal antibody. Many preclinical trials in vitro have demonstrated the ability of sintilimab to block the PD-1 pathway. The results of various completed preclinical pharmacodynamics, animal pharmacokinetics and toxicology studies show that sintilimab has the characteristics of a definite target, reliable cell strain source and good drug stability, and sintilimab has showed good activity in various completed preclinical studies. For the detailed study results, please refer to the Investigator's Brochure.

1.2.2 Clinical Study Results

In September 2016, a phase Ia dose escalation study of sintilimab (study code CIBI308A101-1a) was initiated. Phase 1a study enrolled subjects with advanced solid tumors who had failed standard therapies. Dose escalation followed the classical "3+3" design and four dose levels (1 mg/kg, 3 mg/kg, 200 mg and 10 mg/kg) were evaluated. After completion of the 1 mg/kg dose group, subjects were randomized 1:1 to undergo evaluation independently at two dose groups, 3 mg/kg and 200 mg dose levels. The dose-limiting toxicity (DLT) observation period was 28 days after the first dose in each dose group, and subjects who completed the DLT observation period were allowed to enter subsequent treatment with sintilimab every two weeks (1 mg/kg, 3 mg/kg and 10 mg/kg) or every three weeks (200 mg) until disease progression, intolerable toxicity, withdrawal of consent or occurrence of other reasons for discontinuation of study treatment, whichever occurred first.

Pharmacokinetic study in subjects with stage Ia advanced solid tumors showed that the plasma concentration of sintilimab injection increased gradually from the start of infusion, reached C_{max} after discontinuation, and then decreased slowly. In vivo exposure to sintilimab increased proportionally with increasing dose within the dose range of 1 to 10 mg/kg, suggesting linear kinetics. Elimination half-life of sintilimab in subjects with solid tumors following a single dose (Geo. Mean [CV%]) was 14.4 [28.9%] days, clearance was 11.5 [42.5%] mL/h, volume of distribution at steady state was 5.43 [34.4%] L, and apparent volume of distribution was 5.77 [33.2%] L. PK profiles were similar to those of similar approved anti-PD-1 antibodies (nivolumab, pembrolizumab).

In a pharmacodynamic study in subjects with stage Ia advanced solid tumors, a single 1 mg/kg (N = 3) dose of sintilimab resulted in rapid (24-hour) occupancy (mean ≥ 95%) of PD-1 on the surface of CD3+ cells in peripheral blood of subjects. The occupancy

maintained when the drug concentration decreased in the study (28 days) and in the following consecutive dose. The PD-1 occupancy results in the 3 mg/kg (N = 3), 200 mg (N = 3) and 10 mg/kg (N = 3) dose groups were similar to those in the 1 mg/kg group, suggesting that the PD-1 receptor occupancy level was not dose- or concentration-dependent within the dose range of 1-10 mg/kg. It has also demonstrated promising antitumor activity in subjects with a variety of advanced solid tumors whose standard therapies have failed. The best overall response was PR in 2 subjects and SD in 2 subjects per RECISTv1.1. Two subjects had irPR and three subjects had irSD per irRECIST. One additional subject of hepatocellular carcinoma who had failed sorafenib before enrollment was assessed PD in this study and still continued with sintilimab monotherapy. The subject's tumor burden decreased from PD and was assessed irSD per irRECIST after 3 cycles of post-PD treatment. As of October 30, 2017, this subject was still receiving treatment with sintilimab. Subjects who receive immunotherapy may experience tumor pseudoprogression, which is significantly different from the efficacy profile of conventional chemotherapy. An increase in tumor burden followed by a decrease was observed in 1 of 12 subjects treated with sintilimab. Response criteria for immune solid tumors have been cited in the following sintilimab clinical studies to explore trends in tumor pseudoprogression. As of October 30, 2017, a total of 3 subjects died (due to disease progression) in this phase 1a study.

1.2.3 Phase Ib Preliminary Clinical Efficacy of Sintilimab in First-Line Treatment of Non-Squamous NSCLC

The phase 1b study was a multicenter clinical study in Chinese subjects with advanced solid tumors, in which Cohort D enrolled subjects with advanced, recurrent or metastatic non-squamous NSCLC who had not previously received systemic anti-tumor therapy. Subjects were treated with sintilimab combined with pemetrexed and cisplatin. This cohort was to evaluate safety, tolerability and preliminary efficacy of sintilimab combined with chemotherapy. As of March 30, 2018, 21 subjects were enrolled and treated with the study drug (the maximum cycles of treatment was 13), and 19 of them had at least 1 imaging evaluation. Best overall response (BOR) results, assessed per RECIST v1.1, were 1 complete response (CR), 9 partial response (PR), 6 stable disease (SD), and 3 progressive disease (PD). The objective response rate was 52.6%.

1.3 Risk/Benefit Assessment

Based on the mechanism of drug action and the clinical safety information available for sintilimab, the expected possible adverse events during the clinical study of sintilimab are mainly various immune inflammations caused by the activation of immune system, such as pneumonia, thyroiditis, hepatitis, dermatitis/skin lesions, etc. According to the available clinical data of anti-PD-1 monoclonal antibody drugs, although the incidence of adverse events is high, it can be well tolerated. Only a small proportion of subjects will discontinue the drug due to adverse events, and most adverse events can be solved after related treatment. Due to the variability of early symptoms in immune-related adverse events, investigators should pay special attention to the early symptoms and signs of various immune-related reactions during clinical studies. They should make timely and correct judgment, make dose adjustment and give corresponding effective treatment according to Section 5.2.2 of the protocol, so as to reduce the risk of drug use for subjects. In addition, attention should be paid to exclude subjects with autoimmune diseases in clinical studies to avoid aggravation of the original diseases caused by immune system activation.

Pemetrexed combined with platinum is the current standard chemotherapy regimen for the first-line treatment of advanced non-squamous NSCLC subjects. This study is to evaluate the efficacy and safety of the chemotherapy combined with or without sintilimab in the first-line treatment of advanced non-squamous NSCLC subjects. This study will therefore provide subjects with standard effective first-line chemotherapy to ensure clinical benefit for subjects. The phase I clinical data of sintilimab showed that sintilimab has definite pharmacological activity and good tolerability in subjects with advanced tumors, and demonstrated preliminary anti-tumor activity in treatment-naïve subjects with advanced non-squamous NSCLC. We intend to conduct a large-scale multicenter, randomized, phase III controlled study in subjects with advanced, recurrent or metastatic non-squamous NSCLC who have not previously received systemic anti-tumor therapy. The purpose of this clinical study is to evaluate the efficacy and safety of sintilimab combined with standard chemotherapy regimen in this population and provide data basis for approving in relevant indication.

2. Study Objectives

2.1 Primary Objectives

Progression-free survival (PFS) per RECIST v1.1 in the first-line treatment of advanced or recurrent non-squamous NSCLC treated with sintilimab in combination with pemetrexed and platinum-based chemotherapy versus placebo in combination with pemetrexed and platinum-based chemotherapy.

2.2 Secondary Objectives

- To compare the overall survival (OS) between the two treatment arms;
- To compare the objective response rate (ORR) per RECIST v1.1 between the two treatment arms;
- To compare the disease control rate (DCR) per RECIST v1.1 between the two treatment arms;
- To compare the time to objective response (TTR) per RECIST v1.1 between the two treatment arms;
- To compare the duration of response (DOR) per RECIST v1.1 between the two treatment arms;
- To evaluate the safety and tolerability of sintilimab in combination with pemetrexed and platinum-based chemotherapy.

2.3 Exploratory Objectives

- To evaluate the efficacy of sintilimab in subjects per the immune Response Evaluation Criteria in Solid Tumors (iRECIST);
- To explore the population pharmacokinetic characteristics of sintilimab;
- To explore the biomarkers that can potentially predict the efficacy of sintilimab arm including, but not limited to, PD-L1 expression, and RNA in tumor specimens, circulating tumor DNA (ctDNA) and T cell receptor (TCR) in peripheral blood;
- To compare the quality of life of subjects treated with sintilimab combined with chemotherapy and placebo combined 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);
- To compare PFS in the sintilimab arm receiving subsequent antineoplastic

therapy after disease progression versus placebo arm crossing over to receive sintilimab.

3. Study Design

3.1 Overall Design

This study is a randomized, double-blind, multicenter, phase III study of sintilimab in combination with pemetrexed and platinum chemotherapy or placebo in combination with pemetrexed and platinum chemotherapy in the first-line treatment of subjects with advanced or recurrent non-squamous NSCLC in China.

In this study, subjects will receive 4 cycles of sintilimab or placebo in combination with pemetrexed, cisplatin or carboplatin, followed by maintenance therapy with sintilimab or placebo in combination with pemetrexed. The maximum treatment duration of sintilimab is 24 months. In the study, approximately 378 subjects with advanced or recurrent non-squamous NSCLC who have not previously received systemic therapy will be randomized at a 2:1 ratio to the experimental sintilimab group and the control placebo group, with 252 subjects in the sintilimab group and 126 subjects in the placebo group. The actual number of subjects enrolled may differ from the planned number due to unforeseen reasons, such as faster enrollment speed than expected. The final screening end date will be estimated before the enrollment of 378 subjects and best effort will be made to ensure that the total number of subjects enrolled do not exceed 110% of the planned number, i.e., 414 subjects, of which 276 subjects are expected in the experimental group and 138 subjects are expected in the control group.

The primary efficacy endpoint of the study is PFS per RECIST v1.1 assessed by independent radiographic review committee (IRRC) of sintilimab in combination with pemetrexed and platinum chemotherapy versus placebo in combination with pemetrexed and platinum chemotherapy as the first-line treatment of advanced or recurrent non-squamous NSCLC. Tumor imaging evaluation will be performed at Week 6 (±7 days) and Week 12 (±7 days), and then every 9 weeks (±7 days); after Week 48, tumor imaging evaluation will be performed every 12 weeks (±7 days). Treatment decisions will be made by the investigators based on tumor imaging evalution until the first objective imaging evidence of progressive disease (PD).

After the first evidence of radiographic PD per RECIST v1.1, the investigator should repeat imaging at least 4 weeks later if subject is clinically stable, and if PD is still confirmed, the subject may be unblinded after communicating with the Sponsor. After unblinding, subjects in the experimental group will discontinue study drug treatment, while subjects in the control group can crossover to receive sintilimab monotherapy at the discretion of the investigator until disease progression, intolerable toxicity, withdrawal of consent, death, or other protocol-specified circumstances, whichever occurred first. If clinical instability (refer to Section 7.1.3) coexists at the time of the first PD, radiographic confirmation after 4 weeks is not required. The subject may be unblinded and all study treatment will be discontinued after communicating with the Sponsor.

Subjects should continue to receive treatment during the study until confirmed PD per RECIST v1.1, occurrence of unacceptable adverse events (AEs), presence of concurrent medical conditions that prevent continuation of treatment, decision by the investigator to discontinue treatment, withdrawal of consent by the subject, pregnancy of the subject, non-compliance with study treatment or procedure requirements, administrative reasons, or up to 24 months of treatment with sintilimab. Subjects who discontinue study treatment for reasons other than PD will still need to undergo imaging assessments at protocol-specified imaging time points to monitor disease status until any of the following occur: initiation of new antineoplastic therapy, disease progression, death, or end of study.

Investigators will monitor possible adverse events throughout the study and grade the severity of adverse events according to the guidelines of the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 4.03.

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

The overall flow chart is as follows:

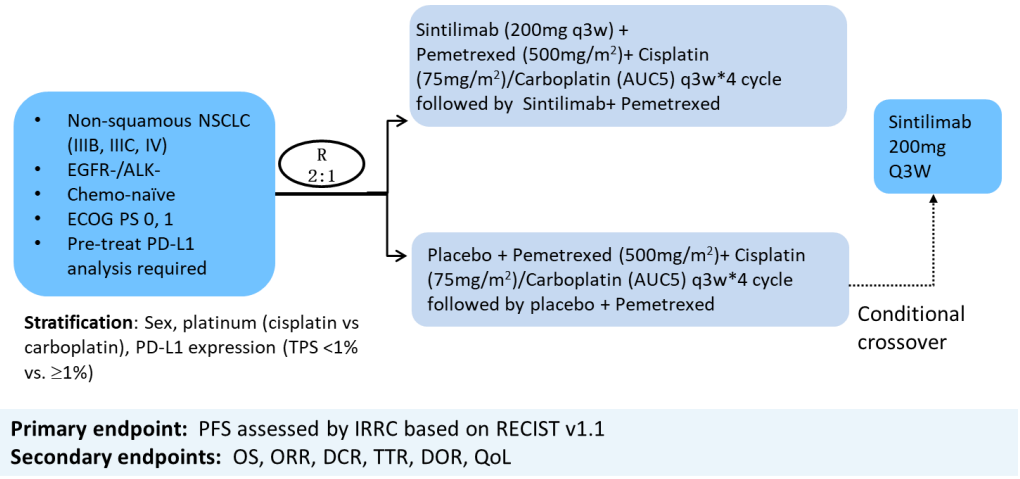

Figure 1. Overall flow chart

Note: The actual number of subjects enrolled may differ from the planned number due to unforeseen reasons, such as faster enrollment speed than expected. The final screening end date will be estimated before the enrollment of 378 subjects and best effort will be made to ensure that the total number of subjects enrolled will not exceed 110% of the planned number, i.e., 414 subjects, of which 276 subjects are expected in the experimental group and 138 subjects are expected in the control group.

3.1.1 Trial Blinding

The same packaging will be used for both sintilimab and placebo in order to maintain blinding. The assignment will be unknown to the subjects, the investigators, Sponsor's staff and Sponsor's designees who are involved in the subject's treatment or clinical evaluation.

Refer to Section 6.4.3 for instructions on how to unblind subjects during the study, if required.

3.1.2 Estimation of Sample Size

It is assumed that the median progression free survival time of subjects receiving sintilimab treatment will be improved from 6 months to 9.2 months (with a hazard ratio = 0.65). With an enrollment time projection of 15 months, a projected follow-up time of 8 months and an estimated dropout rate of 0.5% per month, to provide approximate 90% power under a two-sided $\alpha = 0.05$, a total of 378 subjects need to be randomized to obtain the required 263 PFS events in this study. The actual number of subjects enrolled may differ from the planned number due to unforeseen reasons, such as faster enrollment speed than expected. The final screening end date will be estimated before

the enrollment of 378 subjects and best effort will be made to ensure that the total number of subjects enrolled will not exceed 110% of the planned number, i.e., 414 subjects, of which 276 subjects are expected in the experimental group and 138 subjects are expected in the control group.

There is one interim analysis planned in this study when 70% of total PFS events (184 events) occur, and the primary interim analysis will be based on PFS.

3.1.3 Randomization

Subjects will be randomized at a 2:1 ratio to receive either sintilimab plus chemotherapy or placebo plus chemotherapy. Centralized stratified block randomization will be used regardless of research center effect. Subjects who complete all screening assessments and satisfies the enrollment criteria will be assigned a randomization number generated by IWRS sequentially according to each subject's randomization time. The randomization number will correspond the subject to the associated treatment group assigned (sintilimab or placebo). The corresponding investigational drug will then be dispensed. If a randomized subject withdraw from the study after randomization for any reasons, that randomization number will not be used again. The personnel in charge of the IWRS will only prepare the randomization list and will not involve in any direct study operation.

In this study, central randomization system will set the limit on the percentage of subjects with PD-L1 expression <1% to no more than 33% of the total randomized subjects, i.e. not less than 67% subjects with PD-L1 expression ≥1% of the total randomized subjects .

3.1.4 Stratification

Subjects in this study will be randomized according to the following stratification factors:

- Gender (male vs female)
- Platinum chemotherapy (carboplatin vs cisplatin)
- PD-L1 expression level (< 1% or unevaluable vs ≥1%)

3.2 Design Rationale

3.2.1 Rationale for Selecting Randomized Double-Blind Study Design

This study plans to use a randomized double-blind design. On one hand, bias can be reduced by blinding to make the study results more reliable; on the other hand, the 2:1 randomized distribution of the experimental group and the control group can improve the compliance of the subjects.

3.2.2 Rationale for Selection of Dose Regimen and Dose of Sintilimab

According to current Chinese and international guidelines, platinum-based doublet chemotherapy remains the standard first-line treatment for advanced non-squamous NSCLC without sensitive EGFR mutation/ALK rearrangement [7]. Based on KEYNOTE-021G study results, FDA acceleratedly approved pembrolizumab in combination with pemetrexed and carboplatin for first-line treatment of metastatic non-squamous NSCLC in May 2017. Sintilimab is an anti-PD-1 monoclonal antibody and has demonstrated antitumor activity as a single agent in several immune-competent mouse models (see Investigator's Brochure). In the phase I clinical study of sintilimab (CIBI308A101), pharmacodynamic results showed that sintilimab had a definite PD-1 receptor blocking effect in vivo. The efficacy of sintilimab in combination with pemetrexed and cisplatin was satisfactory in the first-line population with previously untreated advanced non-squamous NSCLC in phase 1b cohort D study. Therefore, this study will evaluate the efficacy and safety of sintilimab in combination with first-line chemotherapy in subjects with locally advanced, metastatic or recurrent non-squamous NSCLC.

In this study, sintilimab 200 mg Q3W will be used. The choice of dosing regimen is primarily based on the safety data and exposure (concentration) -response (PD-1 receptor occupancy) relationship data from previous studies, along with preclinical in vitro/in vivo efficacy data and comparable data from similar drugs.

3.2.3 Rationale for Selection of PFS as the Primary Study Endpoint

PFS is a widely accepted measurement of clinical superiority for a completely new antineoplastic therapy in randomized phase III clinical studies and is able to demonstrate a satisfactory risk-benefit profile for the new therapy. It has also been identified by the FDA and EMA as one of the most important registration endpoints in NSCLC clinical studies in recent years. PFS may be evaluated by an independent central image review according to RECIST v 1.1 to minimize bias. Therefore, PFS is proposed as the primary

study endpoint in this study.

3.2.4 Rationale for Crossover to Sintilimab Monotherapy After Progression in the Control Arm

Anti-PD-1 mAb has been shown to be effective in NSCLC subjects who have failed first-line platinum-based chemotherapy in several studies. It has also been demonstrated in CIBI308A101-1b Cohort C that the continuation of sintilimab monotherapy in subjects with non-squamous NSCLC after failure of first-line platinum-based chemotherapy is beneficial and well tolerated (results not formally published). Therefore, subjects in the control arm of the study are allowed to crossover to continue treatment with sintilimab monotherapy at the discretion of the investigator and subjects after PD is confirmed.

3.2.5 Rationale for the Use of iRECIST to Assess Exploratory Efficacy Endpoints

Available clinical data suggests that a proportion of subjects receiving PD-1 inhibitors may experience "disease progression" (as assessed by RECIST v1.1) before experiencing an objective response and/or stable disease. In this special situation, continued treatment still has the potential for clinical benefit. The mechanism of this phenomenon may be due to the increased severity of inflammation in the tumor, which leads to the increase of tumor mass and even the appearance of new lesions. In addition, anti-tumor immune response may take some time to occur. The so-called "pseudoprogression" rate is found to be slightly less than 10% in melanoma subjects by irRECIST or iRECIST criteria, while a pseudoprogression rate of around 5% has been reported in non-small cell lung cancer [8-9]. Therefore, iRECIST will also be used to assess exploratory efficacy endpoints in this study, allowing subjects to continue treatment with study drug if the subjects are clinically stable after initial disease progression as defined by RECIST v1.1. What's more, these subjects can receive confirmed image assessment after 4 weeks (see Section 7.1.5 for details).

3.3 Independent Data Monitoring Committee

An independent data monitoring committee (IDMC) will be set up in this study to conduct an interim analysis of the efficacy endpoints and safety of the study. The composition, responsibilities and procedures of the IDMC are described in the IDMC charter.

4. Study Population

4.1 Inclusion criteria

Subjects must meet the following criteria for participation in this study:

1) Has signed written informed consent before any study-related procedure;
2) Is ≥ 18 and ≤ 75 years old;
3) Has a life expectancy of at least 3 months;
4) Has at least one measurable lesion based on RECIST v1.1 assessed by the investigator;

   Measurable lesions situated in a previously irradiated area or locally treated area can be selected as target lesions if progression has been demonstrated in such lesions;
5) Has a histologically or cytologically confirmed diagnosis of locally advanced (stage III B/III C), metastatic, or recurrent (stage IV) non-squamous NSCLC according to the 8th edition of the TNM classification in the International Association for the Study of Lung Cancer and the American Joint Committee on Cancer. Meanwhile, subjects with stage IIIB/IIIC non-squamous NSCLC should not be eligible for radical surgery or radical radiochemotherapy;
6) Ineligible for EGFR or ALK-target therapy (documented evidence of absence of sensitizing EGFR mutations and ALK gene rearrangements is required);
7) Eastern Cooperative Oncology Group performance status (ECOG PS) of 0 or 1;
8) Has not received prior systemic antineoplastic therapy for advanced/recurrent non-squamous NSCLC;

   Subjects who have received prior adjuvant chemotherapy are eligible if the adjuvant chemotherapy is completed at least 6 months prior to the recurrence of disease;
9) Has adequate hematopoietic function as defined by an absolute neutrophil count≥ 1.5×10^9 /L, platelet count≥100×10^9 /L, hemoglobin≥90 g/L [without transfusion in 7 days and without dependence on erythropoietin (EPO)];
10) Has adequate hepatic function, defined as a total bilirubin level≤1.5 ×upper limit of normal (ULN); aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels ≤2.5 ×ULN in subjects without liver metastases, AST and ALT levels ≤5 × ULN in subjects with documented liver metastases;
11) Has adequate renal function, defined as serum creatinine (Cr) ≤ 1.5 × ULN or calculated creatinine clearance ≥ 60ml/min (Cockcroft-Gault formula);

    Urine protein < 2 +, or 24-hour urine protein < 1g;

12) Has adequate coagulation function, defined as international normalized ratio (INR) or prothrombin time (PT) ⩽ 1.5 × ULN; if the subject is receiving anticoagulant therapy, as long as the PT is within the proposed range for the anticoagulant, the subject is eligible;
13) Female subjects of childbearing potential should have a negative urine or serum pregnancy test within 3 days prior to receiving the first dose of study drug (Cycle 1, Day 1). If the urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required;
14) If there is a risk of conception, male and female subjects must use highly effective contraception (i.e., a method with a failure rate of less than 1% per year) for at least 180 days after end of treatment.

4.2 Exclusion Criteria

Subjects should be excluded from participating in the study if the subject:

1) Has predominantly squamous cell histology NSCLC;
   Mixed cell types must be primarily (≥90%) adenocarcinoma cells; if small cell elements are present, the subject cannot be enrolled;
2) Is currently participating in an interventional clinical study or received other investigational drugs or used an investigational device within 4 weeks prior to the first dose of drug treatment;
3) Has previously received the following therapies: anti-PD-1, anti-PD-L1, or anti-PD-L2 agents or agents directed at another stimulatory or co-inhibitory T-cell receptor (e.g., CTLA-4, OX-40, CD137);
4) Has received Chinese medicines with anti-lung cancer indications or immunomodulatory drugs (including thymosin, interferon, interleukin, except for local use to control pleural effusion) within 2 weeks prior to first dose of drug treatment, or has undergone major surgery within 3 weeks prior to first dose of drug treatment;
5) Has received radiotherapy in lung with a dose > 30 Gy within 6 months prior to the first dose of study treatment;
6) Has completed palliative radiotherapy within 7 days prior to the first dose of study treatment;

7) Has clinically active diverticulitis, intra-abdominal abscess, gastrointestinal obstruction;
8) Has received solid organ or blood system transplantation;
9) Has clinically uncontrollable pleural effusion or ascites (subjects who doesn't need drainage of effusion or has no significant increase in effusion within 3 days after stopping drainage can be enrolled);
10) Has a known severe allergic reaction (≥grade 3) to any component of sintilimab, pemetrexed, cisplatin, or carboplatin or to any excipients;
11) Has active autoimmune disease that has required systemic therapy (e.g., use of disease modifying agents, corticosteroids, or immunosuppressive drugs) within 2 years prior to the first dose of study treatment. Replacement therapy (e.g., thyroxine, insulin, or physiologic corticosteroids replacement therapy for adrenal or pituitary insufficiency) is not considered a form of systemic therapy;
12) Diagnosed with immunodeficiency or receiving systemic glucocorticoid therapy or any other form of immunosuppressive therapy within 7 days prior to the first dose of study treatment;

    Physiological doses of glucocorticoids (≤10 mg/day of prednisone or equivalent glucocorticoid) is allowed;
13) Has not adequately recovered from toxicity and/or complications caused by any intervention prior to starting study treatment (i.e. ≤Grade 1 or to baseline, excluding asthenia or alopecia);
14) Has other malignancies diagnosed within 5 years prior to the first dose of study treatment, with the exception of radically treated basal cell carcinoma of the skin, squamous cell carcinoma of the skin, and/or radically resected carcinoma in situ;
15) Has symptomatic central nervous metastases. Subjects with asymptomatic metastases or stable metastases after treatment may participate in the study as long as all of the following criteria are met: measurable lesion outside the central nervous system; no meningeal, midbrain, pontine, medullary, or spinal metastases; clinically stable for at least 2 weeks; and discontinuation of hormonal therapy 14 days prior to the first dose of study treatment;
16) Has a known history of non-infectious pneumonitis requiring corticosteroid therapy within 1 year prior to the first dose of study treatment or has current interstitial lung disease;
17) Has active infection requiring systemic therapy;

18) Is unable or unwilling to take folic acid or vitamin B_{12} supplementation;
19) Has psychiatric or substance abuse disorder that would interfere with compliance with the requirements of the study;
20) Has a known history of Human Immunodeficiency Virus (HIV) infection (i.e., HIV 1/2 antibodies positive), known active syphilis infection, active pulmonary tuberculosis;
21) Has known untreated active hepatitis B;

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

    HBV viral load must be < 1000 copies/ml (200 IU/ml) or below the lower limit of detection before the first dose of study treatment. Subjects with active hepatitis B should receive anti-HBV therapy to avoid viral reactivation throughout the study treatment;

    For subjects with anti-HBc (+), HBsAg (-), anti-HBs (-) and HBV viral load (-), prophylactic anti-HBV treatment is not required, but viral reactivation should be closely monitored;
22) Has active HCV infection (HCV antibody positive and HCV-RNA level above the lower limit of detection);
23) Has received a live vaccine within 30 days prior to the first dose (Cycle 1, Day 1);

    Note: Inactivated viral vaccines for seasonal influenza within 30 days prior to the first dose of study treatment are allowed; live attenuated influenza vaccines administered intranasally are not allowed;
24) Has uncontrolled concurrent medical conditions, such as:
    a) Esophageal or gastric varices requiring immediate intervention (e.g., band ligation or sclerotherapy) or with a high risk of bleeding, in the opinion of the investigator or in consultation with a gastroenterologist or hepatologist. Subjects who have portal hypertension (including splenomegaly with the evidence of imaging evaluations) or has a history of variceal bleeding should receive endoscopic examination within 3 months prior to enrollment to evaluate whether the subjects are eligible;
    b) Hepatic encephalopathy, hepatorenal syndrome, or Child-Pugh B or worse cirrhosis;
    c) Significant malnutrition (e.g. need intravenous nutrition supplements). Subjects with malnutrition remedied more than 4 weeks prior to the first dose of study treatment are eligible;

d) The tumor compresses the surrounding vital organs (such as esophagus) accompanied with relevant symptoms, or compresses the superior vena cava or invades the major mediastinal blood vessels, heart, etc.;
e) Class II-IV congestive heart failure (New York Heart Association classification), poorly controlled and clinically significant arrhythmia;
f) Uncontrolled arterial hypertension even after receiving standard treatment (systolic blood pressure≥160 mmHg or diastolic blood pressure≥100 mmHg);
g) Any arterial thrombosis, embolism, or ischemia such as myocardial infarction, unstable angina, cerebrovascular accident, or transient ischemic attack within 6 months prior to enrollment. With a history of deep vein thrombosis, pulmonary embolism, or any other serious thromboembolism within 3 months prior to enrollment (thrombosis caused by implantable venous port or catheter, or superficial venous thrombosis is not considered "serious" thromboembolism);

25) Has a history or current evidence of any disease, treatment, or laboratory abnormality that may interfere with the results of the study, prevent the subject from fully participating in the study, or other condition that the subject is ineligible for enrollment, in the opinion of the investigator;
26) Is breast-feeding.

4.3 Restrictions During the Study

4.3.1 Use in Pregnancy

Human IgG_1 and IgG_4 are known to be able to cross the placental barrier, so the study drug is not recommended during pregnancy. Women who are pregnant cannot be enrolled in this study.

4.3.2 Contraception

A female subject of childbearing potential who is sexually active with a non-sterilized male partner, and a non-sterilized male subject who is sexually active with a female partner of childbearing potential must use at least one of the acceptable methods of effective contraception listed in Table 3. Effective method of contraception (must use at least 1 method) from the start of the screening period to 180 days after receiving the last dose. Subject should discuss with a responsible physician regarding the discontinuation of contraception after the above time point. Periodic abstinence, safe period contraception, and withdrawal are not acceptable methods of contraception.

Women of childbearing potential are defined as those who have experienced menarche, have not undergone sterilization (bilateral tubal ligation, bilateral salpingectomy, or total hysterectomy), and are not postmenopausal.

Table 3. Effective method of contraception (must use at least 1 method)

Barrier method	Intrauterine device method	Hormonal method
Male condom with spermicide	T-ring with copper	Implant
Diaphragm with spermicide	Progesterone containing T-ring [a]	Contraceptive injections or injections
Diaphragm with spermicide	Levonorgestrel-releasing intrauterine device system (e.g. Mirena ®) [a]	Combined contraceptive pill Low dose oral contraceptive pill Contraceptive patch

[a] This is also seen as a hormonal approach

Menopause is defined as no menses without an alternative medical cause for at least 12 months. Requirements based on age are as follows:

- Female ≥50 years old who have at least 12 months of amenorrhea after stopping hormone replacement therapy and whose luteinizing hormone and follicle stimulating hormone levels are within the postmenopausal range are considered menopausal;
- Female <50 years old who have at least 12 months of amenorrhea after stopping hormone replacement therapy, had radiation-induced oophorectomy with last menses > 1 year ago, had chemotherapy-induced amenorrhea with last menses > 1 year ago, or had undergone surgical sterilization (bilateral oophorectomy or hysterectomy) are considered menopausal.

4.3.3 Use in Nursing Women

It is unknown whether sintilimab is excreted in breast milk. Since many drugs are excreted in breast milk, sintilimab may potentially be toxic in infants. Breastfeeding lactating women cannot be enrolled in this study.

4.4 Criteria forDiscontinuation/Withdrawal and Withdrawal of Informed Consent

4.4.1 Discontinuation/Withdrawal

Since some clinical data may be important for the study after treatment

discontinuation/withdrawal, these data and information should be collected until the subject's last scheduled visit, even if the subject has discontinued/withdrawn from treatment.

Subjects may discontinue treatment at any time for any reason at the discretion of subjects' personal or discontinue treatment at the discretion of the investigator should any adverse event occur. In addition, the investigator or Sponsor may discontinue treatment of a subject if the subject is unsuitable for treatment, violates the protocol, or for administrative and/or other safety reasons.

Subjects should discontinue treatment but continue to be followed for any of the following reasons:

- The subject or the subject's legally authorized representative requests treatment discontinuation.
- Occurrence of protocol-specified adverse events requiring discontinuation of treatment (refer to Section 5.2).
- Development of another malignancy that requires active treatment.
- Concurrent illness that precludes further study treatment.
- The investigator decide to withdraw the subject from the treatment.
- Positive serum pregnancy test.
- Poor subject compliance.
- The clinical status or personal circumstances of the subject that, in the opinion of the investigator and/or Sponsor, would put the subject at unnecessary risk if the study drug is to be continued.
- Completed 24 months of treatment with sintilimab.

For subjects who discontinue treatment but continue to be followed in the study, all visits and procedures listed in the Study Flow Chart (Table 1, Table 2Table 2. Flow Chart of Crossover Phase to Sintilimab) should be completed.

4.4.2 Withdrawal of Informed Consent

If a subject or the subject's legally authorized representative withdraws consent of participating in the study, the subject will no longer be treated or followed at the scheduled protocol visit.

4.4.3 Clinical Criteria for Early Study Termination

The study may be terminated early if the following criteria are met:

- Inaccurate or incomplete quality and quantity of data records
- Poor compliance with the protocol and regulatory requirements
- The incidence or severity of adverse drug events in this or other studies suggests a possible hazard to the subject's health
- A change or discontinuation of study drug development is planned.

If the Sponsor decides that the study drug is no longer provided, sufficient notice will be given to appropriately adjust the subject's treatment.

5. Study Treatment

The investigational drugs of this study are defined as sintilimab or placebo and chemotherapy (pemetrexed, carboplatin/cisplatin).

The first dose of study treatment should be started on the day of randomization (Cycle 1, Day 1), and no later than 48 hours after randomization. The Sponsor should be notified if the first dose is not administered within 48 hours. Every effort should be made to conduct the study treatment on the day of randomization. For the rest of the treatment cycles, at the discretion of the investigator, the study treatment can be administered 3 days before or after the scheduled day of administration for administrative reasons.

After completion of all pre-dose procedures and evaluations detailedly listed in the study flow chart, study treatment will be started on Day 1 of each cycle.

Table 4. Study Treatment

Drug	Dose/Potency	Dose Frequency	Route of Administration	Regimen/Treatment Period	Use
Sintilimab [1]	200 mg	Q3W	Intravenous infusion	Cycle every 21 days, dosing on Day 1	Experimental group
Placebo [1]	2 vials	Q3W	Intravenous infusion	Cycle every 21 days, dosing on Day 1	Control group
Pemetrexed[2]	500 mg/m^2	Q3W	Intravenous infusion	Cycle every 21 days, dosing on Day 1	Experimental/ Control group
Cisplatin	75 mg/m^2	Q3W	Intravenous infusion	Cycle every 21 days, dosing on	Experimental/ Control group

Carboplatin	AUC5	Q3W	Intravenous infusion	Day 1, 4 cycles of continuous use Cycle every 21 days, dosing on Day 1, 4 cycles of continuous use	Experimental/ Control group

1. Sintilimab/placebo should be infused prior to the administration of chemotherapy.
2. If a subject's body weight fluctuated less than 10% from baseline (the day of the first dose of study treatment), the baseline body weight will be used to calculate the amount of chemotherapy administered. Otherwise, the actual dose will be calculated based on the body weight on the scheduled day of dosing or the day before it. The actual dose can also be calculated based on the body weight on the day of dosing or the day before it according to clinical practice regardless of the baseline weight. The protocol allows a ±5% deviation from the calculated total infusion dose for dosing convenience.

All the drugs in Table 4 will be supplied by the Sponsor in a unified manner, and all the commercially purchased drugs should be provided with the product/batch number. The local sites are responsible for recording the batch number, manufacturer and expiration date.

5.1 Use of Study Drug

5.1.1 Use of Sintilimab

The main active ingredient of sintilimab is a recombinant fully human anti-programmed death receptor-1 (PD-1) monoclonal antibody at a concentration of 10 mg/mL. This product is a clear, colorless liquid, free from foreign matter, floccules and precipitates. The excipients include 5.88 mg/ml sodium citrate (dihydrate), 30.06 mg/ml mannitol, 3.73 mg/ml histidine, 2.92 mg/ml sodium chloride, 0.0075 mg/ml edetate disodium, 0.2 mg/ml polysorbate 80, and citric acid (monohydrate) to adjust pH to 6.0.

The smallest packaging unit of sintilimab is one box, with each box containing 2 vials of sintilimab injection. The package is printed with the drug name, dosage form, strength, drug code, batch number, shelf life, storage condition and information of the Sponsor. The same information is printed on the label of the vial and the box, but there is no information on dosage form, precautions, dosage and administration on the label of the vial. All boxes and vials are labeled with "For Clinical Study Use Only". Sintilimab should be stored at 2-8℃, protected from light, with a shelf life of 24 months. If any

quality problems such as turbidity and precipitation occur in the injection, it should be sealed up immediately and the Sponsor should be informed immediately.

The preparation and administration of sintilimab is as follows:

1. Fully extract 2 vials of sintilimab injection and transfer it into a 100mL intravenous bag containing 0.9% (weight/volume) sodium chloride solution. Record the time when the preparation process starts.

2. Gently invert the infusion bag to mix the solution, ensuring uniformity of the contents. Do not shake vigorously so as to avoid bubbles. If a large amount of bubbles appear, allow the IV bag to stand until the bubbles disappear.

3. Administer the drug with a 0.2 ~ 1.2 μm in-line filter (the infusion time is recommended to be controlled within 30 ~ 60 min). Record the start and stop time of infusion.

Note: Prior to preparation, make sure that sintilimab injection is clear without any quality issues such as turbidity or precipitation. Ensure that the time from sintilimab drawing to the end of infusion does not exceed 24 hours (the storage condition of prepared drug is at 2-8℃ in refrigerator); avoid mixing with other drugs; avoid administering as an intravenous push.

5.1.2 Use of Chemotherapy

Other concomitant standard chemotherapy will be prepared as described in their approved package inserts, and the doses selected are as follows:

- Pemetrexed: 500 mg/m^2
- Cisplatin: 75 mg/m^2
- Carboplatin: AUC 5 (using Calvert formula). Carboplatin dose should not exceed 750 mg.

Calvert formula

Total Dose (mg) = (target AUC) × (CrCl + 25)

The estimated CrCl used in the Calvert formula should not exceed 125 ml/min

Maximum carboplatin dose (mg) = target AUC 5 (mg×min/ml) × (125 + 25)

= 5 × 150ml/min = 750 mg

5.2 Dose Modification

5.2.1 General Principles

Dose modifications must be based on the maximum toxicity experienced during a cycle. Subject's hematological, hepatic and renal functions must meet the dosing requirements, and the toxicity needs to resolve to CTCAE grade 0 ~ 1 or baseline (except for alopecia, asthenia or other conditions that do not affect the safety of the subject in the judgment of the investigator; HGB≥90 g/L is eligible for treatment) prior to resuming subsequent cycle. Refer to 5.2.2 -5.2.4 for specific toxicity adjustment. Treatment for each new cycle may be delayed if the subject did not recover to the level of dose resumption within the planned dosing interval due to drug toxicity. For one or more drug administrations that delayed due to toxicity, every effort should be made to keep the same cycle of administration as other study drugs after recovery.

All medication modifications should be documented, including reasons and methods used.

5.2.2 Dose Modifications for Sintilimab

Sintilimab dose reduction is not permitted throughout the study, and the principles for the suspension and permanent discontinuation of sintilimab are shown in Table 5. If a dose delay occurs during a 3-week cycle of treatment with sintilimab, all future dosing days will be delayed to ensure that the dosing interval between treatment cycles with sintilimab is 21±3 days. AEs associated with sintilimab are generally immune-related AEs. For suspension due to immune-related AEs, based on the type and severity of the AE, dosing may be resumed after recovery.

Table 5. Dosage Modification Guidelines for Sintilimab

Adverse Events Associated with Sintilimab	Severity	Dose Modification
Pneumonia	Grade 2 pneumonitis	Dose Hold [a]
	Recurrent grade 2 pneumonitis, grade 3 or 4 pneumonitis	Permanent Discontinuation
Diarrhea/enterocolitis	Grade 2 or 3 diarrhea or enterocolitis	Dose Hold [a]

Adverse Events Associated with Sintilimab	Severity	Dose Modification
	Grade 4 diarrhea or enterocolitis	Permanent Discontinuation
Dermatitis	Grade 3 dermatitis	Dose Hold [a]
	Grade 4 dermatitis	Permanent Discontinuation
Hepatitis	Grade 2 elevations in AST, ALT, or TBIL for subjects with normal ALT, AST, or TBIL at baseline; elevations in AST, ALT, or TBIL ⩾ 50% (Grade 2 requirement met) and lasting < 7 days for subjects with AST, ALT, or TBIL > ULN at baseline	Dose Hold [a]
	Grade 3 or 4 elevations in AST, ALT, or TBIL for subjects with normal ALT, AST, or TBIL at baseline; elevations in AST, ALT, or TBIL ⩾50% (Grade 3 or 4 requirement met) and lasting ⩾7 days for subjects with AST, ALT, or TBIL > ULN at baseline	Permanent Discontinuation
Hypophysitis	Grade 2 or 3 hypophysitis	Dose Hold [b]
	Grade 4 hypophysitis	Permanent Discontinuation
Adrenal insufficiency	Grade 2 adrenal insufficiency	Dose Hold[b]
	Grade 3 or 4 adrenal insufficiency	Permanent Discontinuation
Hyperthyroidism	Grade 3 or 4 hyperthyroidism	Permanent Discontinuation
Hypothyroidism	Grade 2-4 hypothyroidism	Continued [b]
Type 1 diabetes	Grade 3 hyperglycemia	Dose Hold[b]
	Grade 4 hyperglycemia	Permanent Discontinuation
Renal insufficiency	Grade 2 or 3 Cr increase	Dose Hold[a]
	Grade 4 Cr increase	Permanent Discontinuation
Neurotoxicity	Grade 2 neurotoxicity	Dose Hold[a]
	Grade 3 or 4 neurotoxicity	Permanent Discontinuation

Adverse Events Associated with Sintilimab	Severity	Dose Modification
Other AEs	First occurrence of other grade 3 AE	Dose Hold[a]
	Grade 2 myocarditis	Dose Hold[a]
	Grade 3 AE that cannot be reduced to Grade 0-2/baseline within 7 days or recovered to Grade 0-1/baseline within 14 days	Permanent Discontinuation
	Recurrent grade 3 or 4 (except endocrine disorders)	Permanent Discontinuation [c]

[a]: Resume dosing after improvement to Grade 0-1 or baseline.

[b]: Hypophysitis, adrenal insufficiency, thyroid insufficiency/hypothyroidism, and type 1 diabetes may be reintroduced if adequately controlled or only physiologic hormone replacement therapy required.

[c]: For recurrent Grade 3 or 4 laboratory abnormalities, discontinuation should be based on concomitant clinical symptoms/signs and clinical judgment of the investigator.

The maximum length allowed for drug suspension is 12 weeks. If after 12 weeks, the subject cannot recover to the state that he/she can be re-administered with sintilimab, the subject must permanently discontinue sintilimab and enter the follow-up phase of the study, except for the following two cases:

- Corticosteroids are used for the treatment of immune-related adverse events and the course of corticosteroid taper leads to the delay of sintilimab administration for more than 12 weeks. In this case, the decision on whether to continue treatment with sintilimab should be discussed with the Sponsor's medical manager. Tumor imaging evaluation should not be affected by treatment interruption and will be performed as scheduled.
- Treatment of an AE unrelated to sintilimab leads to treatment interruption for more than 12 weeks. In this case, the decision on whether to continue treatment with sintilimab should be made through discussion with the Sponsor's medical manager. Tumor imaging evaluation should not be affected by treatment interruption and will be performed as scheduled.

The related AE should be recovered to grade 0 ~ 1 or baseline or the level that investigator consider be eligible for treatment, with ECOG PS score of 0 ~ 1.

5.2.3 Management of Infusion Reactions Related to Sintilimab

Sintilimab may cause severe or life-threatening infusion reactions, including severe hypersensitivity or anaphylactic reactions, with signs and symptoms usually appearing during or shortly after the drug infusion and usually resolving completely within 24 hours of completing the infusion. See Table 6 for guidance on the management of sintilimab-related infusion reactions.

Table 6. Guidelines For The Management of Sintilimab-related Infusion Reactions

NCI CTCAE Grade	Treatment	Premedication at Subsequent Dosing
Grade 1 Mild reaction; infusion interruption not indicated; intervention not indicated	Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator.	None
Grade 2 Requires infusion interruption but respond promptly to symptomatic treatment (e.g. antihistamines, NSAIDS, narcotics, IV fluids); prophylactic medications indicated for ≤24 h	**Stop the infusion and monitor symptoms.** Additional appropriate medical therapy may include but is not limited to: IV fluids Antihistamines NSAIDS Acetaminophen Narcotics Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator. If symptoms resolve within 1 h of stopping drug infusion, the infusion may be restarted at 50% of the original infusion rate (e.g. from 100 mL/h to 50 mL/h). Otherwise dosing will be held until symptoms resolve and the subject should be premedicated for the next scheduled dose. **Subjects who develop Grade 2 toxicity despite adequate premedication should be**	Subject may be premedicated 1.5 h (± 30 min) prior to sintilimab infusion: Diphenhydramine 50 mg PO (or equivalent dose of antihistamine). Acetaminophen 500–1000 mg PO (or equivalent dose of antipyretic).

NCI CTCAE Grade	Treatment	Premedication at Subsequent Dosing
	permanently discontinued from further study treatment administration.	
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 infiltrates) Grade 4: Life threatening; pressors or ventilatory support indicated	**Stop infusion.** Additional appropriate medical therapy may include but is not limited to: Epinephrine** IV fluids Antihistamines NSAIDS Acetaminophen Narcotics Oxygen Pressors Corticosteroids Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator. Hospitalization may be indicated. **Epinephrine should be used immediately for allergic reactions. **Subjects is permanently discontinued from further study drug administration.**	No subsequent dosing
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 CTCAE v4.03 (http://ctep.cancer.gov).		

Other Allowed Circumstances for Dose Modifications of Sintilimab

Circumstances other than treatment-related AEs, such as medical/surgical events not related to study treatment, or administrative reasons, may result in interruption of treatment with sintilimab. Subjects should resume study treatment within 3 weeks of the interruption unless there are other results made from discussions with the Sponsor. Reasons for interruption should be documented in the subject's study records.

5.2.4 Dose Modification of Chemotherapy

If, in the opinion of the investigator, the toxicity is mainly caused by a certain

chemotherapy agent, dose reduction of one chemotherapy agent is acceptable; if it is thought that the toxicity is caused by two or more drugs, dose of relevant drugs can be simultaneously reduced. According to the toxicity of the drug, subjects may have chemotherapy discontinued and continue sintilimab (or placebo) alone or subjects may have sintilimab discontinued and continue chemotherapy alone. Chemotherapy may be interrupted for a maximum of 6 weeks after the last administration. Hematologic toxicity due to chemotherapy may be treated with colony-stimulating factor support (e.g., GM-CSF, etc.) prior to the initiation of any chemotherapy, but prophylaxis prior to the first dose of chemotherapy is contraindicated. Different dose modifications for chemotherapy agents are detailed in the below table.

Table 7. Dose Modifications for Chemotherapy agents

	Original dose	Dose Level -1	Dose Level -2
Pemetrexed	500 mg/m^2	375 mg/m^2	250 mg/m^2
Cisplatin	75 mg/m^2	56 mg/m^2	38 mg/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 Modifications for Chemotherapy Hematological Toxicity

Table 8. Dose Modifications for Chemotherapy based on Hematologic Nadir from Previous Cycle

		Pemetrexed	Cisplatin/Carboplatin
Platelets	Neutrophils	Dose modification according to Table 7	
≥50×10^9/L and	≥0.5×10^9/L	Original dose	Original dose
≥50×10^9/L and	< 0.5×10^9/L	75% of the original dose	75% of the original dose
< 50×10^9/L, no bleeding and	Any circumstances	75% of the original dose	75% of the original dose
< 50 × 10^9/L, and ≥Grade 2 bleeding and	Any circumstances	50% of the original dose	50% of the original dose
Any circumstances	< 1×10^9/L combined with fever ≥38.5℃	75% of the original dose	75% of the original dose

Recommended Dose Modifications for Chemotherapy Non-Hematological Toxicity

Table 9. Dose Modifications for Chemotherapy based on AE grade

Adverse Events	CTCAE grade	Pemetrexed	Cisplatin	Carboplatin
Nausea or vomiting	Grade 3 or 4	Original dose	Original dose	Original dose
Diarrhea	Grade 3 or 4	75% of the original dose	75% of the original dose	Original dose
Mucositis	Grade 3 or 4	50% of the original dose	Original dose	Original dose
Neurotoxicity	Grade 2	Original dose	50% of the original dose	Original dose
	Grade 3 or 4	75% of the original dose	Drug discontinuation	75% of the original dose
Transaminase increased	Grade 3	75% of the original dose	75% of the original dose	75% of the original dose
	Grade 4	Drug discontinuation	Drug discontinuation	Drug discontinuation
Other	Grade 3 or 4	75% of the original dose	75% of the original dose	75% of original dose

Creatinine Clearance (CrCl):

CrCl will be calculated based on the original weight-based Cockcroft-Gault formula (Appendix 2). CrCl must be ⩾45ml/min prior to administration of chemotherapy. Pemetrexed and/or platinum may be delayed for up to 6 weeks to allow the subject time to recover from the toxicity. If a subject's CrCl has not recovered to ⩾45 ml/min within 6 weeks after the previous dose, platinum and/or pemetrexed must be discontinued.

5.3 Principles for Managing Immune Checkpoint Inhibitor Toxicities

The AE associated with the exposure to sintilimab may be of immunological etiology. These irAEs may occur shortly after the first dose or several months after the last dose and may affect more than one system at the same time. Therefore, early detection and initiation of therapy is essential to mitigate complications. Based on the available clinical study data, the majority of irAEs are reversible and manageable with dose interruption, corticosteroid administration, and/or other supportive care. For suspected irAEs, ensure appropriate assessment is performed to confirm etiology or rule out alternative causes. Other procedures or tests such as bronchoscopy, endoscopy, or skin biopsy may be included as part of this assessment. Based on the severity of the irAE, suspend or permanently discontinue treatment with sintilimab and administer corticosteroids.

Guidelines for dose modification and toxicity management of potential irAEs are provided in the "Manual for the Management of Immune-related Adverse Events" provided by the Sponsor.

5.4 Concomitant Therapy

5.4.1 Acceptable Concomitant Medications

- Medications that are in compliance with the protocol, as determined by the investigator (e.g., concomitant therapies used for disease-related symptoms and various treatment-related AEs).

- Subjects with underlying diseases such as hypertension and diabetes requiring long-term medication can continue medication.

- Local surgery or radiotherapy used for isolated lesions (excluding target lesions) during study treatment period (radiation fields excluding lungs).

- Supportive care for relieving tumor-related symptoms, such as bisphosphonate treatment for bone metastases.

- Topical glucocorticoids, such as topical application to the skin, eye drops, nasal spray, and inhalation, are allowed.

- Subjects taking NSAIDS or salicylates will not take the NSAIDS or salicylate (other than an aspirin dose ≤1.3g per day) for 2 days before and 2 days after receiving pemetrexed. Subjects taking NSAIDS or salicylates with a long half-life (such as naproxen, piroxicam, diflunisal, or nabumetone) will not take the NSAIDS or salicylates for 5 days before and 2 days after pemetrexed.

5.4.2 Prohibited Concomitant Medications

Subjects are prohibited from receiving the following treatments during the treatment period of this study (including crossover to receive sintilimab monotherapy after confirmation of PD in the control group):

- Systemic chemotherapy or biotherapy with anti-tumor effect (except for cytokine drugs used to treat chemotherapy-induced adverse events), as well as Chinese medicines with anti-tumor effects;

- Drugs with immunomodulatory effects, including but not limited to non-specific immunomodulators (such as thymosin, interferon, interleukin, immunoglobulin, gamma globulin) and proprietary Chinese medicines with immunomodulatory effects;

    - Note: Interleukin-11 is allowed for the treatment of AEs.

- Chemotherapy not specified in this protocol;
- Investigational agents other than sintilimab;
- Radiation therapy for tumor control ;
    - Note: Radiation therapy to symptomatic discrete lesions, such as radiation therapy to relieve pain of bone metastases may be approved and allowed by the Sponsor as long as a target lesion is not included.
- Live vaccinations within 30 days prior to the first dose of study treatment and while participating in the study. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, varicella, yellow fever, rabies, BCG, typhoid (oral) vaccine. Receipt of inactivated viral vaccines administered as an injection against seasonal influenza is permitted; live attenuated influenza vaccines administered intranasally are not permitted;
- Corticosteroids. Inhaled steroids for asthma or chronic obstructive pulmonary disease (COPD) as part of fixed therapy are allowed. Corticosteroids for the management of adverse events with an underlying immune etiology are allowed. The use of physiological doses of corticosteroids may be approved after consultation with the Sponsor;

Note: Prophylactic corticosteroids are allowed to avoid allergic reactions (e.g., premedication before administration of intravenous contrast or chemotherapy).

Based on the assessment of the investigator, subjects requiring any one of the treatment methods above must be excluded from the study. Subjects may be treated with other medications deemed medically necessary by the investigator.

It is important that the investigator review each medication (prescription and nonprescription) that the subject receives prior to the start of the study and at each study visit.

- At each visit, subjects must be asked about any new medications received.
- To minimize the risk of drug-drug interactions, all measures must be taken to limit concomitant medications that are truly necessary.
- During administration, hepatotoxic drugs should be avoided (i.e., hepatotoxic drugs with warnings in the package insert). The investigators are encouraged to search through www.livertox.nih.gov website to review each potentially hepatotoxic drug.

Restrictions specific to concomitant medications during the study are listed below.

The following medications/therapies must be avoided during the dosing and for 14 days after dosing:

Known hepatotoxic drugs, including but not limited to:

- Etifoxine
- Isoniazid
- Nitrofurantoin
- Ketoconazole
- Amiodarone
- Phenytoin

Prohibited medications as described in the exclusion criteria are not allowed to be used.

There are no prohibited medications during the post-treatment follow-up period.

5.4.3 Drug Interactions

- Sintilimab: No drug interaction information is currently available.
- Pemetrexed: In subjects with mild to moderate renal insufficiency, the use of NSAIDS with a short half-life is not recommended for at least 2 days before, the day of, and at least 2 days after receiving pemetrexed. The use of NSAIDS with a long half-life is not recommended for at least 5 days before, the day of, and at least 2 days after receiving pemetrexed.
- Cisplatin: Aminoglycoside antibiotics, amphotericin B or cephalothin, etc. used in combination with cisplatin, have additive nephrotoxic effect. When probenecid is used in combination with cisplatin, it may cause hyperuricemia; chloramphenicol or its furosemide acid or sodium diuretic may increase the ototoxicity of cisplatin; antihistamines may mask the symptoms of tinnitus and vertigo caused by cisplatin.
- Carboplatin: May alter renal function, although increased nephrotoxicity with aminoglycosides and other nephrotoxic agents has not been confirmed, it is recommended to avoid using these drugs together.

5.5 Drug Management

5.5.1 Drug Management

Sintilimab should be refrigerated at 2 ~ 8°C, protected from light, and should not be

frozen. All study drugs are to be transported to each local site by cold chain transportation, and should be kept and dispensed by a designated personnel.

The study drug should be stored in the refrigerator that only the authorized personnel can open. After receiving the drug, the investigator should ensure that the temperature during the transport is maintained within the specified range. After verification, the study drug should be signed for receipt and stored at the specified temperature. If abnormalities of the storage temperature during transportation or storage at the local site arise, the drug should be transferred to the specified temperature as soon as possible to relieve the temperature and not be used for the time being. This matter should be reported to the Sponsor in a timely manner, and the drug should be handled according to the Sponsor's advice.

All the study drugs provided by the Sponsor should only be used for this clinical study and should not be used for any purposes other than those specified in this protocol. The investigator must commit to not provide the study drug to any person unrelated to this study.

Sintilimab that is discontinued for special reasons should be stored under the same storage conditions until the inspector has checked it and arranged it to be recycled.

5.5.2 Drug Dispensation

Stratified randomization will be used in this study, and the randomization list will be provided and generated by statisticians using SAS statistical software. After confirming that the subject meets all of the inclusion and exclusion criteria, the local site will log into the IWRS, which will assign a random number to the subject and provide the subject with a medication number.

5.5.3 Drug Return and Destruction

In this study, used sintilimab containers need to be recycled, and chemotherapy containers will be destroyed on site according to applicable guidelines and procedures established at the local site and local facilities.

All unused study drugs should be returned to the Sponsor for destruction after the study is completed/terminated or beyond the shelf life. The return of study drug will be arranged by the CRA designated by the Sponsor.

5.6 Study Drug Records

The designated personnel of the local site should timely record the receipt, distribution, use, inventory, destruction, recovery and destruction of the study drugs according to the requirements of relevant laws and regulations and guidelines.

5.7 Complaint Handling

In order to ensure the safety, monitor the quality of study participants and assist in process and drug improvement, the Sponsor will collect product complaints related to the investigational product used in the clinical study.

Complaints related to concomitant medications will be reported directly to the manufacturer according to the product instructions.

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

A study-specific complaint form is to be used to document the reported product complaint and the associated full description.

Fax the completed Product Complaint Form to the Sponsor or its designee within 24 hours.

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

6. Study Procedures

6.1 Enrollment and Randomization

6.1.1 Enrollment and Randomization

Investigators will enroll subjects as follows:

1. Obtain signed informed consent from the subject prior to any study-related procedures.
2. Confirm the subject's eligibility for inclusion by the principal investigator or appropriately trained designee after reviewing the inclusion/exclusion criteria.

3. Randomize the subjects, stratified by gender (male or female), platinum chemotherapy (cisplatin or carboplatin), and PD-L1 expression level (< 1% or ≥1%).

Subjects who do not meet the relevant criteria for this study (screen failure) may be re-screened. If re-screening is considered, the investigator must contact the Sponsor. Each subject can be re-screened only once. The subject must re-sign the informed consent form (ICF) and will be reassigned with a new identification number when re-screened.

6.1.2 Enrollment Error Handeling

Inclusion criteria must be strictly adhered to. If subjects who do not meet the inclusion and exclusion criteria are found to be enrolled, the Sponsor's medical manager and the investigator will discuss whether to continue the subject's participation in the study with study drug. If the investigator determines that it is appropriate for the subject to continue the study from a medical perspective, and the Sponsor's medical manager agrees with the investigator's decision, the subject may continue the study and receive treatment with the study drug. If, in the opinion of the investigator, it is medically appropriate for the subject to continue in the study, but the Sponsor's medical manager disagrees with the investigator's decision, the subject must not continue the study. Subjects accidentally enrolled in the study will be allowed to continue in the study only after the investigator has received written approval from the Sponsor.

6.2 Study Plan and Schedule

6.2.1 Screening Period

The following study procedures must be completed at screening (Day -28 ~ -1) to ensure subject eligibility:

- Signing informed consent form
- Checking inclusion/exclusion criteria
- Recording the demographics, past medical history and past medications
- Recording the vital signs, height and weight
- Physical examination
- ECOG PS score

- 12-lead ECG
- Hematology/blood biochemistry/urinalysis/blood cardiac biomarker and troponin testing (within 7 days before the first administration)
- Coagulation function test (within 7 days before the first administration)
- Pregnancy test (within 3 days prior to the first dose)
- Thyroid function test (within 28 days prior to the first dose)
- HIV antibody, Treponema pallidum specific antibody, hepatitis B tests (HBsAg, HBsAb, HBcAb, HBeAg, HBeAb) and HBV-DNA, HCV antibody and HCV-RNA (within 28 days before the first administration)
- Adverse events evaluation
- Concomitant medications
- Tumor imaging evaluation
- Archived or fresh tumor tissue samples

Detailed instructions for tumor imaging evaluations and safety evaluations are provided in Sections 7.1 and 7.2.

6.2.1.1 Past Medical History

Past medical history will be collected by the investigator or qualified designee. Medical history will include all active conditions, as well as any condition diagnosed within the last 10 years and considered clinically significant by the investigator. The detailed disease information of NSCLC will be recorded separately, including history of smoking, surgery and drug allergy, but will not be listed as a medical history. Any autoimmune disease, regardless of the date of onset, should be documented.

6.2.1.2 Prior Medications

The investigator or qualified designee will review the subject's prior medications, including any washout requirements specified in the protocol, and document medications, including alternative/supplemental medications, taken by the subject within 30 days prior to the first dose of study drug.

6.2.1.3 Concomitant Medications

The investigator or qualified designee will document all the medications the subject used throughout the study (from signing of ICF through the safety follow-up visit).

All medications associated with the reporting of SAEs should be recorded as defined in Section 8.4.

6.2.2 Baseline (prior to Cycle 1 Day 1)

- Recording the vital signs
- Weight
- ECOG PS score
- 12-lead ECG
- Adverse events evaluation
- Concomitant medications
- EORTC QLQ-C30 V3.0 Chinese version
- PK and immunogenicity
- Whole Blood Biomarker Specimen Collection

6.2.3 Treatment Period Visits

- Recording vital signs and body weight, and baseline body weight will be used to calculate the amount of chemotherapy administered if a subject's body weight fluctuated less than 10% from baseline (the day of the first dose of study treatment), the baseline body weight was used to calculate the amount of chemotherapy administered. Otherwise, the dose will be calculated based on the body weight on the scheduled day of dosing or the day before it. The actual dose can also be calculated based on the body weight on the day of dosing or the day before it according to clinical practice regardless of the baseline weight. The protocol allows a ±5% deviation from the calculated total infusion dose for dosing convenience.
- ECOG PS score
- 12-lead ECG

- Hematology/blood biochemistry/urinalysis/cardiac enzymes and troponin
- Thyroid function
- HBV-DNA and/or HCV-RNA (if applicable)
- PK and immunogenicity
- Adverse events evaluation
- Concomitant medications
- Tumor imaging evaluation
- Study drug administration
- EORTC QLQ-C30 V3.0 Chinese version
- Whole blood sample collection for biomarkers

See Table 1 for a flow chart of study treatment period visits. Details of the physical examination are provided in Section 7.2.1 and details of tumor imaging evaluation, safety evaluation, and PK/immunogenicity blood sampling are provided in Sections 7.1-7.4.

6.2.4 End of Treatment Visit/Safety Follow-Up Visit

There will be an end of treatment visit and a safety follow-up visit. The end of treatment visit will occur within 7 days of the end of treatment; the safety follow-up visit will occur 30 ± 3 days after the last dose, or before the start of a new antineoplastic therapy. If the end of treatment visit and safety follow-up visit are within 7 days, only the end of treatment visit will be performed. If the safety follow-up visit is prior to the end of treatment visit, only the end of treatment visit will be performed. The following contents are included: (See Study Flow Chart Table 1, Table 2 for details)

- Recording the vital signs
- Weight
- Physical examination
- ECOG PS score

- 12-lead ECG
- Hematology/blood biochemistry/urinalysis
- Coagulation test
- Thyroid function
- HBV-DNA and/or HCV-RNA (if applicable)
- Immunogenicity
- Adverse events evaluation
- Concomitant medications
- Document subsequent antineoplastic therapy (if applicable)
- EORTC QLQ-C30 V3.0 Chinese version

6.2.5 Survival Follow-up

Subjects who experience disease progression (as assessed by the IRRC) or who initiate new antineoplastic therapy or discontinue treatment for other reasons will enter the survival follow-up phase. Date of first survival follow-up contact should be 90 days (±7 days) after safety follow-up visit.

Note: If a subject does not have a 30-day safety follow-up visit, then this date should be calculated from the end of treatment.

6.2.6 Subsequent Anti-tumor Therapy

The investigator or qualified designee will collect all the information about new anti-tumor therapies initiated after the last dose of the study drugs and the corresponding efficacy. If a subject starts a new antineoplastic therapy within 30 days after the last dose of study treatment, a safety visit must be performed prior to the first dose of new therapy.

Subjects will enter the survival follow-up visit after starting a new antineoplastic therapy. Refer to Section 6.2.5 survival follow-up visits for detailed instructions regarding survival status follow-up.

6.3 Crossover for Subjects of Control Arm after Documented Disease Progression

Subjects of control arm will have the opportunity to be unblinded and crossover to receive sintilimab monotherapy once they experience disease progression (confirmed by

IRRC). Subjects who permanently discontinue chemotherapy due to an adverse event, withdrawal of consent, or for any reasons other than progressive disease, will not be eligible for crossover to sintilimab monotherapy. Crossover subjects must not initiate treatment with sintilimab earlier than 21 days after their last dose of chemotherapy regardless of the time of progression.

Subjects in the control arm whose disease progression per RECIST v1.1 is confirmed by IRRC may crossover to receive sintilimab monotherapy at the discretion of the investigator (with the Sponsor's agreement) and subject's will. Subjects who meet the following conditions are eligible for crossover:

- The evidence of disease progression per RECIST v1.1 (confirmed by IRRC);
- Treatment-related AEs (except for asthenia or alopecia) must be have recovered to ≤Grade 1 or baseline (HGB ≥90 g/L);
- If a subject is unstable as a result of a new or progressing brain metastasis, the subject can not receive crossover treatment;
- ECOG PS score 0 ~ 1;
- Subject has not received any systemic chemotherapies other than the chemotherapy administered during the treatment phase;
- If the subject received radiotherapy, palliative radiotherapy (less than or equal to 30 Gy) needs to be completed at least 7 days prior to the first dose of crossover treatment.

The study procedure for crossover phase is as follows.

6.3.1 Assessment before the first dose (Crossover Phase)

The following study procedures must be completed prior to the first dose to ensure the subject is eligible for this study, and the examination at the end of the last chemotherapy may be used as a pre-crossover assessment:

- Verify whether the subject meets the requirements in Section 6.3
- Record vital signs, height and weight
- Physical examination
- ECOG PS score

- 12-lead ECG
- Hematology/blood biochemistry/urinalysis/cardiac biomarkers and troponin test (within 7 days prior to the first dose)
- Coagulation test (within 7 days before the first administration)
- Pregnancy test (within 3 days prior to the first dose)
- Thyroid function (within 14 days before the first dose)
- HIV antibody, specific antibody to Treponema pallidum, hepatitis B tests (HBsAg, HBsAb, HBcAb, HBeAg, HBeAb) and HBV-DNA, HCV antibody and HCV-RNA (within 14 days before the first dose)
- Adverse events evaluation
- Concomitant medications
- Tumor imaging evaluation

6.3.2 Concomitant medications (Crossover Phase)

The investigator or qualified designee will document the subject's medication use throughout the duration of the study (from the time of the first dose of sintilimab until the safety follow-up visit).

All medications associated with the reporting of SAEs should be recorded as defined in Section 8.4.

6.3.3 Treatment Period Visits (Crossover Phase)

- Recording vital signs
- ECOG PS score
- 12-lead ECG
- Hematology/blood biochemistry/urine routine/blood cardiac biomarker and troponin test
- Thyroid function
- HBV-DNA and/or HCV-RNA (if applicable)
- Adverse events evaluation

- Concomitant medications
- Tumor imaging evaluation
- Study drug administration

See Table 2 for a study flow chart of study treatment period visits. Details of the physical examination are provided in Section 7.2.1 and details of the tumor imaging evaluation and safety evaluation are provided in Sections 7.1-7.2.

6.3.4 End of Treatment Visit/Safety Visit (Crossover Phase)

There will be an end of treatment visit and safety follow-up visit. The end of treatment visit should occur within 7 days of the end of treatment; the safety follow-up visit should occur 30 ± 3 days after the last dose of study treatment or before the initiation of a new antineoplastic therapy. If the end of treatment visit and safety follow-up visit are within 7 days, only the end of treatment visit will be performed. If the safety follow-up visit is prior to the end of treatment visit, only the end of treatment visit will be performed. Include the following:

- Record vital signs
- Physical examination
- ECOG PS score
- 12-lead ECG
- Hematology/blood biochemistry/urinalysis
- Coagulation test
- Thyroid function
- HBV-DNA and/or HCV-RNA (if applicable)
- Adverse events evaluation
- Concomitant medication
- Document subsequent antineoplastic therapy (if applicable)

6.3.5 Survival Follow-up Visit (Crossover Phase)

Once a subject experiences disease progression (based on the evaluation of the local site) or starts a new anti-cancer therapy or discontinue treatment for other reasons ,

the subject moves into the survival follow-up phase. The date of first survival follow-up should be 90 days (±7) after the safety follow-up visit.

Note: If the subject does not have a 30-day safety follow-up visit, then this date should be counted from the end of treatment.

6.3.6 Subsequent Anti-tumor Treatment (Crossover Phase)

The investigator or qualified designee will collect all new anti-tumor treatment and corresponding efficacy information after the last dose. If a subject starts a new antineoplastic therapy within 30 days after the last dose of study treatment, a safety follow-up visit must be performed prior to the first dose of new therapy.

Subjects will enter the survival follow-up phase after initiation of new antineoplastic therapy. Refer to Section 6.3.5 Survival Follow-up Visit for detailed instructions regarding survival status follow-up.

6.4 Other Procedures

6.4.1 Treatment Discontinuation/Withdrawal

Subjects who discontinue treatment/withdraw from treatment prior to complection of the treatment regimen should be encouraged to continue to be followed for all remaining study visits.

When a subject discontinues/withdraws from the treatment, all applicable activities scheduled for the end of treatment visit should be performed. Any adverse events which are present at the time of discontinuation/withdrawal should be followed up in accordance with the safety requirements outlined in Section 8.4 (Recording Adverse Events). Subjects who have completed 24 months of treatment with sintilimab may be discontinued. Subjects who discontinue treatment after completing 24 months of sintilimab treatment should return to the local site for a end of treatment visit and then enter the follow-up phase of this study.

6.4.2 Lost to Follow-up

If the subject fails to return to the local site for the required study visits and/or the local site can not contact the subject, then the following procedures will be performed:

- The local site must attempt to contact the subject and reschedule the missed visit. If the subject is contacted, the subject should be informed of the importance of

adhering to the protocol-specified visit schedule.

- At each missed visit, the investigator or designee must make every effort to resume contact with the subject (e.g., by calling and/or mailing to the subject's last known address). These contact attempts should be documented in the subject's medical record.
- Note: A subject is not considered lost to follow-up until the last scheduled visit for an individual subject has been reached. The amount of missing data for a subject should be managed according to pre-specified guidelines for data handling and analysis.

6.4.3 Unblinding

In general, after initial imaging of disease progression is assessed by the investigator based on RECIST v1.1, if the subject is clinically stable, the current treatment can be continued followed by imaging assessment confirmation 4-8 weeks later (based on RECIST v1.1). If progression is confirmed and the investigator assesses that the subject can not benefit from current treatment, unblinding may be performed with permission from the Sponsor. Subjects in the experimental group will end the study treatment and subjects in the control group can conditionally cross over to sintilimab monotherapy based on the investigator's assessment and the subject's will, until disease progression, intolerable toxicity, new anti-tumor treatment, withdrawal of ICF, lost to follow-up, death and occurrence of other reasons for discontinuation of study treatment, whichever occurs first. If progression is not confirmed, the study treatment can be continued until imaging PD is confirmed and the investigator assesses that there is no benefit to continue treatment, unblinding will be handled as before. If the subject is clinically unstable after the initial imaging of disease progression, confirmation after 4-8 weeks is not required. Unblinding will be performed directly after obtaining permission from the Sponsor, and unblinding will be handled as before. When the principle investigator or sub-investigator needs to identify the blinded therapy used by a subject and the dosage administered to the subject in an emergency (e.g., in the event of a serious adverse event), he/she will contact the Sponsor and CRO by telephone and make a request for emergency unblinding. The severity/toxicity grade of AE, AE's relation to study drug, and reason for the observed AE must be documented by the principle investigator or sub-investigator in the medical charts prior to unblinding. Before emergency unblinding, the investigator should

complete the unblinding request form.

In addition, the investigator must log into the IWRS system and perform the unblinding in the IWRS system to update drug disposition. The IWRS must be used for emergency unblinding in the event that unblinding is required for subject safety.

After unblinding, the information of unblinding (e.g., date, reason, and person responsible for unblinding) must be documented promptly and the Sponsor's medical manager should be notified as soon as possible. Only the principal investigator or designee should unblind the corresponding subject's code. The unblinding result should not be informed to Sponsor personnel involved in this study. If, after unblinding, the investigator assesses that the subject can benefit from continuation of the original on-protocol treatment, the medication can be continued until any of the following events occurred: disease progression, intolerable toxicity, new antineoplastic therapy, withdrawal of ICF, lost to follow-up or death, or other reasons for treatment discontinuation, whichever occurs first.

7. Study Evaluation

7.1 Efficacy Evaluation

7.1.1 Tumor Imaging and Assessment of Disease

Tumor imaging usually includes contrast-enhanced computed tomography (CT) or magnetic resonance imaging (MRI). The examination sites must include brain, chest, abdomen and pelvic cavity. For subjects without brain metastases at baseline, routine cranial imaging is not required thereafter. The same imaging technique should be used for the same subject during the study.

The investigator at the local site will confirm the presence of measurable lesions based on RECIST v1.1 at screening to determine subject eligibility. Per RECIST v1.1, a maximum of 5 target lesions in total and 2 target lesions per organ. The time windows for RECIST v1.1 assessment and iRECIST assessment are to be consistent.

All scheduled imaging for all subjects at the local site will be submitted to the IRRC facilitator. Furthermore, additional imaging (including other modalities) that are obtained at unscheduled time points to evaluate disease progression, as well as imaging obtained for other reasons but captures radiographic progression, should also be submitted to the IRRC facilitator.

7.1.2 Initial Tumor Imaging

Initial tumor imaging at screening must be performed within 28 days prior to the date of randomization. Prior to randomization, the site investigator must confirm that the subject has measurable disease per RECIST v1.1.

Scans performed as part of routine clinical management may be evaluated by the investigator as a screening tumor imaging assessment if its quality meets diagnostic quality and the imaging is performed within 28 days prior to the date of randomization.

The method used for tumor burden assessment at baseline must be consistent with that used for each subsequent follow-up assessment (CT/MRI). Additional parts of involvement will be examined as indicated by each subject's symptoms and signs.

7.1.3 Tumor Imaging During the Study

Tumor imaging evaluation will be performed once at Week 6 (±7 days) and Week 12 (±7 days), respectively, and then once every 9 weeks (±7 days). After 48 weeks, tumor imaging evaluation will be performed every 12 weeks (±7 days). Subjects with initial investigator assessed radiographic PD should undergo imaging evaluation at least 4 weeks after the date of the first tumor imaging indicating PD and no later than 8 weeks to confirm PD if clinically stable. Subjects in the control group may start the crossover phase after confirmation and/or verification of PD by IRRC vendor. In the crossover phase, tumor imaging evaluation will be performed every 9 weeks (±7 days) from the start of treatment with sintilimab until radiographic PD is initially documented. Imaging evaluation should be performed at least 4 weeks after the date of the first tumor imaging indicating PD and no later than 8 weeks to confirm PD if clinically stable.

Subjects assessed to be clinically unstable should be discontinued from the study treatment with the agreement of the Sponsor after initial evaluation of radiographic PD. For the clinically unstable subjects, repeating imaging confirmation of PD is not needed.

Clinical stability is defined as follows:

- Absence of clinically significant symptoms and signs indicating disease progression (including worsening of laboratory values)
- No reduction in ECOG PS
- Absence of rapid disease progression
- Absence of progressive tumors at important anatomical sites requiring other urgent medical intervention (e.g. spinal cord compression)

For subjects who discontinue treatment for reasons other than radiographic disease progression, imaging evaluations should continue at protocol-specified imaging intervals until any of the following events occur: initiation of new antineoplastic therapy, disease progression, subject's withdrawal of ICF, and death.

CT/MRI of the brain should be performed for all subjects prior to initiation of study treatment. Brain metastases will be assessed as non-target lesions. For subjects without brain metastases prior to the first dose, routine cranial imaging is not required thereafter.

If the investigator is unable to assess disease progression, particularly for non-target and new lesions, the subject may continue treatment until the evaluation time point that clinical disease status indicate an unscheduled evaluation or it is the following next scheduled evaluation. If progression is confirmed by repeat imaging evaluation, the date of progression should be the date of initial new lesion appeared.

The primary analysis of this study will be based on tumor evaluation by IRRC per RECIST v1.1. See Appendix 3 for the evaluation method.

7.1.4 End of Treatment and Follow-up of Tumor Imaging

In subjects who discontinue study treatment without documented PD by IRRC, efforts should be made to continue monitoring their disease status by using the same imaging schedule used if on treatment (every 6 weeks or every 9 weeks or every 12 weeks) until disease progression, intolerable toxicity, withdrawal of ICF, death, or other protocol-specified circumstances that treatment should be discontinued, whichever occurs first.

Imaging at the end of treatment visit is not mandatory if the timing of the previous scan was obtained within 4 weeks prior to the date of end of treatment.

7.1.5 iRECIST Assessment of Disease

As described below, iRECIST is a modified version of RECIST v1.1 for the pharmacological treatment of immune checkpoint inhibitors in order to account for the unique tumor response to immunotherapeutic agents. Tumor response and progression will be assessed using iRECIST by the site investigator/local imaging evaluation. This data will be collected in the clinical database.

See Appendix 4 for the main contents of iRECIST.

7.2 Safety Assessment

Each subject will be assessed by the investigator or qualified designee to evaluate possible new or worsening adverse events as specified in the study flow chart, in which evaluations may be more frequently done if clinical status indicates. Adverse events will be graded and recorded according to NCI CTCAE (Version 4.03) during the study and follow-up. The toxicity profile will be based on the following aspects: severity, causality, toxicity grade, and action taken for the study treatment.

All AEs of unknown etiology associated with study treatment exposure should be evaluated whether they are events of potential immunological etiology.

Refer to Sections 8.3 and 8.4 for detailed instructions on the assessment and recording of AEs.

7.2.1 Physical Exam

7.2.1.1 Full Physical Exam

The investigator or clinical designee will perform a complete physical exam during the screening period. Clinically significant abnormal findings should be recorded as medical history. In addition, a complete physical examination will be performed as described in the test flow chart. After the first dose of study treatment, new clinically significant abnormal findings should be recorded as AEs.

7.2.1.2 Directed Physical Exam

For cycles that do not require a full physical exam per the study flow chart, the investigator or qualified designee will perform a directed physical exam as clinically indicated prior to dosing on Day 1 of each treatment cycle. New clinically significant abnormal findings should be recorded as AEs.

7.2.1.3 Height, Weight, and Vital signs

Vital signs will be recorded by the investigator or qualified designee during the screening period, prior to each dose of study treatment and at discontinuation of treatment as indicated in the study flow chart. Body weight are to be measured prior to each scheduled dose, at the end of treatment visit, at the safety visit, and prior to the first dose (crossover phase) during the course of the study. Baseline body weight will be used to calculate the amount of chemotherapy administered if the subject's body weight fluctuated less than 10% from baseline (day of first dose of study treatment). Otherwise, the actual dose will be calculated based on the body weight on the scheduled day of dosing or the day before it. The actual dose can also be calculated based on the body weight on the day of dosing or the day before it according to clinical practice regardless of the baseline weight.

Height will only be measured at the first visit. Vital signs will include body temperature, pulse, respiratory rate, blood pressure.

7.2.1.4 12-Lead Electrocardiogram (ECG)

A standard 12-lead ECG will be performed using local standard procedures once at screening. Clinically significant abnormal findings should be recorded as medical history. Additional ECGs may be performed at other time points as clinically necessary.

7.2.1.5 ECOG Performance Status

The investigator or qualified designee will assess ECOG status at screening, prior to the administration of each dose of study treatment, and at discontinuation of study treatment as indicated in the study flow chart.

7.2.2 Laboratory Procedures/Assessments

Details regarding specific laboratory procedures/assessments are provided below. The total amount of blood/tissue to be drawn/collected throughout the study (from pre-study to post-study visits), including approximate blood/tissue volumes drawn/collected by visit and by sample type, is provided in the Study Procedures Manual. Refer to the laboratory assessment section of the study flow chart.

7.2.2.1 Laboratory Safety Evaluations (Hematology, blood coagulation, urinalysis, Chemistry, etc.)

See Table 10 for laboratory tests for analysis of hematology, coagulation, urinalysis and chemistry.

Table 10. Laboratory Tests

Hematology	Chemistry	Urinalysis	Other
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 aminotransferase	Specific gravity	HCV-RNA
Hematocrit	Calcium	Urine leukocyte	HBsAg
INR	Chloride	Urine red blood cells	HBV-DNA

Hematology	Chemistry	Urinalysis	Other
PT	Creatinine		Anti-HBc
	Blood glucose		HBeAg
	Phosphorus		HBsAb
	Magnesium		HBeAb
	Potassium		HIV antibody
	Sodium		Treponema pallidum specific antibody
	Total bilirubin		Creatine phosphokinase CK
	Direct bilirubin		Creatine phosphokinase isoenzyme CK-MB
	Total protein		Troponin T or Troponin I
	Blood urea or urea nitrogen		
	Amylase		
	Lactate dehydrogenase		
	Γ-GT		

FT4 = free thyroxine; anti-HBc = hepatitis B core antibody; 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. Perform on women of childbearing potential only, within 72 hours prior to Cycle 1 Day 1.

b. Total T3 is preferred; if not available, free T3 may be tested.

c. Leukocyte differential included lymphocytes, neutrophils, monocytes, basophils, and eosinophils.

d. If urine protein is ≥ 2 +, 24h urine protein quantitative examination should be performed.

Laboratory tests for screening should be performed within 7 days prior to the first dose of study treatment. Exceptions include hepatitis and thyroid serology, which may be performed within 28 days prior to the first dose (blinded phase) or within 14 days prior to the first dose (crossover phase). After Cycle 1, pre-dose laboratory safety tests can be conducted up to 3 days prior to dosing, unless otherwise specified in the flow chart.

Laboratory test results must be reviewed by the investigator or qualified designee prior to each study treatment administration and assessed to be acceptable, unless otherwise specified in the flow chart. Unresolved abnormal labs that are drug-related AEs should be followed until resolution. Labs do not need to be repeated after the end of treatment if labs are within normal range.

7.2.2.2 Pregnancy Test

All women who are considering to participate in the study and are not surgically sterile or postmenopausal must undergo a pregnancy test within 3 days prior to the first dose of study drug. If urine tests are not negative, a serum test is required. Subjects must be excluded/terminated in the event of a positive or borderline positive test result.

7.2.2.3 Central Laboratory Evaluations

Refer to the Procedures Manual for sample collection, storage, and shipment instructions for central laboratory evaluations.

7.3 Pharmacokinetics

Pharmacokinetic test will only be performed during combination phase. PK sampling will be performed within 1 hour before the infusion of sintilimab in Cycle 1, immediately (+ 5 min) after the infusion of sintilimab in Cycle 1 and within 1 hour before the infusion of sintilimab in Cycle 2/4/12.

Every time point, 3.5 mL of whole blood will be collected in clotting vacuum tubes, then serum is separated and frozen in aliquots for PK analysis. Sample collection, storage, shipment and analysis are described in the Laboratory Manual provided by the Sponsor's designated central laboratory.

7.4 Immunogenicity

Immunogenicity tests will be performed during Cycles 1/2/4/8/12/16, and every 8 cycles thereafter (Cycles 24, 32, etc.) within 1 hour prior to the start of sintilimab/placebo infusion and safety follow up. If an infusion-related reaction occurs during sintilimab/placebo infusion, blood samples should be taken near the start of the event, end of event, and around 30 days after the reaction for immunogenicity analysis. Tests should be conducted at the central lab.

Each subject will be tested for anti-drug antibody (ADA) titers, and ADA positive serum specimens will be further tested for neutralizing antibodies (NAbs).

Every time point, 5 mL of whole blood will be collected in a coagulation promoting vacutainer, and serum will be separated and frozen in aliquots for ADA and NAb analysis.

See the Laboratory Manual provided by the central laboratory designated by the Sponsor for details of the sample collection, storage, transportation and analysis.

7.5 Quality of Life Assessment

Quality of life will be assessed using the LCSS and EORTC QLQ-C30 (V3.0 Chinese version) scales before the first dose, at each imaging evaluation, and at the first end of treatment visit.

The LCSS consists of nine graphical subscales that measure a subject's quality of life over the past 24 hours. The scale is divided into subject-completed and physician-completed sections, with the subject section consisting of nine items, each of which has its responses drawn on a line segment. The physician mainly evaluates the number and severity of the subject's symptoms and uses the hierarchical method to answer. The nine sub-scales of the LCSS include the six main symptoms of lung cancer: loss of appetite, fatigue, cough, dyspnea, hemoptysis, and pain. The remaining three sub-scales include the subject's self-rating of lung cancer symptoms, and how the disease affects daily activities.

The EORTC's 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.

7.6 Biomarker analysis

7.6.1 Tissue Biomarkers

With the permission from ethics committee (EC), all subjects who meet the inclusion criteria are required to provide acceptable tumor tissues (blocks or unstained slides) at baseline for analysis of PD-L1 expression levels and RNA detection. The following two tissues are acceptable:

1. Archival tumor tissue: Surgery should be be within one year, and biopsy should be within 6 months;

2. The fresh tumor tissues in the screening period; 5 ~ 10 unstained specimen with a section thickness of 4 ~ 5 μm.

See the Laboratory Manual provided by the central laboratory designated by the Sponsor for detailed requirements for section sample collection, sample storage, transportation and analysis.

The test results of PD-L1 expression level will be used for randomization stratification. To ensure the compliance to the study, the test results will be provided to the randomization system directly without being provided to the investigator and subject.

7.6.2 Blood Biomarkers

Subjects need to provide 10 mL of whole blood sample at the following time points: prior to the first dose, at each efficacy evaluation during the treatment period and before the initiation of the next treatment, and at the time of confirmation of disease progression for biomarker studies, including ctDNA and TCR detection.

The sample collection, sample storage, transportation and analysis are described in the Laboratory Manual provided by the Sponsor's designated central laboratory.

7.7 Storage and Destruction of Biological Samples

Samples will be be desensitized (including anonymized and pooled) and then disposed or destroyed. Additional analyses of anonymized, pooled samples may be performed to further assess and validate the analytical methods. Any results obtained from these analyses may be reported separately from the CSR.

Sample reproducibility analysis (if performed) will be assessed simultaneously with the biological samples. The results of these evaluations will not be reported in the CSR but will be presented separately in a biological analysis report.

8. Safety Reporting and Adverse Event Management

8.1 Definition of Adverse Events

An adverse event is defined as any untoward medical occurrence, whether or not there is a causal relationship with the study drug, in a clinical study subject from the time informed consent form is signed through 90 days after the last dose of study drug, and includes, but is not limited to, the following:

- Exacerbation of pre-existing (prior to clinical study) medical conditions/diseases (including worsening of symptoms, signs, laboratory abnormalities);
- Any newly developed adverse medical conditions (including symptoms, signs and newly diagnosed diseases);
- Clinically significant abnormal laboratory values or results.

8.2 Definition of Serious Adverse Event

A serious adverse event is an adverse event that meets at least one of the following criteria:

- Results in death, excluding death due to disease progression in the study indication.
- Is life threatening (life threatening is defined as an AE that places the subject at risk of death, and does not include an AE that, had it occurred in a more severe form, might cause death).
- Requires hospitalization or prolongation of hospitalization, excluding the following:
  - ✓ Rehabilitation institutions
  - ✓ Nursing homes
  - ✓ Routine emergency room admissions
  - ✓ Same-day surgery (e.g., outpatient/same-day/ambulatory surgery)
  - ✓ Hospitalization or prolonged hospitalization is unrelated to AE itself. For example, hospitalization due to original disease and there are no new adverse events and aggravation of the original diseases (e.g. to check for laboratory abnormalities that persist even before the study); hospitalization for management reasons (e.g. annual routine physical examination); hospitalization during the clinical trial as specified in the study protocol (e.g. procedures required according to the study protocol); and hospitalization that is unrelated to adverse events (e.g. elective surgery); scheduled treatment or surgery; admission only to use blood products.
- Results in a persistent or significant disability/incapacity.
- Congenital anomaly/birth defect.
- Other important medical events: defined as events that jeopardize the subject or require medical intervention to prevent one of outcomes listed above.

8.3 Evaluating Adverse Events

The investigator will assess all adverse events per NCI CTCAE Version 4.03. Any adverse event which changes CTCAE grade will be recorded on the adverse event case report forms/worksheets.

All adverse events regardless of CTCAE grade must also be evaluated for seriousness.

Table 11. Detailed Rules for the Evaluating Adverse Events

CTCAE Grading	**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 daily activities**
	Grade 3	**Severe or medically significant event requiring medication 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	A serious adverse event is any adverse event occurring at any dose or during any use of study drug that:	
	† **Results in death**;	
	† **Is life-threatening;** or places the subject, in the view of the investigator, at immediate risk of death (Note: This does not include an adverse event that, had it occurred in a more severe form, might cause death);	
	† **Results in a persistent or significant disability/incapacity** (substantial disruption of one's ability to conduct normal life functions);	
	† **Results in or prolongs an existing inpatient hospitalization** (hospitalization is defined as an inpatient admission, regardless of length of stay, even if the hospitalization is a precautionary measure for continued observation. Note: Hospitalization for an existing condition that did not worsen during the study [including hospitalization for elective procedure] does not constitute a serious adverse event. A pre-existing condition is a clinical condition that is diagnosed prior to the use of the study drug and is recorded in the subject's medical history);	
	† **Is a congenital anomaly/birth defect** (in offspring of subject taking the product regardless of time to diagnosis);	
	Other important medical events Although not fatal, life-threatening, or requiring hospitalization, such an event may also be considered a serious adverse event if, based on appropriate medical judgment, the event may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed previously (designated above by a †).	
Duration	Record the start and stop dates of the adverse event. If less than 1 day, indicate the appropriate length of time and units.	
Action taken	Did the adverse event cause the study drug to be discontinued?	

Relationship to Sponsor's Product	Did the Sponsor's product cause the adverse event? A medically qualified investigator will be required to provide assessment of causality of the relationship between the study drug and the AE. The investigator's signed/dated initials on the source document or worksheet that supports the causality noted on the AE form, ensures that a medically qualified assessment of causality was done. This signed document must be retained for the required regulatory time frame. The criteria below are intended as reference guidelines to assist the investigator in assessing the likelihood of a relationship between the test drug and the adverse event based upon the available information. **The following components are to be used to assess the relationship between the study drug and the AE;** the greater the correlation with the components and their respective elements (in number and/or intensity), the more likely the study drug caused the adverse event;	
	Exposure	Is there evidence that the subject was actually exposed to study drug, such as: reliable history, acceptable compliance assessments (pill count, diary, etc.), expected pharmacological effect, or measurements of drug/metabolite in bodily specimen?
	Time course	Did the AE follow in a reasonable temporal sequence from administration of the study drug? Is the time of onset of the AE compatible with a drug-induced effect (applies to studies with investigational medicinal product)?
	Likely cause	Is the AE not reasonably explained by another etiology such as underlying disease, other drugs/vaccines, or other host or environmental factors?
	Dechallenge	Was study drug discontinued or dose/exposure/frequency reduced? If yes, did the AE resolve or improve? If yes, this is a positive rechallenge. If no, this is a negative rechallenge. Note: This criterion is not applicable if: (1) the AE resulted in death or permanent disability; (2) the AE resolved/improved despite continuation of study drug; (3) the study is a single-dose drug study; (4) the study drug is only used one time
	Rechallenge	Was the subjet re-exposed to the study drug in this study? If yes, did the AE recur or worsen? If yes, this is a positive rechallenge. If no, this is a negative rechallenge. Note: This criterion is not applicable if: (1) the initial AE resulted in death or permanent disability, or (2) the study is a single-dose study, or (3) the study drug is only used one time

		Note: If a rechallenge is planned for an adverse event which was serious and which may have been caused by the Sponsor's product, or if reexposure to the Sponsor's product poses additional potential significant risk to the subject, then the rechallenge must be approved in advance by the Sponsor clinical director as per dose modification guidelines in the protocol.
	Consistency with study treatment profile	Is the clinical/pathological presentation of the AE consistent with previous knowledge regarding the Sponsor's product or drug class pharmacology or toxicology?
The assessment of relationship will be reported on the case report forms/worksheets by an investigator who is a qualified physician according to his/her best clinical judgment, including consideration of the above elements.		
Document causality		**Use of the following scale of criteria as guidance (not all criteria must be present to be indicative of a study drug relationship).**
Related		There is evidence of exposure to the Sponsor's product. The temporal sequence of the AE onset relative to the administration of the study drug is reasonable. The AE is more likely explained by the Sponsor's product than by another cause.
Unrelated		Subject did not receive the study drug or temporal sequence of the AE onset relative to administration of the study drug is not reaosonable or the AE is more likely explained by another cause than the study drug. (Also be applicable for a subject with overdose without an associated AE).

8.4 Recording Adverse Events

Investigators should use medical terminology/concepts to record AEs or SAEs. Spoken languages and abbreviations should be avoided. All AEs (including SAEs) should be recorded on the adverse event form in the electronic case report form (eCRF).

8.4.1 Adverse Event Collection and Times

The investigator should ask subjects non-inductive questions to be informed of the adverse events.

All adverse events, including serious adverse events, whether observed by the investigator or spontaneously reported by the subject, will be collected from the time of signing the informed consent through 90 days after the last dose. During this period, if a subject starts a new antineoplastic therapy, only SAEs considered related to study drug will be recorded and reported.

After 90 days of the last dose, the investigator should report SAEs considered related to the study drug or procedure.

8.4.2 Follow-up of Adverse Events

The subjects should be followed up until they recover to baseline or grade 0 ~ 1 or the investigator considers that follow-up is not necessary for reasonable reasons (such as can not be recovered or improved). If the AE cannot be recovered, a reasonable explanation should be recorded in the eCRF. The subject's recovery from AEs or SAEs, whether related to study drug or not, and their dates should be recorded in the eCRF and medical records.

8.4.3 Contents of AE records

The investigator is to fully document any adverse event, including diagnosis (if not, symptoms, signs including laboratory abnormalities), start and stop date and time (if applicable), CTCAE severity grade and change (Grade 3 or higher), whether a SAE, the action taken with the study drug, the treatment given for the AE, the outcome of the event, and the relationship of the AE to the study drug.

For SAEs, the investigator should also provide the date when the AE meets the criteria for an SAE, the date the investigator becomes aware of the SAE, the basis for the SAE, the date of hospitalization, the date of discharge, the probable cause of death, the

date of death, whether an autopsy is performed, the causality assessment with the study procedures, the causality assessment with other drugs, and other possible causes of the SAE. The investigator shall also provide the judgment basis of relevance as well as the description of SAE. In the description of SAE, it is also required to include the subject's identification number, age, gender, height and weight; the indication of study drug, disease stage and the subject's relevant general conditions; the occurrence, development, outcome and results of the SAE and other clinical course; the laboratory test results related to the SAE (the examination time, unit and normal range must be provided); the SAE-related past history, concomitant diseases and their occurrence and duration; the SAE-related medication history, the initiation, duration and dosage of the concomitant drugs and their treatment; the initiation, duration, dosage and administration of the study drug treatment and other detailed information.

The matters concerning the recording of AEs are described below:

Diagnosis, symptoms and signs

If a diagnosis has been made, the diagnosis should be recorded in the eCRF instead of the individual symptoms, signs and laboratory tests (e.g. recording of hepatic failure instead of jaundice, transaminase elevation and asterixis). If symptoms and signs cannot be assessed to be caused by this diagnosis at the time of reporting, they will be recorded as separate AEs/SAEs. If it is assessed that the symptoms and signs are due to the diagnosis, the diagnosis will be reported only and the symptoms and signs are included in the diagnosis. For AEs, the recording of signs and symptoms should be deleted, and for SAEs, a follow-up update report should be sent.

Adverse events secondary to other events

In general, adverse events secondary to other events (e.g. caused by other events or clinical sequelae) should have their primary event recorded unless the secondary event is serious or is a serious adverse event. Secondary events of significant clinical significance, if different from the primary event, should be recorded as independent adverse events in the eCRF. If the relationship between events is unclear, it should be recorded separately in the eCRF.

Persistent or recurrent adverse events

Persistent adverse events are those that persist without resolution between two

evaluation time points.

Recurrent adverse events are those that resolved between the two evaluation time points but recurs later on. The occurrence of the event should be recorded separately in the eCRF.

Laboratory Abnormalities

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

Death

All deaths occurring during the entire study period, including the 90-day follow-up period after the last dose, whether or not related to study drug, should be recorded on the Death Report Form in the eCRF and reported to the Sponsor in a timely manner.

When recording the death event, if the cause of death is confirmed, the cause of death shall be recorded as adverse event, the result of event is death, and the event shall be reported as SAE; if the cause of death is unknown at the time of reporting, it shall be recorded as unexplained death on the adverse event form of eCRF, and unexplained death shall be reported as SAE first, and then the exact cause of death shall be further investigated.

Pre-existing medical status

The existing symptoms/signs of subjects in the screening period of the study shall be recorded and reported as adverse events only when there is aggravation of severity, frequency and nature (except for the deterioration of the disease condition under study) after enrolled in the study. Changes from previous states, such as increased headache frequency, should be reflected in the recording.

Disease progression

Disease progression is defined as a worsening of the subject's condition caused by the primary tumor targeted by the study drug, appearance of new lesions relative to the primary tumor, or progression of the original lesion. Expected disease progression is not reported as an AE; death due to expected symptoms and signs of disease progression, life-threatening, requires hospitalization or prolongation of existing hospitalization, results in

persistent or significant disability/incapacity, results in congenital anomaly/birth defect, or other important medical events are not to be reported in an expedited manner as SAEs.

New antineoplastic therapies

Only SAEs considered related to study drug should be recorded and reported within 90 days of the subject's last dose if the subject starts a new antineoplastic therapy.

8.5 Expedited Reporting of SAEs and Pregnancy

SAE reporting

The reporting period of SAEs is from the signing of informed consent to 90 days (inclusive) after the last dose. In case of an SAE, whether it is an initial report or a follow-up report, the investigator must complete the Serious Adverse Event Report Form immediately and report to the Sponsor (drugsafety@innoventbio.com) within 24 hours after awareness. It shall be reported to the national regulatory authority and the ethics committee according to Chinese regulatory requirements.

SAEs occurring outside of the above reporting period should also be reported if they are considered related to study drug.

The investigator must complete the SAE Report Form and report to the Sponsor as soon as possible within 24 hours of awareness. For deaths and life-threatening SAEs, the investigator should urgently follow up the missing information and provide a complete SAE report. The investigator should also report to the ethics committee of the national regulatory authority according to the regulatory requirements.

Pregnancy

The risk of embryotoxicity exists for drugs of the same class. All subjects of childbearing potential participating in the clinical study must take effective contraceptive measures.

If a female subject exposed to the study drug becomes pregnant during the study, the subject should be excluded from the study. The investigator should report the pregnancy to the Sponsor within 24 hours after being informed of the pregnancy, and complete the Clinical Study Pregnancy Report/Follow-up Form.

If the partner of a male subject exposed to the study drug becomes pregnant during the study, the subject should continue the clinical study. The investigator should report

the pregnancy to the Sponsor within 24 hours after being informed of the pregnancy, and complete the Clinical Study Pregnancy Report/Follow-up Form.

The investigator must continuously monitor the subject or the subject's partner who becomes pregnant and follow up with the outcome of the pregnancy until 8 weeks after delivery of the baby and report the results to the Sponsor.

If the outcome of pregnancy is stillbirth, spontaneous abortion, fetal malformation (any congenital anomaly/birth defect), or medically-induced abortion, it should be considered as an SAE and be reported according to the SAE procedures and time limits.

If a subject experiences a concurrent SAE during pregnancy, the event should be reported according to SAE procedures.

8.6 Events of Abnormal Hepatic Function

Drug-induced liver injury will be considered if abnormal AST and/or ALT levels are combined with abnormally elevated total bilirubin levels, and the following conditions are met without other causes of liver injury. Such situations should always be considered as important medical events.

Table 12. Hepatic impairment requiring reporting as an SAE

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

Subjects should return to the local site for evaluation as soon as possible (ideally within 48 hours) after being notified with the abnormalities. The evaluation should include laboratory tests, a detailed history and physical assessment, and should consider the possibility of hepatic tumor (primary or secondary).

In addition to repeated AST and ALT tests, laboratory tests to be performed should also include albumin, creatine kinase, total bilirubin, direct and indirect bilirubin, gamma-glutamyl transferase, prothrombin time/international normalized ratio, and alkaline phosphatase. Detailed medical history collection should include: history of alcohol consumption, acetaminophen, soft drugs, various types of supplements, traditional

Chinese medicine, chemical drug exposure history, family history, occupational exposure, sexual history, travel history, contact with jaundiced subjects, surgery, blood transfusion, history of liver disease or allergic disease, history of heart disease, and history of immune disease. Further examinations may also include the detection of acute hepatitis A, B, C and E, liver imaging (such as biliary tract), autoantibodies and cardiac ultrasound. If repeat testing still confirms compliance with the laboratory criteria defined in Table 12, the possibility of potential drug-induced liver injury should be considered in the absence of other causes of abnormal liver function tests, without waiting for all etiologic liver function test results. Cases of such potential drug-induced liver injury should be reported as SAEs.

8.7 Management of Drug-Related Toxicity

The Sponsor will conduct study-level safety reviews periodically during the study. Details including frequency of review, type of data reviewed will be documented in a separate study-level safety review plan.

8.8 Immune-related Adverse Events

Since the mechanism of sintilimab involves T-cell activation and proliferation, irAEs are likely to be observed during this study. Signs and symptoms of irAEs should be monitored. If there are no alternative causes (e.g. infections), signs and symptoms of the subjects during the study may be related to the immune system.

Refer to Section 5.2 for dose adjustments of sintilimab and principles of AE management.

8.9 Emergency Unblinding

During the study, if there are cases that need unblind, such as the occurrence of an SAE, the investigator in charge of the site should make a request for unblinding, and the Sponsor and the principal investigator should jointly decide whether to unblind or not. If emergency unblinding is required, the investigator may discuss with the Sponsor and make a request for unblinding. After gaining authority of unblinding, the investigator can know the subject’s treatment allocation through the IWRS system and which treatment group the subject is randomized to. If emergency unblinding is conducted, it must be recorded in the eCRF and immediately reported to the IWRS system supplier and the Sponsor. After unblinding, whether it is appropriate to continue the original on-protocol

treatment subsequently will be decided by the investigator after communicating with the Sponsor.

9. Statistical Considerations

9.1 Statistical Analysis Plan

A detailed statistical analysis plan (SAP) will be written after the first subject is enrolled and will be finalized before database lock and unblinding. The SAP will provide details of the analysis.

9.2 Statistical Assumptions and Sample Size

The primary analysis of this study is to confirm that sintilimab in combination with chemotherapy prolongs PFS compared to placebo in combination with chemotherapy. The following statistical hypotheses will be tested for the primary study endpoint in this study:

Null hypothesis H_0: PFS (t) (Placebo) = PFS (t) (Sintilimab)

Alternative hypothesis H_a: PFS (t) (Placebo) $\neq$ PFS (t) (Sintilimab)

Here PFS (t) denotes the survival function of time.

It is assumed that the median PFS of subjects receiving sintilimab treatment will be improved from 6 months to 9.2 months (with a hazard ratio = 0.65). With an enrollment time projection of 15 months, a projected follow-up time of 8 months and an estimated dropout rate of 0.5% per month, to provide approximately 90% power under a two-sided α of 0.05, a total of 378 subjects need to be randomized to obtain the required 263 PFS events in this study. The actual number of subjects enrolled may differ from the planned number due to unforeseen reasons, such as faster enrollment speed than expected. The final screening end date will be estimated before the enrollment of 378 subject and best effort will be made to ensure that the total number of subjects enrolled will not exceed 110% of the planned number, i.e., 414 subjects, of which 276 subjects are expected in the experimental group and 138 subjects are expected in the control group.

9.3 Definition of Analysis Set

Full Analysis Set (FAS): According to the principle of intention to treat, efficacy evaluation will be performed on all randomized subjects who receive at least one dose of the study drug. Treatment groups will be analyzed based on randomization. FAS is the

primary analysis set and will be used for all efficacy and baseline characteristic analysis.

Safety Set Analysis (SS): All enrolled subjects who receive at least one dose of study drug will be analyzed based on the actual treatment received during the study. The SS data will be used for all the safety analysis. Treatment groups will be analyzed based on the actual allocations.

Per Protocol Set (PPS): a subset of FAS, i.e., subjects who do not have major protocol deviation that affect efficacy assessment (use of other antineoplastic drugs during the study, dose, method or course of treatment for serious protocol deviations), complete at least 1 cycle of medication, and have imaging evaluation results (or disease progression with imaging evidence). The PPS will be used for sensitivity analyses of primary and key secondary efficacy endpoints.

9.4 Statistical Analysis Methods

Analysis Endpoints

Primary endpoint:

- Progression Free Survival (PFS) per RECIST v1.1 by Independent Central Image Review

Secondary endpoints:

- Overall survival (OS) in both groups;
- Objective response rate (ORR) in both groups;
- Disease control rate (DCR) in both groups;
- Time to objective response (TTR) in both groups;
- Duration of response (DOR) in both groups;
- Safety and tolerability of sintilimab in combination with pemetrexed plus platinum chemotherapy.

Exploratory endpoints:

- Efficacy of sintilimab in subjects per the immune Response Evaluation Criteria in Immune Solid Tumors (iRECIST);

- Population pharmacokinetic characteristics of sintilimab;
- Biomarkers that can potentially predict the efficacy of sintilimab arm including, but not limited to, PD-L1 expression, and RNA in tumor specimens, circulating tumor DNA (ctDNA) and T cell receptor (TCR) in peripheral blood ;
- Quality of life of subjects between sintilimab plus chemotherapy and placebo plus chemotherapy by LCSS and EORTC QLQ-C30 (V3.0 Chinese version) scale;
- PFS in the sintilimab arm receiving subsequent antineoplastic therapy after disease progression versus placebo arm crossing over to receive sintilimab.

9.4.1 Statistical Analysis General Method

All statistical analysis will be generated using SAS version 9.2 or higher. All statistical tests will be performed using two-sided α of 0.05, and 95% confidence interval will be used.

In this study, drug administration will be statistically analyzed to calculate the drug exposure throughout the study. Baseline data will be analyzed according to full analysis set. All efficacy endpoints will be analyzed according to full analysis set and per protocol set (based on the randomized treatment). Safety analysis set will be used for safety analysis (based on the actual treatment). If a subject receives incorrect medication in one cycle but receives the correct medication in all other cycles, the subject will be assigned to the correct treatment group for safety analysis.

Measurement data of each visit will be statistically described using mean ± standard deviation or median (minimum, maximum). The enumeration data of each visit in the groups will be statistically described using frequency (composition ratio).

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

9.4.1.1 Analysis of primary endpoint indicators

- PFS

PFS: 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.

A p-value by stratified log-rank test will also be provided for PFS. The HR and its 95% CI will be estimated using the stratified Cox proportional hazards regression model. Stratification factors (gender, PD-L1 expression level, platinum), age (> 60, ≤60), smoking (former/current smoker, non-smoker), number of organs with metastatic lesions (>2, ≤2), and other significant covariates will be considered in the model, and their HR and 95% CI will be estimated. Median PFS and its 95% CI will be estimated using the Kaplan-Meier method, and survival curves will be plotted.

9.4.1.2 Analysis of secondary endpoint indicators:

- ORR

$ORR = \frac{CR + PR\text{Subjects}}{Total Subjects} * 100\%$ Binomial distribution will be used to calculate 95% CI.

- DCR

$DCR = \frac{CR + PR + SD Subjects}{Total Subjects} * 100\%$ Binomial distribution will be used to calculate 95% CI.

The calculation of objective response rate and disease control rate is based on the optimal efficacy assessment of the second confirmed tumor during the study.

- OS

OS: 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 is known to be alive or at the study cut-off date, whichever is earlier.

A p-value by stratified log-rank test will be provided for OS. The HR and its 95% CI will be estimated using the stratified Cox proportional hazards regression model. Stratification factors (gender, PD-L1 expression level, platinum), age (> 60, ≤60), smoking (former/current smoker, non-smoker), number of organs with metastasis (> 2, ≤2), and other significant covariates will be considered in the model, and their HR and 95% CI will be estimated. Median OS and its 95% CI will be estimated using the Kaplan-

Meier method, and survival curves will be plotted.

Given that subjects in the placebo plus chemotherapy group can cross over to receive sintilimab monotherapy after disease progression, the effect of crossover on OS will be adjusted using accepted statistical methods. For example, subjects undergoing crossover will be censored at the time of crossover using a 2-step approach or the Rank Preservation Structure Failure Time (RPSFT) method proposed by Robin and Tsiatis[8] after checking for methodological assumptions/applicability based on the data obtained.

- Quality of life scores of subjects in both groups

According to the scores of LCSS and EORTC QLQ-C30 (V3.0, Chinese version), the quality of life of the two groups will be analyzed.

9.4.2 Safety Analysis

Safety analysis will be based on the SS population. Analysis of safety will include adverse events, clinical laboratory variables, vital signs, ECG, immunogenicity and other safety variables. Data will be summarized by treatment groups, and all adverse events from both treatment groups will be summarized. For subjects in the placebo plus chemotherapy group who cross over to receive sintilimab, the primary safety analysis will only be performed until the time of the cross over (e.g., for the placebo plus chemotherapy group, AEs during the period with sintilimab will not be involved in the analysis). Exploratory analysis will be performed on safety data from the first administration of sintilimab in subjects who crossover to the sintilimab monotherapy group.

Safety analysis: The exposure of subjects to the study drug will be summarized. The subject number of completing X cycles, the dose adjustment during treatment, and the cumulative number of dose adjustments during treatment will be summarized.

The cumulative incidence of adverse events, adverse events leading to withdrawal from the study, adverse events leading to death and serious adverse events will be summarized. The severity of adverse events: if the same subject has experienced the same adverse event many times, the most serious one will be counted for analysis; if the same subject has experienced different adverse events, the most serious adverse event will be counted for analysis.

9.4.2.1 Drug Exposure

Summarize the study drug exposure and administration time (number of cycles) of

subjects during the study.

9.4.2.2 Adverse Events

All adverse events will be coded using MedDRA.

The incidence (frequency) and severity (according to NCI CTCAE Version 4.03) of adverse events (AEs), treatment-emergent adverse events (TEAEs), adverse drug reactions (ADRs), serious adverse events (SAEs), AEs leading to discontinuation, etc. will be summarized by system organ class and preferred term in the MedDRA code.

Subjects who discontinue treatment due to an AE, subjects who experience an SAE, and subjects who die due to an AE will be tabulated (including at least the AE start date and end date, severity, relationship with drug, action taken, and outcome).

9.4.2.3 Laboratory Tests

Hematology, blood biochemistry and other indicators, mean ± standard deviation, maximum, minimum and median will be used to describe measured values and changes before and after treatment. Cross classification table will be used to describe normal and abnormal changes before and after treatment.

Urinalysis: Cross classification table will be used to describe normal and abnormal changes before and after treatment.

The proportion of subjects with changes that are abnormal and clinically significant will be described, in which the investigator will judge whether the abnormality is clinically significant or not.

A list of subjects with laboratory abnormalities (with or without clinical significance) after treatment will be provided.

9.4.2.4 Immunogenicity Indicators

The positive rates of anti-drug antibody (ADA) and neutralizing antibody (NAb) will be calculated and summarized using descriptive statistical analysis. Antibody levels of positive subjects will be described.

9.4.2.5 ECG Examination

The changes of ECG indicators from baseline will be descriptively analyzed. Cross classification table will be used to describe the normal and abnormal ECG changes before

and after treatment, and data lists will be provided.

9.4.2.6 Vital signs, Physical examination, and Other safety related examinations

Vital signs and changes from baseline will be descriptively analyzed.

Subjects with abnormal changes from baseline in physical examination will be listed.

9.4.3 Compliance Analysis

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

The proportion of subjects whose study drug dose is 80% ~ 120% of the dose specified in the protocol will be calculated.

The proportion of subjects completing the study and proportion of subjects completing different treatment cycles will be summarized.

9.4.4 Baseline Characteristics of Subjects

Demographic characteristics (gender, age) of subjects, diagnosis and treatment information of diseases with indications (tumor type, pathological diagnosis, clinical stage, previous treatment), tumor baseline detection (number of target lesions, non-target lesions, site, total diameter, etc.), other baseline information: height and weight (body mass index, body surface area), vital signs, ECOG PS score, laboratory tests, previous/new concomitant medication and etc will be descriptively analyzed.

9.4.5 Interim Analysis

An interim analysis will be conducted during the study when 70% PFS events occur. The objective of the interim analysis is to establish the superiority of sinitilimab in combination with chemotherapy over placebo in combination with chemotherapy in PFS. The interim analysis report will be reviewed by IDMC. The IDMC will make recommendation on whether the study result can be submitted in advance for application based on whether the interim results of this study meet the pre-specified efficacy boundary. IDMC charter will be finalized and approved before the interim analysis. If the study continues, the IDMC will periodically review and evaluate the safety data of the study until the final analysis of this study.

9.4.6 Subgroup Analysis

Subgroup analysis of antitumor activity (objective response rate) will be based on factors that are clinically considered to potentially affect prognosis such as gender, age, ECOG PS score and ect.

9.4.7 Adjustment for Multiple Comparisons and Multiplicity

The study includes a primary study endpoint of PFS (assessed by IRRC). An interim analysis is planned in this study when 70% of total PFS events (184 events) occur, and the primary interim analysis will be based on PFS. The O'Brien-Fleming spending function will be used to adjust alpha value for the interim analysis. The two-sided p-value for the interim analysis will be 0.015 (corresponding to a HR of 0.683) and the p-value for the final analysis will be 0.046. The overall false positive rate will be controlled at a level of 0.05.

All other analyses, unless otherwise specified, will be evaluated at a level of 0.05 (two-sided).

9.4.8 Data Lists of Responsive Subjects

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

9.4.9 Exploratory Analysis

Parameters such as iORR, iDOR, iPFS and iDCR are included in the clinical benefit evaluation based on iRECIST (see Section 9.4.1 for analytical methods).

The overall baseline PD-L1 expression (<1%，≥1%), the proportion of subjects with different expression levels, and the corresponding ORR and DOR will be descriptively analyzed.

Population PK profile of sintilimab in advanced non-squamous NSCLC population will be analyzed using nonlinear mixed effects model.

10. Quality Assurance and Quality Control

According to the GCP guidelines, the Sponsor is responsible for implementing and maintaining the quality assurance and quality control system per corresponding standard operating procedures, to ensure that the study is implemented and the authentic data is

collected, documented, and reported in accordance with the requirements of the protocol, GCP, and applicable regulations.

10.1 Clinical Monitoring

The Sponsor or CRO authorized by the Sponsor will conduct clinical monitoring of the study. The CRA should conduct monitoring according to the standard operating procedures of the Sponsor or CRO, and have the same rights and responsibilities as the Sponsor's inspector. The inspector should maintain regular communication with the investigator and the Sponsor.

Prior to the start of the study, the inspector will assess the competence of each local site and report problems with facilities, technical equipment, or medical personnel to the Sponsor. During the study, the inspector will be responsible for monitoring whether the investigator has obtained written informed consent from all subjects and whether the data records are correct and complete. The inspector will also compare the data entered into the eCRF with the raw data and inform the investigator of any errors or omissions. The inspector will also control protocol compliance at the local site, arrange for the supply of study drugs, and ensure that the drugs are kept in appropriate conditions.

Monitoring visits will be conducted in accordance with applicable laws and regulations. Each site will receive periodic monitoring visits from the time of subject enrollment. The inspector should submit a written report to the Sponsor after each visit to the investigator.

10.2 Data Management/Coding

An electronic data capture (EDC) system will be used for this study and study data will be entered into the eCRF by the investigator or its authorized study personnel. Prior to the initiation of the study or data entry, the investigator and its authorized study personnel should be properly trained and appropriate safety measures should be taken for the computer and other equiments.

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 conditions of the subjects. To avoid variations in outcome evaluations by different evaluators, it is recommended that the baseline and all subsequent efficacy and safety evaluations of a given subject should be performed by the same individual. The

investigators are required to review the data to ensure the accuracy and correctness of all the data entered into the eCRFs. If no evaluations are conducted during the study, or some information obtained are not evaluable, not applicable, or unknown, the investigators should record the above information in the eCRFs. The investigator should sign the verified data electronically.

The CRA will review the eCRFs and evaluate the completeness and consistency by comparing them with the original document, ensuring consistency of key data. Data entry, corrections, and modifications should be performed by the investigator or 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 modifications. The roles and permission levels of the personnel responsible for data entry in the study site will be determined in advance. The CRA or data management personnel may raise a query in the EDC for suspicious data. The study site personnel are responsible for dealing with such query. The EDC system will record the audit trail of the query, including the investigator name, time, and date.

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

The investigator is responsible for the maintenance of all source documents and should 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 identities (including the subjects' names) should be deleted or made illegible to protect the privacy of the subjects. The investigator verifies that the record has been reviewed and ensures the accuracy of the recorded data by using an electronic signature. The electronic signature should be completed using the investigator's user ID and password. The system will automatically attach the date and time for signing to the signature. The investigator cannot share his/her user ID and password with others. If the data in the eCRFs is required to be changed, the change should be performed according to the procedure outlined by the EDC system. All the

changes and corresponding reasons should be recorded in the audit trail.

AEs and concomitant diseases/history should be coded. The dictionary used for coding will be described in the CSR.

10.3 Quality Assurance Audits

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

The Sponsor's quality assurance department will audit the clinical study sites. The audits include the supply of drugs, required trial documents, records of the informed consent process, as well as the consistency of the CRFs with the source documents. The content and scope of the audit can also be increased as the circumstances require. After reasonable notice, the investigator should allow auditors commissioned by the Sponsor and the regulatory authorities access to the site so that they can conduct inspections. The primary purpose of an audit or an inspection is to verify that the rights or health of the trial subjects are protected, the informed consent form is properly signed, the trial process is correctly implemented, and all data related to the evaluation of the investigational drug is collected and, if necessary, reported. In addition, the audit will ensure that ethical standard operating procedures, GCP and applicable regulatory requirements are used. The investigators should have direct accesses to all trial files, original records, and raw data.

11. Ethics

11.1 Ethics Committee

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

approval of the study.

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

11.2 Ethics of this Study

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

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

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

11.3 Subject Information and Informed Consent

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

It is the responsibility of the investigator to explain the content of the informed consent to the subject and to obtain a signed and dated informed consent form from the subject or the subject's legally acceptable representative prior to the start of the study. After signing, the investigator should send the subject a copy of the signed informed

consent form. The investigator should record the informed consent process in the study source documents.

11.4 Data Protection for Subjects

Information on data protection and privacy protection will be included (or in some cases, along with the use of separate files) in the ICF.

Take preventive measures to ensure the confidentiality of the document and prevent the identification of the subject. However, under special circumstances, some people may see a subject's genetic data and personal identification number. For example, in the event of medical emergency, the Sponsor, its physician or investigator may know the subject identification number and have access to the subject's genetic data. In addition, relevant regulatory authorities may require access to relevant documents.

12. Study Management

12.1 Data Processing and Record Keeping

The documents in the clinical study (protocol and protocol amendment, completed eCRF, signed ICF, etc.) should be preserved and managed according to the requirements of GCP. The site will retain these documents for 5 years after the end of the study.

Study documents should be reasonably maintained for later access or data traceability. Safety and environmental risks should be considered when saving documents.

No study documents may be destroyed without the written permission of the Sponsor and the investigator. The investigator/local site will forward the study documents to another party who complies with the document retention requirements or to another location that meets the requirements for retention only after notification to and written consent from the Sponsor.

12.2 Access to Raw Data/Documents

The investigator agrees that the Sponsor, CRO and relevant authorized regulatory authorities will have direct access to all study-related documents, including the subject's medical records.

12.3 Protocol Amendment

Any potentially appropriate amendments to the protocol during the conduct of the

study will be communicated and agreed by the Sponsor to the investigator. The Sponsor should ensure timely submission of protocol amendments to the regulatory authority.

All amendments to the protocol should be kept as protocol amendments. Any amendment to the protocol should be submitted to the Ethics Committee for approval or filing according to the regulations of the Ethics Committee. If necessary, it should also be submitted to the regulatory authority for review and approval, and can be implemented only after approved by EC and regulatory authority (if necessary) (except for changes to the protocol to eliminate immediate hazards to study subjects).

12.4 Responsibilities of Investigators

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

The detailed responsibilities of relevant investigators are listed in Chapter 5 (Responsibilities of Investigators) of China GCP (CFDA Order No. 3).

12.5 Publication Policy

All data generated from this study are confidential information of the Sponsor. The Sponsor has the right to publish the study results. Information regarding the Sponsor's and investigator's publication policy will be described in the clinical study agreement.

All information related to this study (not limited to the following documents: protocol, Investigator's Brochure) must be kept strictly confidential. The investigator must recognize that the scientific or medical information derived from this study may be of commercial value to the Sponsor. The investigator should keep the information and data related to this study confidential. In order to publish the information related to this study or the conclusions drawn from the study, it is necessary to negotiate with the Sponsor in advance and obtain the written consent of the Sponsor. In order to protect their rights and interests, the Sponsor may require the investigator not to publish the information about the study before the product is approved.

The Sponsor has the right to publish the information or data related to this study or submit it to the drug administration department. If the Sponsor needs to display the name of the investigator in a publication or advertisement, the consent of the investigator should be obtained.

12.6 Finance and Insurance

The Sponsor will purchase insurance for subjects participating in this study in accordance with local regulations and minimum requirements. The terms of the insurance will be maintained in the study binder.

13. References

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14. Appendix

Appendix 1: ECOG PS

Grade	ECOG DESCRIPTION
0	Asymptomatic, fully active, and able to carry on performance without restriction
1	Symptomatic, restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	Symptomatic, ambulatory and capable of all selfcare but unable to carry out any work activities, awake more than 50% of the time (< 50% of bed time during the day)
3	Symptomatic, capable of only limited selfcare, confined to bed or chair for > 50% of waking hours, but not yet bedridden
4	Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair
5	Dead

Appendix 2: Calculation of creatinine clearance and body surface area

Creatinine Clearance by Cockcroft-Gault Formula

Formula for calculating serum creatinine concentration (mg/dL):

$$\text{Creatinine clearance in men (mL/min)} = \frac{(140 - \text{age}) \times (\text{weight})^{a}}{72 \times \text{serum creatinine}}$$

$$\text{Creatinine clearance in women (mL/min)} = \frac{0.85 \times (140 - \text{age}) \times (\text{weight})^{a}}{72 \times \text{serum creatinine}}$$

Formula for calculating serum creatinine concentration (μ mol/L):

$$\text{Creatinine clearance in men (mL/min)} = \frac{(140 - \text{age}) \times (\text{weight})^{a}}{0.81 \times \text{serum creatinine}}$$

$$\text{Creatinine clearance in women (mL/min)} = \frac{0.85 \times (140\text{-age}) \times (\text{weight})^{A}}{0.81 \times \text{serum creatinine}}$$

a: Age in years and weight in kg.

Formula for calculating body surface area

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

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

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

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 more than 5 mm)
- 10 mm by conventional instruments in clinical exam (lesions which cannot be accurately measured by calipers should be recorded as non-measurable)
- 20 mm by chest X-ray
- Malignant lymph nodule: pathologically enlarged and measurable, single lymph nodule must be ≥ 15mm in short axis by CT scan (CT scan slice thickness no greater than 5 mm). At baseline and during follow-up, only the short axis will be measured and followed.

1.1.2 Non-measurable

All other lesions, including small lesions (longest diameter <10 mm or pathological lymph nodule with ≥ 10 mm 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 that cannot be diagnosed and followed by reproducible imaging techniques, and cystic lesions.

1.1.3 Special considerations regarding lesion measurability

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

Bone lesions:

1) Bone scan, PET scan or plain films are not considered adequate to measure bone 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 subject, 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. Measurements of lesions

All measurements should be recorded in metric notation when clinically assessed. All baseline measurements of tumor lesions should be performed as close as possible to the treatment start and must be within 28 days (4 weeks) 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 being followed cannot be imaged but is assessable by clinical exam.

Clinical lesions: Clinical lesions will only be considered measurable when they are superficial and ≥ 10 mm diameter (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. 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. 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. When CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situations (e.g. for body scans).

Ultrasound: Ultrasound should not be used as a method of measurement to assess lesion size. Ultrasound examinations cannot be reproduced for 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, 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. This means that when lymph nodes are included as target lesions, the "sum" of lesions may not be zero even if complete response criteria are met, since a normal lymph node is defined as having a short axis of < 10 mm Electronic CRFs 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 become too small to measure: While on study, all lesions (nodal and non-nodal) recorded at baseline should have their actual measurements recorded at each subsequent evaluation, even when very small (e.g. 2 mm). However, sometimes lesions or lymph nodes which are recorded as target lesions at baseline become so faint on CT scan that the radiologist may not feel comfortable assigning an exact measure and may report them as being "too small to measure". When this occurs it is important that a value be recorded on the case report form. If it is the opinion of the radiologist that the lesion has likely disappeared, the measurement should be recorded as 0 mm. If the lesion is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned. (Note: It is less likely that this rule will be used for lymph nodes since they usually have a definable size when normal and are frequently surrounded by fat such as in the retroperitoneum; however, if a lymph node is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned in

this circumstance as well). This default value is derived from the 5 mm CT slice thickness (but should not be changed with varying CT slice thickness). The measurement of these lesions is potentially non-reproducible, therefore providing this default value will prevent false responses or progressions based upon measurement error. To reiterate, however, if the radiologist is able to provide an actual measure, that should be recorded, even if it is below 5 mm.

Lesions that split or coalesce on treatment: When non-nodal lesions "fragment", the longest diameters of the fragmented portions should be added together to calculate the target lesion sum. Similarly, as lesions coalesce, a plane between them may be maintained that would aid in obtaining maximal diameter measurements of each individual lesion. If the lesions have truly coalesced such that they are no longer separable, the vector of the longest diameter should be the maximal longest diameter for the coalesced lesion.

2.3 Evaluation of non-target lesions

This section provides the definitions of the criteria used to determine the tumor response of 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): Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (< 10 mm short axis).

Non-Complete Response/Non-Progressive Disease (Non-CR/Non-PD): Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits.

Progressive Disease (PD): Unequivocal progression of existing non-target lesions. Note: the appearance of one or more new lesions is also considered progression.

2.4 Special notes on assessment of progression of non-target disease

The concept of progression of non-target disease requires additional explanation as follows: When the subject also has measurable 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. A modest "increase" in the size of one or more non-target

lesions is usually not sufficient to qualify for unequivocal progression status. The designation of overall progression solely on the basis of change in non-target disease in the face of SD or PR of target disease will therefore be extremely rare.

When the subject only has non-measurable disease: This circumstance arises in some phase III trials when it is not a criterion of study entry to have measurable disease. The same general concepts apply here as noted above, however, in this instance there is no measurable disease assessment. Because worsening in non-target disease cannot be easily quantified (by definition: if all lesions are truly non-measurable) a useful test that can be applied when assessing subjects for unequivocal progression is to consider if the increase in overall disease burden based on the change in non-measurable disease is comparable in magnitude to the increase that would be required to declare PD for measurable disease: i.e. an increase in tumor burden representing an additional 73% increase in "volume" (which is equivalent to a 20% increase diameter in a measurable lesion). Examples include an increase in a pleural effusion from "trace" to "large", an increase in lymphangitic disease from "localized" to "widespread", or may be described in protocols as "sufficient to require a change in therapy". Examples include an increase in a pleural effusion from "trace" to "large", an increase in lymphangitic disease from "localized" to "widespread", or may be described in protocols as "sufficient to require a change in therapy". If "unequivocal progression" is seen, the subject should be considered to have had overall PD at that point. While it would be ideal to have objective criteria to apply to non-measurable disease, the increase must be substantial.

2.5 New lesions

The appearance of new malignant lesions denotes disease progression; therefore, some comments on detection of new lesions are important. There are no specific criteria for the identification of new radiographic lesions; however, the finding of a new lesion should be unequivocal. For example, progression should not be attributable to differences in scanning technique, change in imaging modality or findings thought to represent something other than tumor (for example, some "new" bone lesions may be simply healing or flare of pre-existing lesions) This is particularly important when the subject’s baseline lesions show partial or complete response. For example, necrosis of a liver lesion may be reported on a CT scan report as a "new" cystic lesion, which it is not.

A lesion identified on a follow-up study in an anatomical location that was not scanned at baseline is considered a new lesion and will indicate PD. An example of this is the

subject who has visceral disease at baseline and while on study has a CT or MRI brain ordered which reveals metastases. The subject'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 equivocal, for example because of its small size, continued therapy and follow-up evaluation will clarify if it represents truly new disease. If repeat scans confirm there is definitely a new lesion, then progression should be declared using the date of the initial scan.

While FDG-PET response assessments need additional study, it is sometimes reasonable to incorporate the use of FDG-PET scanning to complement CT scanning in assessment of progression (particularly possible "new" disease). New lesions on the basis of FDG-PET imaging can be identified according to the following algorithm:

Negative FDG-PET at baseline, with a positive FDG-PET at follow-up is a sign of PD based on a new lesion.

No FDG-PET at baseline and a positive FDG-PET at follow-up:

If the positive FDG-PET at follow-up corresponds to a new site of disease confirmed by CT, this is PD.

If the positive FDG-PET at follow-up is not confirmed as a new site of disease on CT, additional follow-up CT scans are needed to determine if there is truly progression occurring at that site (if so, the date of PD will be the date of the initial abnormal FDG-PET scan).

If the positive FDG-PET at follow-up corresponds to a pre-existing site of disease on CT that is not progressing on the basis of the anatomic images, this is not PD.

2.6 Missing assessments and inevaluable designation

When no imaging/measurement is done at all at a particular time point, the subject is not evaluable (NE) at that time point. If only a subset of lesion measurements are made at an assessment, usually the case is also considered NE at that time point, unless a convincing argument can be made that the contribution of the individual missing lesion(s) would not change the assigned time point response.

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. This

measurement should be recorded even though the nodes are normal in order not to overstate progression should it be based on increase in size of the nodes. As noted earlier, this means that subjects with CR may not have a total sum of "zero" on the eCRF.

In trials where confirmation of response is required, repeated "NE" time point assessments may complicate best response determination. The analysis plan for the trial must address how missing data/assessments will be addressed in determination of response and progression. For example, in most trials it is reasonable to consider a subject with time point responses of PR-NE-PR as a confirmed response.

Subjects with a global deterioration of health status requiring discontinuation of treatment without objective evidence of PD at that time should be reported as "symptomatic deterioration". Every effort should be made to document objective progression even after discontinuation of treatment. Symptomatic deterioration is not a descriptor of an objective response: it is a reason for stopping study therapy. The objective response status of such subjects is to be determined by evaluation of target and non-target disease as shown in 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).

In some circumstances it may be difficult to distinguish residual disease from normal tissue. When the evaluation of complete response depends upon this determination, a biopsy of the residual lesion is recommended before assigning a status of complete response. FDG-PET may be used to upgrade a response to a CR in a manner similar to a biopsy in cases where a residual radiographic abnormality is thought to represent fibrosis or scarring. The use of FDG-PET in this circumstance should be prospectively described in the protocol and supported by disease specific medical literature for the indication. However, it must be acknowledged that FDG-PET and biopsy may lead to false positive CR due to limitations of both approaches (resolution/sensitivity).

Table 1. Time point response: subjects with target (with or without non-target) disease.

Target Lesions	Non-Target Lesions	New Lesions	Overall Response
CR	CR	No	CR
CR	Non-CR/Non-PD	No	PR
CR	Not evaluated	No	PR

PR	Non-PD or not all evaluated	No	PR
SD	Non-PD or not all evaluated	No	SD
Not all evaluated	Non-PD	No	NE
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD
CR = complete response	PR = partial response	SD = stable disease	PD = progressive disease NE = inevaluable

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

Non-Target Lesions	New Lesions	Overall Response
CR	No	CR
Non-CR/Non-PD	No	Non-CR/Non-PD
Not all evaluated	No	Not evaluated
Unequivocal PD	Yes or No	PD
Any	Yes	PD

Note: "Non-CR/non-PD" is preferred over "stable disease" for non-target disease. Since SD is increasingly used as endpoint for assessment of efficacy in some trials so to assign Non-CR/non-PD when no lesions can be measured is not advised.

For equivocal findings of progression (e.g. very small and uncertain new lesions; cystic changes or necrosis in existing lesions), treatment may continue until the next scheduled assessment. If at the next scheduled assessment, progression is confirmed, the date of progression should be the earlier date when progression was suspected.

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

Overall response first time point	Overall response subsequent time point	Best overall response
CR	CR	CR
CR	PR	SD, PD, or PR[a]
CR	SD	SD provided minimum criteria for SD duration met, otherwise, PD
CR	PD	SD provided minimum criteria for SD

		duration met, otherwise, PD
CR	NE	SD provided minimum criteria for SD duration met, otherwise, NE
PR	CR	PR
PR	PR	PR
PR	SD	SD
PR	PD	SD provided minimum criteria for SD duration met, otherwise, PD
PR	NE	SD provided minimum criteria for SD duration met, otherwise, NE
NE	NE	NE

Note: CR = complete response, PR = partial response, SD = stable disease, PD = progressive disease, and 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). Best response would depend on whether minimum duration for SD is met. However, sometimes "CR" may be claimed when subsequent scans suggest small lesions were likely still present and in fact the subject had PR, not CR at the first time point. Under these circumstances, the original CR should be changed to PR and the best response is 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 r studies where stable disease or progression 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 duration of overall response is measured from the time measurement criteria are first met for CR/PR (whichever is first recorded) until the first date that recurrent or PD is objectively documented (taking as reference for PD the smallest measurements recorded on study). The duration of overall complete response is measured from the time

measurement criteria are first met for CR until the first date that recurrent disease is objectively documented.

2.8.3 Duration of SD

Stable disease 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 relevance of the duration of SD varies in different studies and diseases. If the proportion of subjects achieving stable disease for a minimum period of time is an endpoint of importance in a particular trial, the protocol should specify the minimal time interval required between two measurements for determination of stable disease.

Note: The duration of response and stable disease as well as the progression-free survival are influenced by the frequency of follow-up after baseline evaluation. It is not in the scope of this guideline to define a standard follow-up frequency. The frequency should take into account many parameters including disease types and stages, treatment periodicity and standard practice. However, these limitations of the precision of the measured endpoint should be taken into account if comparisons between trials are to be made

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

iRECIST: Efficacy Assessment Guidelines for Use in Clinical Trials Evaluating Immunotherapy (Appendix) (excerpt)

1. Evaluation of iRECIST efficacy

Immunotherapy may promote the infiltration of immue cells, leading to a temporary increase in the volume of tumors or detection of undetectable diseases. This criterion is identical to RECIST 1.1 in many respects, but it has been adjusted to assess cases that may not reflect the true progress of tumors, such as increased tumor load or new lesions.

The key differences are described below. All efficacy indicators assessed with iRECIST are prefixed with the prefix "i". The efficacy and best overall efficacy of iRECIST at each time point will be recorded separately.

1.1 Confirmed Progression

Unlike RECIST 1.1, iRECIST requires the confirmation of progression to rule out or confirm pseudoprogression. iRECIST defines iUPD (unconfirmed progression) and iCPD (confirmed progression). Scans to confirm progression can be performed as early as 4 weeks after iUPD and not later than 8 weeks after iUPD.

Progressive disease is confirmed (iCPD) if the next imaging assessment confirms further increase in lesion size from last asseesment. The specific evidence refers to the following items:

- On the basis of disease progression (compared with the lowest point) of target, non-target or new lesions defined by RECIST 1.1, the tumor burden continues to increase.
  - Target lesions deteriorated, showing an absolute increase of at least 5 mm in the sum of measurements.
  - The progression of non-target lesions is clear, showing an increase in tumor load.
  - Englargement of new lesions (absolute increase of the sum of new target lesions by at least 5 mm) or discovery of other new lesions.

- Other lesions (target lesions, non-target lesions or new lesions) that had not previously been found to progress were in line with RECIST 1.1 progress criteria, including the detection of other new lesions.

If iUPD is not confirmed in the next evaluation, the outcome of the corresponding efficacy evaluation will be recorded (if it still meets iUPD and does not deteriorate, recorded as iUPD; if it meets iSD, iPR or iCR criteria compared with baseline, then recorded as iSD, iPR or iCR, respectively). As shown in Table 2, in the case that the next efficacy evaluation of iUPD did not reach iCPD, previous iUPD did not affect the recording of iCR, iPR or iSD at subsequent evaluation time points or at the best overall efficacy.

1.2 New lesions

New lesions should be measured and evaluated according to RECIST 1.1 criteria (up to 5 lesions, no more than 2 lesions per organ and at least 10 mm in the longest diameter, at least 15 mm in the short diameter of lymph node lesions). They should be clearly recorded as new target lesions and new non-target lesions to distinguish them from baseline target lesions and non-target lesions.

New lesions should be in line with the definition of new target lesions and new non-target lesions so as to be defined as iUPD (or iCPD). The measurements of such target lesions should not be counted into the sum of measurements of target lesions defined at baseline. Measurements of these new target lesions should be recorded in a separate CRF.

Disease progression of new lesions can be confirmed in the following cases:

imaging evaluation performed at least 4 weeks (not more than 8 weeks) after iUPD found that the absolute value of the sum of new target lesions increased by at least 5 mm or the volume of new non-target lesions increased (no clear increase) or other lesions appeared.

The best overall immune response (iBOR) for all patients from the beginning of treatment to the end of treatment will be defined according to Table 3.

2. Response and disease stabilization time (RECIST v1.1 and iRECIST)

The response time will be counted from the time that the CR/PR or iCR/iPR criteria are met (whichever happens first) until recurrence or disease progression. The minimum

measurements (including baselines) during the study period are also recorded for reference.

The duration of disease stabilization will be counted from the start of treatment until the disease progresses, and the minimum measurements (including baselines) during the study period will also be recorded for reference.

Table 1. Comparison of RECIST v1.1 and iRECIST

	RECIST 1.1	iRECIST
Definitons of measurable and non-measurable disease; numbers and site of target disease	Measurable lesions are 10 mm in diameter (15 mm for nodal lesions); maxium of five lesions (2 per organ); all other disease is considered non-target (must be 10 mm in short axis for nodal disease)	No change from RECIST 1.1; however, new lesions are assessed as per RECIST 1.1 but are recorded separately on the case report form (but not included in the sum of lesions for target lesions identified at baseline)
Complete response, partial response , or stable disease	Cannot have met criteria for progression before complete response, partial response, or stable disease	Can have had iUPD (one or more instances), but not iCPD, before iCR, iPR, or iSD
Confirmation of complete response or partial response	Only required for non-randomised trials	As per RECIST 1.1
Confirmation of stable disease	Not required	As per RECIST 1.1
New lesions	Result in progression; recorded but not measured	Results in iUPD but iCPD is only assigned on the basis of this category if at next assessment additional new lesions appear or an increase in size of new lesions is seen (5 mm for sum of new lesion target or any increase in new lesion non-target); the appearance of new lesions when none have previously been recorded, can also

		confirm iCPD.
Independent blinded review and central collection of scans	Recommended in some circumstances—eg, in some trials with progression-based endpoints planned for marketing approval	Collection of scans (but not independent review) recommended for all tirals.
Confirmation of progression	Not required (unless equivocal)	Required
Consideration of clinical status	Not included in assessment	Clinical stability is considered when deciding whether treatment is continued after iUPD

CR: Complete Response; PR: Partial Response; SD: Stable Disease; PD: Progressive Disease; iCR: Immune Complete Response; iPR: Immune Partial Response; iSD: Immune Stable Disease; iUPD: Immune Unconfirmed Progression; iCPD: Immune Confirmed Progression.

Table 2. Assignment of timepoint response per iRECIST

	Timepoint response with no previous iUPD in any category	**Timepoint response with previous iUPD in any category***
Target lesions: i CR; non-target lesions: iCR; new lesions: no	iCR	iCR
Target lesions: iCR; non-target lesions: non-iCR/non-iUPD; new lesions: no	iPR	iPR
Target lesions: iPR; non-target lesions: non-iCR/non-iUPD; new lesions: no	iPR	iPR
Target lesions: iSD; non-target lesions: non-iCR/non-iUPD; new lesions: no	iSD	iSD
Target lesions: iUPD with no change, or with a decrease from last timepoint; non-target lesions: iUPD with no change, or decrease from last timepoint; new lesions: yes	Not applicable	New lesions confirm iCPD if new lesions were previously identified and they have increased in size (≥ 5 mm in sum of measures for new lesion target or any increase for new lesion non-target) or number; if no change is seen in new lesions (size or number) from last timepoint, assignment remains iUPD

	Timepoint response with no previous iUPD in any category	**Timepoint response with previous iUPD in any category***
Target lesions: iSD, iPR, iCR; non-target lesions: iUPD; new lesions: no	iUPD	Remains iUPD unless iCPD is confirmed on the basis of a further increase in the size of non-target disease (does not need to meet RECIST 1.1 criteria for unequivocal progression)
Target lesions: iUPD; non-target lesions: non-iCR/non-iUPD, or iCR; new lesions: no	iUPD	Remains iUPD unless iCPD is confirmed on the basis of a further increase in sum of measures ⩾ 5 mm; otherwise, assignment remains iUPD
Target lesions: iUPD; non-target lesions: iUPD; new lesions: no	iUPD	Remains iUPD unless iCPD is confirmed based on a further increase in previously identified target lesion iUPD in sum of measures > 5 mm or non-target lesion iUPD (previous assessment need not have shown unequivocal progression)
Target lesions: iUPD; non-target lesions: iUPD; new lesions: yes	iUPD	Remains iUPD unless iCPD is confirmed on the basis of a further increase in previously identified target lesion iUPD sum of measures ⩾ 5 mm, previously identified non-target lesion iUPD (does not need to be unequivocal), or an increase in the size or number of new lesions previously identified
Target lesions: non-iUPD or progression; non-target lesions: non-iUPD or progression; new lesions: yes	iUPD	Remains iUPD unless iCPD is confirmed on the basis of an increase in the size or number of new lesions previously identified

ICR: immunologic complete response; iPR: immunologic partial response; iSD: immunologic stable disease; iUPD: immunologic unconfirmed progression; iCPD: immunologic confirmed progression; SOM: sum of measurements; NA: not applicable: NE: not assessable.

Table 3. Best Overall Response per iRECIST Criteria

Best overall response					
Timepoint response 1	Timepoint response 2	Timepoint response 3	Timepoint response 4	Timepoint response 5	Immune Best Overall

					Response
iCR	iCR, iPR, iUPD, NE	iCR, iPR, iUPD, NE	iUPD	iCPD	iCR
iUPD	iPR, iSD, NE	iCR	iCR, iUPD, NE	iCR, iPR, iSD, iUPD, iCPD, NE	iCR
iUPD	iPR	iPR, iSD, iUPD, NE	iPR, iSD, iUPD, NE, iCPD	iPR, iSD, iUPD, NE, iCPD	iPR
iUPD	iSD, NE	iPR	iPR, iSD, iUPD, NE	iPR, iSD, iUPD, iCPD, NE	iPR
iUPD	iSD	iSD, iUPD, NE	iSD, iUPD, iCPD, NE	iSD, iUPD, iCPD, NE	iSD
iUPD	iCPD	Arbitrary	Arbitrary	Arbitrary	iCPD
iUPD	iUPD (without iCPD)	iCPD	Any	Any	iCPD
iUPD	NE	NE	NE	NE	iUPD

- For example only - more cases may exist but follow the same principle
- This form assumes a randomized study design and does not require confirmation of CR or PR
- For subjects with only non-target lesions at baseline, the evaluation at each time point is only recorded as iCR or non-CR/non-PD, but not shown in the table for convenience

ICR: immunologic complete response; iPR: immunologic partial response; iSD: immunologic stable disease; iUPD: immunologic unconfirmed progression; iCPD: immunologic confirmed progression; SOM: sum of measurements; NA: not applicable: NE: not assessable.

Investigator Statement and Signature Page

Study drug: Recombinant fully human anti-programmed death receptor-1 (PD-1) monoclonal antibody

Study drug code: Sintilimab (R & D code: IBI308)

Trial Name: A Randomized, Double-blind, Phase III Study Evaluating the Efficacy and Safety of Sintilimab or Placebo in Combination with pemetrexed and Platinum-based Chemotherapy in the First-line Treatment of Advanced or Recurrent Non-squamous Non-small Cell Lung Cancer (ORIENT-11)

Approval Letter No.: 2016L08025

Protocol No.: CIBI308C302

Investigator Statement

I have received and read the investigator's Brochure for this study and understood recombinant fully human anti-programmed death receptor-1 monoclonal antibody injection relevant information about the nature, effect, efficacy and safety. I have read and understood the contents of this protocol in detail. It is approved that this clinical study is ethical. I will obtain the consent of relevant departments of my unit.

In accordance with the provisions of GCP, I will earnestly perform the responsibilities of the investigator, agree to carry out this clinical study in accordance with the design and provisions of this protocol, and explain the materials, regulations and responsibilities of the study to all the personnel participating in this study. I will ensure that I have sufficient time to be responsible for and complete this clinical study within the time limit specified in the protocol, and ensure that all relevant information and data will be truthfully, accurately, completely, timely and legally recorded in the medical records and case report forms.

I will strictly abide by the Declaration of Helsinki, explain the details of this clinical study approved by the Ethics Committee to the subjects, and obtain the informed consent. I will be responsible for making medical decisions related to this clinical study and ensuring that subjects receive appropriate treatment for adverse events during the study. If serious adverse events occur during the study, I will immediately take appropriate treatment measures to ensure the safety of subjects and report to the Sponsor.

I agree to accept the monitoring and audit by the inspector or auditor designated by

the Sponsor and the inspection by drug regulatory authorities to ensure the quality of the clinical study.

I agree to keep all information received or obtained in the study related to this protocol confidential.

Clinical study institution: _____

Principal investigator (signature): _____ Date: _____