Clinical Protocol

Study Title:	A Multicenter, Double-Blind, Randomized Phase 3 Clinical Trial Evaluating the Efficacy and Safety of Sintilimab vs. Placebo, in Combination with Chemotherapy, for First-Line Treatment of Unresectable, Locally Advanced, Recurrent, or Metastatic Esophageal Squamous Cell Carcinoma (ORIENT-15)
Protocol Number:	CIBI308A301
Version and Date:	August 26, 2021, Version 4.0
Product Name:	Sintilimab (Recombinant Fully Human Anti-PD-1 Monoclonal Antibody Injection, R&D Code: IBI308)
Study Phase:	3
Sponsor:	Innovent Biologics (Suzhou) Co., Ltd. No. 168 Dongping Street, Suzhou Industrial Park, Jiangsu, China
Sponsor Contact:	[redacted]

Sponsor Signature Page

Protocol Title: A Multicenter, Double-Blind, Randomized Phase 3 Clinical Trial Evaluating the Efficacy and Safety of Sintilimab vs. Placebo, in Combination with Chemotherapy, for First-Line Treatment of Unresectable, Locally Advanced, Recurrent, or Metastatic Esophageal Squamous Cell Carcinoma (ORIENT-15)

Project Number: CIBI308A301

Position	Name	Signature (Print)	Date
Executive Medical Director	[redacted]		
Executive Director, Biostatistics	[redacted]		

Protocol Synopsis

Protocol Number	CIBI308A301
Sponsor	Innovent Biologics (Suzhou) Co., Ltd.
Investigational Drug	Sintilimab (R&D Code: IBI308)
Active Ingredient	Recombinant fully human anti-PD-1 monoclonal antibody
Study Title	A Multicenter, Double-Blind, Randomized Phase 3 Clinical Trial Evaluating the Efficacy and Safety of Sintilimab vs. Placebo, in Combination with Chemotherapy, for First-Line Treatment of Unresectable, Locally Advanced, Recurrent, or Metastatic Esophageal Squamous Cell Carcinoma (ORIENT-15)
Study Phase	3
Study Objectives	Primary Objectives: • To compare overall survival (OS) of sintilimab vs. placebo, in combination with chemotherapy, as first-line treatment in subjects with unresectable, locally advanced, recurrent or metastatic esophageal squamous cell carcinoma (ESCC); • To compare OS of sintilimab vs. placebo, in combination with chemotherapy, as first-line treatment in subjects with PD-L1 positive (CPS ≥10, i.e., combined positive score), unresectable, locally advanced, recurrent or metastatic ESCC. Secondary Objectives: • To compare progression-free survival (PFS), objective response rate (ORR), disease control rate (DCR), and duration of response (DoR) between two treatment arms in the overall ITT population;

	• To compare objective response rate (ORR), progression-free survival (PFS), disease control rate (DCR), and duration of response (DoR) between two treatment arms in subjects with PD-L1 positive (CPS ≥10) ESCC; • To compare safety between the two treatment arms. Exploratory Objectives: • To compare the changes in quality of life between the two treatment arms; • To study the pharmacokinetic (PK) characteristics of sintilimab in combination with chemotherapy in subjects with unresectable, locally advanced, recurrent or metastatic ESCC; • To evaluate the correlation between biomarkers in tumor tissue and efficacy, including PD-L1 expression level.
Study Design	This is a multi-regional, double-blind, randomized Phase 3 clinical trial evaluating the efficacy and safety of sintilimab vs. placebo, in combination with chemotherapy, as first-line treatment in subjects with unresectable, locally advanced, recurrent or metastatic ESCC. An open-label phase is added to the protocol after completion of enrollment in the randomization phase of the study. In the randomization phase, subjects with unresectable, locally advanced, recurrent or metastatic ESCC will be randomly assigned to the sintilimab arm or placebo arm in a 1:1 ratio. A total of 676 subjects will be enrolled, of which 338 subjects will be in the sintilimab arm and the other 338 subjects will be in the placebo arm. Stratification factors include the Eastern Cooperative Oncology Group Performance Status (ECOG PS) score (0 or 1), hepatic metastasis (positive or negative), chemotherapy regimens (TP or CF), and PD-L1 expression (TPS < 10% or ≥ 10%). Chemotherapy regimen and PD-L1 expression status must be determined before randomization or before the first dose administration for the open-label phase. Specifically, approximately 250 subjects will be PD-L1 subjects

	expressing TPS ⩾10% (TPS is defined as the proportion of positive tumor cells). Subjects will be treated with sintilimab (weight < 60 kg: 3 mg/kg IV on Day 1 Q3W; weight ≥ 60 kg: 200 mg IV on Day 1 Q3W) or placebo, in combination with investigator's choice of cisplatin (75 mg/m^2 IV on Day 1 Q3W) plus either paclitaxel (Cycle 1: 87.5 mg/m^2 IV on Day 1 and Day 8 Q3W; from Cycle 2: 175 mg/m^2 IV on Day 1 Q3W) (referred as TP regimen) or fluorouracil (800 mg/m^2 IV continuous infusion over 24 hours daily on Days 1-5 Q3W) (CF regimen). The treatment will repeat every 3 weeks until progressive disease (PD), intolerable toxicity, initiation of new anti-tumor therapy, withdrawal of informed consent, lost to follow-up, death, completion of therapy, or any other investigator-determined reasons for treatment discontinuation (whichever occurs first). A maximum of 6 cycles is recommended for TP regimen and CF regimen, and if tolerated by the subject, the duration of chemotherapy will be determined by the investigator. Treatment with sintilimab or placebo will be infused for a maximum period of 24 months (starting from the first dose). Sintilimab/placebo can be used alone if chemotherapy is intolerable. Chemotherapy will not be allowed to switch between TP and CF regimens during the study. Tumor imaging evaluation will be performed by investigator per RECIST V1.1. Subjects will undergo imaging assessment once Q6W (± 7 days) for 48 weeks during the initial study dosing period, then once Q12W (± 7 days) until disease progression, start of new antineoplastic therapy, withdrawal of consent, lost to follow-up, death, or study termination, whichever occurs first. After the completion or discontinuation of the study treatment, safety follow-up and survival follow-up will be performed. The primary endpoints of the trial are the OS in the intention-to-treat (ITT) population and PD-L1 positive (CPS ⩾10) subjects. An interim analysis of OS will be performed at least once and no more than twice during the trial. The results and report will be submitted to the independent Data Monitoring Committee (iDMC). The iDMC will determine whether the treatment effect

	crossed the efficacy boundaries then provide advice to the sponsor on whether the trial data can be submitted and the trial can be discontinued early. Open-label Phase: As of April 9, 2021, a total of 659 subjects have been randomized, with 640 subjects in China and 19 subjects outside of China. Based on the interim analysis conducted by the iDMC in the overall population and PD-L1 positive population, sintilimab in combination with chemotherapy significantly prolonged the overall survival of subjects compared with placebo in combination with chemotherapy. In order to further evaluate the efficacy and safety of sintilimab in combination with chemotherapy in subjects representing the western population with advanced esophageal squamous cell carcinoma, when the randomization of 676 subjects is completed then randomization will be stopped and an open-label assignment of experimental arm therapy will continue in regions outside of China. The open-label usage is referred to as the 'open-label phase' within this protocol. An additional 70 subjects will be treated in this open-label phase. Assignment to the open-label phase will follow the same inclusion/exclusion criteria as specified in the protocol.
Inclusion Criteria	1. Histopathologically confirmed unresectable, locally advanced, recurrent or metastatic ESCC (excluding mixed adenosquamous carcinoma and other histological subtypes). 2. Aged ≥ 18. 3. ECOG PS of 0 or 1. 4. Subject must be unsuitable for definitive treatment, such as definitive chemoradiotherapy and/or surgery. For subjects who have received (neo)adjuvant or definitive chemotherapy/radiochemotherapy, time from the completion of last treatment to disease recurrence must be > 6 months. 5. Could provide archival or fresh tissues for PD-L1 expression analysis with obtainable results.

	6. Have at least one measurable lesion per RECIST v1.1. 7. Adequate organ and bone marrow functions, as defined below: 1) Complete blood count: absolute neutrophil count (ANC) ≥ 1.5×10^9/L, platelet (PLT) count ≥ 100×10^9/L, hemoglobin (HGB) ≥ 9.0 g/dL. Note: Subjects cannot receive blood transfusion, erythropoietin (EPO), or granulocyte-colony stimulating factor (GSF) within 7 days prior to the blood collection. 2) Hepatic function: total bilirubin (TBIL) ≤ 1.5 × upper limit of normal (ULN), alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ≤ 2.5 × ULN in subjects without hepatic metastasis; TBIL ≤ 1.5 × ULN, ALT and AST ≤ 5 × ULN in subjects with hepatic metastasis. 3) Renal function: urine protein < 2+ from random sample or < 1 g from 24-hour urine collection, and creatinine clearance rate (Ccr) ≥ 60 mL/min by Cockcroft-Gault formula: Female: $Ccr = \frac{(140-age)\times \text{weight(kg)}\times 0.85}{72\times \text{serum creatinine(mg/dL)}}$ Male: $Ccr = \frac{(140-age)\times \text{weight(kg)}\times 1.00}{72\times \text{serum creatinine(mg/dL)}}$ Note: for subjects aged ≥ 65 or with Ccr < 60 mL/min by Cockcroft-Gault formula but normal serum creatinine, the Ccr can be recalculated from 24-hour urine collection by the formula: $Ccr = \frac{urine\ creatinine(\mu mol/L) \times urine\ volume\ per\ minute(mL/min)}{\text{serum creatinine(μmol/L)}}$ The calculations of Ccr for one subject must use the same formula through the entire study. 4) Adequate coagulation function, defined as international normalized ratio (INR) ≤ 1.5 or prothrombin time (PT) ≤ 1.5 × ULN; if the subject is receiving anticoagulant therapy, the results of coagulation tests need to be within the acceptable range for anticoagulants.

	8. Expected survival ≥ 12 weeks. 9. Subject (female subjects of childbearing age or male subjects whose partners are of childbearing age) must take effective contraceptive measures during the entire course of the trial and until 180 days after the last dose (see Section 4.3). 10. Signed the informed consent form (ICF) and be able to comply with the scheduled follow-up visits and related procedures required in the protocol.
Exclusion Criteria	1. ESCC with endoscopy-confirmed near-complete obstruction requiring interventional therapy. 2. Post stent implantation in the esophagus or trachea with risk of perforation. 3. Received systemic treatment for advanced or metastatic ESCC. 4. Received a cumulative dose of cisplatin ≥ 300 mg/m^2 and the last cisplatin dose was within 12 months of randomization or the first dose of study treatment in the open-label phase. 5. High risk of hemorrhage or perforations due to tumor invasion in adjacent organs (aorta or trachea), or have fistula formation. 6. Hepatic metastasis > 50% of the total liver volume. 7. Received treatment with an anti-PD-1, anti-PD-L1, anti-PD-L2, anti-CD137, or anti-CTLA-4 antibody, or any other antibody or drug that specifically targets T-cell co-stimulation or immune checkpoint pathways. 8. Enrolled in another interventional clinical study, unless only involved in an observational study (non-interventional) or in the follow-up phase of an interventional study. 9. Received palliative therapy for a local lesion within 2 weeks prior to the first dose.

	10. Received systemic treatment with Chinese traditional medicines with anti-cancer indications or immunomodulators (including thymosins, interferons, and interleukins) within 2 weeks prior to the first dose of study treatment. 11. Received systemic immunosuppressants within 2 weeks prior to randomization or the first dose of study treatment in the open-label phase, excluding local use of glucocorticoids administered by nasal, inhaled, or other routes, and systemic glucocorticoids at physiological doses (no more than 10 mg/day of prednisone or equivalents), or glucocorticoids to prevent allergies to contrast media. 12. Received a live attenuated vaccine within 4 weeks prior to the first dose of study treatment or be scheduled to receive live attenuated vaccine during the study period. Note: Seasonal inactivated influenza virus vaccines within 4 weeks prior to the first dose of study treatment are permitted, but attenuated influenza vaccines are not. 13. Received major surgery (craniotomy, thoracotomy, or laparotomy) within 4 weeks prior to the first dose of study treatment or is scheduled to receive major surgery during the course of the trial. 14. Any toxicity (excluding alopecia, events that are not clinically significant, or asymptomatic laboratory abnormalities) due to prior anti-tumor therapy that has not yet resolved to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) v5.0 grade 0 or 1 prior to the first dose of study treatment. 15. Known symptomatic central nervous system (CNS) metastasis or carcinomatous meningitis. Subjects with brain metastases who have received prior treatment can be enrolled if the disease is stable (no imaging evidence of PD for at least 4 weeks prior to the first dose of study treatment), there is no evidence of new brain metastases or progression of the existing metastatic lesion(s) upon repeated imaging, and corticosteroids have not been required for at least 14 days prior to the first dose of study

	treatment. Patients with carcinomatous meningitis are ineligible, regardless of whether the disease is clinically stable or not. 16. Clinically significant ascites, including ascites that could be detected on physical examination, has been treated with a prior procedure, or currently requires treatment. Asymptomatic subjects with a small amount of ascitic fluid demonstrated by imaging can be enrolled. 17. Moderate bilateral pleural effusion or large unilateral pleural effusion, or effusion resulting in respiratory dysfunction and requiring drainage. 18. Subjects with bone metastases at risk of paraplegia. 19. Known active autoimmune disease requiring treatment or previous disease history within 2 years (subjects with vitiligo, psoriasis, alopecia, or Graves' disease not requiring systemic treatment, hypothyroidism only requiring thyroid replacement, or type I diabetes only requiring insulin can be enrolled). 20. Known history of primary immunodeficiency diseases. 21. Known active pulmonary tuberculosis. 22. Known history of allogeneic organ transplantation or allogeneic hematopoietic stem cell transplantation. 23. Known allergy to any monoclonal antibody or any formulation or excipient of the chemotherapy agents (e.g., paclitaxel, fluorouracil, or cisplatin) in that the subject is inappropriate to receive TP or CF regimen. 24. HIV-infected subjects (positive anti-HIV antibody). 25. Active or poorly controlled serious infections. 26. Symptomatic congestive heart failure (NYHA Class II–IV) or symptomatic or poorly controlled arrhythmia. 27. Uncontrolled hypertension (systolic blood pressure ≥ 160 mmHg or diastolic blood pressure ≥ 100 mmHg) despite standard treatment.

	28. Any arterial thromboembolic event within 6 months prior to enrollment, including myocardial infarction, unstable angina, cerebrovascular accident, or transient cerebral ischemic attack. 29. Significant malnutrition, such as those requiring continuous parenteral nutrition ≥7 days; excluding those having received intravenous treatment for malnutrition for more than 4 weeks before the first dose of study treatment. 30. History of deep venous thrombosis, pulmonary embolism, or other serious thromboembolic events within 3 months prior to enrollment (implantable port or catheter-related thrombosis, or superficial venous thrombosis are not considered as "serious" thromboembolisms). 31. Uncontrolled metabolic disorders, non-malignant organ or systemic diseases, or cancer-related secondary diseases that may lead to higher medical risks and/or survival evaluation uncertainties. 32. Severe pulmonary dysfunction. 33. Hepatic encephalopathy, hepatorenal syndrome, or cirrhosis with Child-Pugh Class B or C. 34. Bowel obstruction or history of the following diseases: inflammatory bowel disease, extensive bowel resection (partial colectomy or extensive small intestine resection accompanied with chronic diarrhea), Crohn's disease, or ulcerative colitis. 35. Known acute or chronic active hepatitis B (positive HBsAg and HBV DNA viral load ≥ 10^3 copies/mL or ≥ 200 IU/mL), or acute or chronic active hepatitis C (positive HCV antibody and detectable HCV RNA). 36. History of gastrointestinal (GI) perforation and/or fistula within 6 months prior to the enrollment, excluding gastrostomy or enterostomy. 37. Interstitial lung disease requiring corticosteroids. 38. History of other primary malignant tumors, excluding:

	• Malignant tumors that achieved a complete response (CR) at least 2 years prior to enrollment and expected to require no treatment during the trial. • Adequately treated nonmelanoma skin cancer or lentigo maligna with no sign of disease recurrence. • Adequately treated carcinoma in situ with no sign of disease recurrence. • Prostate cancer under active surveillance. 39. Pregnant or breastfeeding female subjects. 40. Acute or chronic diseases, psychiatric disorders, or laboratory abnormalities that may lead to the following consequences: increased investigational drug-related risks, interference with interpretation of trial results, or considered ineligible for participating in the trial by the investigators.
Study Drugs, Strengths, and Administrations	● Sintilimab/Placebo – Administration: weight < 60 kg: 3 mg/kg IV D1 Q3W weight ≥ 60 kg: 200 mg IV D1 Q3W ● Paclitaxel – Administration: Cycle 1: 87.5 mg/m^2 IV D1, D8 Q3W From Cycle 2: 175 mg/m^2 IV D1 Q3W ● Cisplatin – Administration: 75 mg/m^2 IV D1 Q3W ● 5- fluorouracil (5-FU) – Administration: 800 mg/m^2 IV continuous infusion over 24 hours daily on Days 1-5 Q3W
Evaluation Criteria	**Efficacy evaluation:** • Primary endpoints: OS in the overall ITT population; OS in PD-L1 positive subjects in the ITT population.

	• Key secondary endpoints: ORR, PFS in the overall ITT population; ORR, PFS in PD-L1 positive subjects in the ITT population. • Other secondary endpoints: DCR, DoR in the overall ITT population; DCR, DoR in PD-L1 positive subjects in the ITT population. **Safety evaluation:** • The incidence and severity of treatment-emergent adverse events (TEAEs), treatment-related adverse events (TRAEs), serious adverse events (SAEs), TEAEs leading to discontinuation, TEAEs leading to death, and immune-related adverse events (irAEs). • Changes in vital signs, physical examination, and laboratory tests results before, during, and after treatment. **Immunogenicity evaluation (for sintilimab in combination with chemotherapy arm only):** • Incidence of positive anti-drug antibodies (ADAs) and neutralizing antibodies (NAbs). **Biomarker evaluation:** • Evaluate the correlation between biomarkers in the tumor tissue and efficacy, including PD-L1 expression level. **Quality of life evaluation:** • Quality of life and health status will be compared between sintilimab vs. placebo, in combination with chemotherapy, as per EQ 5D-5L, EORTC QLQ-C30, and EORTC QLQ-OES18.
Statistical Analysis Method	**<u>Randomization Phase</u>** **Sample size estimation:** This is a Phase 3 trial with OS as the primary endpoint. The overall type I error of the hypothesis testing on the two populations for the efficacy endpoint of OS was tightly controlled by initially assigning a one-sided α of 0.0125 to the

	overall population OS hypothesis and a one-sided α of 0.0125 to the PD-L1 positive population OS hypothesis. For OS in the overall population, assuming that the hazard ratio (HR) of sintilimab to placebo, in combination with chemotherapy, is 0.75 [the median OS (mOS) is 13.3 and 10 months, respectively], 500 OS events are required to provide approximate 83% power (one-sided α for OS in the overall population is 0.0125, which accounts for one interim analysis). It is estimated that approximately 55% of the overall population is PD-L1 positive (CPS ≥10%). For OS in the PD-L1 positive population, assuming that the HR of sintilimab to placebo, in combination with chemotherapy, is 0.65 (the mOS is 15.4 and 10 months, respectively), 240 OS events are required to provide approximate 86% power (one-sided α level of 0.0125, which accounts for one interim analysis). It is estimated that 676 subjects need to be enrolled to observe the 500 OS events required for the randomization phase in this study. **Hypothesis test:** This is a superiority trial. The primary efficacy endpoints are the OS in the overall ITT population and PD-L1-positive population. The hypotheses of superiority are: Null hypothesis H0: HR ≥ 1 Alternative hypothesis Ha: HR < 1 **Interim analysis:** This study is designed to have at least 1 and no more than 2 interim analyses. OS will be statistically tested separately for the overall population and the PD-L1-positive population (CPS ⩾ 10) at the interim analysis for the randomization phase. Considering that the time to reach the preset events may be different between the overall population and the PD-L1-positive population, the final number of interim analyses will be determined according to the estimated time to reach the preset number of OS events in each population in a blind manner just before planned interim analysis timepoint. This decision was

made prior to unblinding of the first interim analysis and the number of prespecified interim analyses would not be modified afterwards.

The type I error boundary for the interim analysis was determined using the Lan-DeMets spending function in combination with the O'Brien-Fleming boundary in both populations. The analysis time points for each population are: interim analysis of OS in the overall population at approximately 70% (350) OS events; interim analysis of OS in the PD-L1-positive population at approximately 70% (168) OS events. Assuming that at the time of the first OS analysis for the PD-L1-positive population, the number of OS events in the overall population is far below the preset 350 (less than approximately 310, 62% of the overall number of events), 3 OS analyses will be performed for the overall population, that is, an interim analysis will be performed based on the actual number of OS events in the overall population when the prespecified number of OS events in the interim analysis for PD-L1-positive population is reached; a second interim analysis of OS in the overall population will be performed when the preset number of OS events in approximately 70% of the overall population occurs; and a final OS analysis will be performed when approximately 500 OS events in the overall population occur. As mentioned above, the decision on whether to add an interim analysis or not must be made before the first interim analysis event, based on the blind data, and using the same preset O'Brien-Fleming spending function. The alpha boundary under the different scenarios of number of interim analyses is shown in the table below.

PD-L1 positive (CPS ≥ 10) Subgroup			
Number of events	Nominal alpha Boundary	Type I error	HR Boundary
168 (70%)	0.0028	0.0028	0.652
240 (final analysis)	0.0116	0.0097	0.746

Overall Population (1 time Interim Analysis)

Number of events	Nominal alpha Boundary	Type I error	HR Boundary
350 (70%)	0.0028	0.0028	0.744
500 (final analysis)	0.0116	0.0097	0.816

Overall Population (2 times Interim Analysis: Scenario 1)

Number of events	Nominal alpha Boundary	Type I error	HR Boundary
310 (62%)	0.0015	0.0015	0.714
350 (70%)	0.0024	0.0013	0.740
500 (final analysis)	0.0116	0.0097	0.816

Overall Population (2 times Interim Analysis: Scenario 2)

Number of events	Nominal alpha Boundary	Type I error	HR Boundary
290 (58%)	0.0010	0.0010	0.697
350 (70%)	0.0025	0.0018	0.741
500 (final analysis)	0.0116	0.0097	0.816

If the interim analysis does not reach statistical significance under any of the actually used interim analysis strategies, and the actual number of events at the time of final analysis is different from the preset number of events, the boundary for the last analysis will be adjusted using the Hwang-Shih-DeCani spending function based on the actual number of events.

Primary efficacy endpoint:

A stratified log-rank test will be used to compare the OS between treatment arms. The HR and corresponding 95% CI will be estimated using a stratified Cox proportional hazards model that considers stratifying factors and important covariates. The adjusted confidence interval using actual risk will also be provided for HR if required by the regulatory authorities. The median OS (mOS) and corresponding 95% CI

	will be estimated via the Kaplan-Meier method and survival plots will be presented. **Key and other secondary efficacy endpoints:** The ORR, DCR, and the corresponding 95% CIs will be estimated for both treatment arms. The difference between treatment arms and 95% CI will be calculated. The DoR and PFS will be analyzed using the same methods as OS analysis. **Safety data:** The incidence and severity of AEs will be summarized for each treatment arm. Laboratory abnormalities will be presented. **Immunogenicity data:** Immunogenicity data will be presented with descriptive statistics. The number and percentage of subjects with ADAs and NAbs will be summarized for the arm of sintilimab plus chemotherapy treatment. **Quality of life measures:** Quality of life and health status will be compared between sintilimab in combination with chemotherapy vs. chemotherapy alone as per EQ 5D-5L, EORTC QLQ-C30, and EORTC QLQ-OES18. Changes in quality of life scores will be presented according to each follow-up for each treatment arm. **Biomarkers:** PD-L1 expression levels and distribution, and other potential biomarkers will be analyzed, and the potential correlation between these biomarkers and efficacy will be explored. **PK data:** The PK analysis will include but is not limited to descriptive statistical analysis of trough concentrations of sintilimab. **<u>Open-label Phase</u>** Only descriptive statistics will be provided for both efficacy and safety endpoints. A sample size of 70 subjects will be adequate for descriptive summaries. Descriptive statistics will be provided for all the applicable

	endpoints that are described in the randomization phase.

Table 1 Schedule of visits

Study Period	**Screening**	**Treatment**							**End-of-Treatment Visit[24]**	**Safety Follow-Up**		**Survival Follow-Up[27]**
		Cycle 1[23]		**Cycle 2**	**Cycle 3**	**Cycle 4**	**Cycle 5**	**Cycle 6**	**From Cycle 7 Onwards**			
Visits	1	2	3	4	5	6	7	8	9–N	Within ±7 days after end of treatment	30th day (± 7 days) after the last dose[25]	90th day (±7 days) after the last dose[26]	Every 60 days (± 7 days)
Day	-28 to -1	1	8 (± 3 days)	22 (± 3 days)	43 (± 3 days)	64 (± 3 days)	85 (± 3 days)	106 (± 3 days)	Every 3 weeks (± 3 days)				
General Study Procedures													
Written ICF[1]	×												
Inclusion/Exclusion Criteria	×												
Demographics/Medical History/Previous Medication[2]	×												
Vital Signs[3]	×	×	×	×	×	×	×	×	×	×	×	×	
Weight/Height[4]	×	×	×	×	×	×	×	×	×	×	×		
Physical Examination	×		×	×	×	×	×	×	×	×	×	×	

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Day	-28 to -1	1	8 (± 3 days)	22 (± 3 days)	43 (± 3 days)	64 (± 3 days)	85 (± 3 days)	106 (± 3 days)	Every 3 weeks (± 3 days)				
ECOG PS	×	×	×	×	×	×	×	×	×	×	×	×	
12-Lead ECG[5]	×			×	×	×	×	×	×	×	×		
Laboratory Tests													
CBC/Blood Biochemistry/Routine Urinalysis[6]	×		×	×	×	×	×	×	×	×	×		
Coagulation Function[7]	×									×			
Pregnancy Test[8]	×			×	×	×	×	×	×	×			
Thyroid Function[9]	×			×	×	×	×	×	×	×			
HIV, HBV, and HCV[10]	×												

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Day	-28 to -1	1	8 (± 3 days)	22 (± 3 days)	43 (± 3 days)	64 (± 3 days)	85 (± 3 days)	106 (± 3 days)	Every 3 weeks (± 3 days)				
Safety Evaluation													
AE Evaluation[11]	×	×	×	×	×	×	×	×	×	×	×	×	
Concomitant Medication[12]	×	×	×	×	×	×	×	×	×	×	×	×	
Survival Status		⟷											
Subsequent Anti-Tumor Therapy										×	×	×	×
Efficacy Evaluation													
Tumor Imaging Evaluation[13]	×				×		×		×	×			
Randomization													

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Day	-28 to -1	1	8 (± 3 days)	22 (± 3 days)	43 (± 3 days)	64 (± 3 days)	85 (± 3 days)	106 (± 3 days)	Every 3 weeks (± 3 days)				
IWRS[14]		×											
Study Drug Infusion													
Sintilimab/Placebo[15]		×		×	×	×	×	×	×				
Cisplatin[16]		×		×	×	×	×	×	×				
Paclitaxel[17]		×	×	×	×	×	×	×	×				
5-FU[18]		×		×	×	×	×	×	×				
Quality of Life Evaluation[19]													
EQ 5D-5L/ EQ QLQ-C30/ EORTC QLQ-OES18		×			×		×		×	×	×		

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Biomarker Study													
Archival or Fresh Tumor Tissue Sample[20]	×												
PK and Immunogenicity													
PK[21]		×	×	×		×			×		×		
Immunogenicity[22]		×		×		×			×		×		

Note:

1. The ICF should be signed by subjects prior to any procedures outlined in the protocol.
2. Medical history includes all active diseases and diseases diagnosed within the past 10 years that are clinically significant as determined by the investigator, including history of cigarette use, alcohol use, surgery, and drug allergy. Detailed disease information regarding esophageal cancer should be documented separately and not listed as a part of the disease history. All autoimmune diseases should be documented, regardless of the date of onset. All medications

(including replacement/supplement drugs) used within 30 days prior to the first dose of study treatment, including any washout requirements specified in the protocol, should be documented.

3. Vital signs: body temperature, pulse, respiratory rate, and blood pressure.
4. Height will only be measured during screening.
5. 12-lead ECG: within 7 days prior to the first dose during screening, within 3 days prior to administration of study treatment in each cycle (except Cycle 1), during end-of-treatment visit, and during the first safety follow-up.
6. Complete blood count: red blood cell (RBC) count, hemoglobin (HGB), white blood cell (WBC) count, platelet (PLT), WBC differentials [lymphocyte (LYM) count and absolute neutrophil count (ANC)]. Blood biochemistry: hepatic function [total bilirubin (TBIL), ALT, AST, γ-glutamyl transferase (γ-GT), alkaline phosphatase (ALP), albumin (ALB), total protein (TP), and lactate dehydrogenase (LDH)], renal function [blood urea nitrogen (BUN) or urea (UREA) and creatinine (Cr)], electrolytes [sodium (Na), potassium (K), chloride (Cl), magnesium (Mg), calcium (Ca), and phosphorus (P)], amylase, and fasting blood glucose (FBG). Routine urinalysis: pH (PH), urine white blood cell (UWBC), urine protein (UPRO), urine red blood cell (URBC), and urine glucose (UGLU). Complete blood count, blood biochemistry, and routine urinalysis are performed within 7 days prior to the first dose during screening, within 3 days prior to each dose, during the end-of-treatment visit, and during the first safety follow-up. Tests will be conducted in each local lab. Complete blood count/biochemistry will only be performed on Day 8 of Cycle 1.
7. Coagulation function tests: PT and INR. The test will be conducted within 7 days prior to the first dose and during the end-of-treatment visit. Tests will be conducted in each local lab.
8. Women of childbearing potential will undergo a blood pregnancy test within 3 days prior to the first dose and during the end-of-treatment visit and a urine pregnancy test will be done prior to each cycle. If the urine pregnancy test is not conclusive, then a blood pregnancy test should be performed. The conclusion should be based on the blood pregnancy test. Tests will be conducted in each local lab.
9. The tests will be conducted during screening, within 3 days prior to the administration of the study drugs from Cycle 2 onwards, and during send-of-treatment visit. Thyroid function tests: thyroid stimulating hormone (TSH), free triiodothyronine (FT3), and free tetraiodothyronine (FT4). Tests will be conducted in each local lab. The results obtained within 28 days prior to randomization or before the first dose of study treatment in the open-label phase can be accepted during screening.
10. Hepatitis B panel (HBsAg, HBsAB, HBcAB, HBeAg, and HBeAb), HCV antibody, and HIV antibody will be tested during screening. If the result shows HBsAg positive, then HBV DNA test should be further conducted. If the result shows HCV antibody positive, then HCV RNA test should be further conducted. The results obtained within 28 days prior to randomization or before the first dose of study treatment in the open-label phase can be accepted. Prophylactic antiviral therapy is suggested to be performed according to the local treatment guidelines for HBV carriers. HBV activity should be monitored regularly during the trial. Tests will be conducted in each local lab.

11. AE and laboratory safety evaluations will be performed according to NCI CTCAE v5.0. Refer to Section 8 for AE and SAE definitions, recording, determination of causal relationship, severity, reporting deadlines, and processing.
12. Concomitant medications: including all concomitant medications up to 30 days post dose (the first safety follow-up visit), and all concomitant medications for AE from 30 days post dose (the first safety follow-up visit) to 90 days post dose (the second safety follow-up visit). Within 90 days post dose (the 2nd safety follow-up visit), if a subject starts a new anti-tumor therapy, only concomitant medications taken for irAE and study drug or study procedure-related SAEs will be recorded after the new anti-tumor therapy. Concomitant medication taken for SAEs related to sintilimab or to the procedure 90 days post dose will be recorded.
13. Tumor imaging evaluations will be performed based on RECIST v1.1 and the same imaging method should be used for the same subject during the trial. Baseline evaluation will be conducted within 28 days prior to the first dose of the study treatment. The investigator can evaluate imaging results within 28 days prior to enrollment and document the TNM classification based on AJCC 8th edition. After the first dose of study treatment, tumor imaging evaluation will be performed once Q6W (± 7 days) for 48 weeks, then once Q12W (± 7 days) until initiation of a new anti-tumor therapy, PD, withdrawal of informed consent, lost to follow up, completion of treatment, or death. If the subject has confirmed or suspected bone metastatic lesion presents at baseline, an additional bone scan should be performed within 28 days prior to the first dose. If the bone metastasis is confirmed at baseline, bone scan is recommended every 12 weeks or as clinical indicated. For subjects who discontinue the treatment for reasons other than imaging-confirmed PD, if the subject's last imaging evaluation is greater than 4 weeks prior to discontinuation, the imaging evaluation should be performed at the end-of-study treatment visit and be reperformed Q6W/Q12W (± 7 days) thereafter until one of the followings occurs: start of new anti-tumor therapy, PD, withdrawal of informed consent, lost to follow-up or death.
14. Only used for the randomization phase. Prior to the first administration of study treatment, eligible subjects will be randomized to the sintilimab or placebo group, in combination with chemotherapy, in a 1:1 ratio. Stratifying factors include ECOG PS score (0 or 1), hepatic metastasis (positive or negative), chemotherapy regimens (TP or CF), and PD-L1 expression (TPS < 10% or ≥ 10%).
15. For the randomization phase, sintilimab/placebo: weight < 60 kg: 3 mg/kg IV Q3W; weight ≥ 60 kg: 200 mg, IV Q3W; for the open label phase, sintilimab weight < 60 kg: 3 mg/kg IV Q3W; weight ≥ 60 kg: 200 mg, IV Q3W for up to 24 months (starting from the first dose), or until PD, death, intolerable toxicity, withdrawal of informed consent, completion of treatment, or any other investigator-determined reason for treatment discontinuation. Administration on Day 1 of Cycle 1 should be on the day of randomization (or first day of open-label phase), if possible and no later than 48 h after randomization. Treatment can be delayed for up to 1 week if the administration day is on a holiday.
16. Cisplatin: 75 mg/m^2 IV D1 Q3W, until PD, death, intolerable toxicity, withdrawal of informed consent, or other reasons stated in the protocol. Administration on Day 1 of Cycle 1 should be on the day of randomization (or first day of open-label phase), if possible and no later than 48 h after

randomization, synchronized with sintilimab/placebo. Treatment can be delayed for up to 1 week if the administration day is on a holiday. During treatment, particular attention should be paid to adequate hydration and antiemetic treatment.

17. Paclitaxel: For Cycle 1, 87.5 mg/m^2 IV D1, D8 Q3W; from Cycle 2 onwards, 175 mg/m^2 IV D1 Q3W until PD, death, intolerable toxicity, withdrawal of informed consent, or other reasons stated in the protocol. Administration on Day 1 of Cycle 1 should be on the day of randomization (or first day of open-label phase), if possible and no later than 48 h after randomization, synchronized with sintilimab/placebo. Treatment can be delayed for up to 1 week if the administration day is in a holiday.
18. 5-FU: 800 mg/m^2 IV continuous infusion over 24 hours daily on Days 1-5 Q3W until PD, death, intolerable toxicity, withdrawal of informed consent, or other reasons stated in the protocol. Administration on Day 1 of Cycle 1 should be on the day of randomization (or first day of open-label phase), if possible and no later than 48 h after randomization, synchronized with sintilimab/placebo. Treatment can be delayed for up to 1 week if the administration day is on a holiday.
19. Quality of life evaluation: on the day of the first dose, during each imaging evaluation, and during the first safety follow-up, including EQ 5D-5L, EORTC QLQ-C30, and EORTC QLQ-OES18.
20. Subjects are required to provide at least 5 slides of archived or fresh tumor tissue samples during screening to test for PD-L1 expression. The submitted specimens should be an adequate tumor sample for assessment of PD-L1 status. Subjects who are successfully screened could optionally provide an additional 5 tumor tissue slides from the same paraffin block for a supplemental test for PD-L1 expression.
21. PK samples will be collected at the following time points: within 1h before, immediately after (+ 5 min), any point within 2-24h after, any point within 144-192h after sintilimab/placebo infusion in Cycle 1, within 1h before sintilimab/placebo infusion in Cycle 2/4/8, immediately after (+ 5 min), any point within 2-24h after, any point within 144-192h after sintilimab/placebo infusion in Cycle 12, within 1h before sintilimab/placebo infusion in Cycle 13 and 16, within 1h before sintilimab/placebo infusion in every 8 cycles thereafter (e.g. Cycle 24, 32, etc.), and at the first safety follow-up.
22. Immunogenicity samples will be collected within 1h prior to sintilimab/placebo infusion in combination with chemotherapy in Cycles 1/2/4/8/12/16, then every 8 cycles thereafter (e.g. Cycle 24, 32, etc.), and during the first safety follow-up. If an infusion-related reaction occurs during sintilimab/placebo administration, blood samples should be taken near the start of the event, at the end of the event, and around 30 days after the reaction for immunogenicity analysis. Tests will be conducted in the central lab.
23. Cycle 1 Visit 3 C1D8 is not applicable to subjects who choose chemotherapy regimen in combination with 5-fluorouracil.
24. The end-of-treatment visit should be conducted within ±7 days after the end of treatment is confirmed.
25. Safety follow-up at 30th day (± 7 days) after the last dose or before initiation of a new anti-tumor therapy. If the safety follow-up is performed within 7 days of the end-of-treatment visit, then the safety follow-up may be replaced by the end-of-treatment visit and does not need to be repeated. However, all procedures for the safety follow-up should be completed (immunogenicity).

26. Safety follow-up at 90th day (±7 days) after the last dose. All AEs including SAEs and irAEs will be collected within 90 days (±7 days) after the last dose if new anti-tumor therapy has not been initiated. Only irAEs and sintilimab- or procedure-related SAE will be collected if a new anti-tumor therapy has been initiated.
27. Survival follow-up: once every 60 days (± 7 days) after the safety follow-up. Telephone visits are allowed.

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List of Abbreviations

Abbreviations	Full Name
5-FU	5-fluorouracil
ADA	Anti-drug antibody
AE	Adverse event
ALB	Albumin
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
AMY	Amylase
ANC	Absolute neutrophil count
APTT	Activated partial thromboplastin time
AST	Aspartate aminotransferase
ATG	Antithymocyte globulin
AUC	Area under the curve
β-hCG	β-human chorionic gonadotropin
BUN	Blood urea nitrogen
Ccr	Creatinine clearance rate
CK	Creatine Kinase
CPS	Combined Positive Score
CRA	Clinical Research Associate
CRO	Contract Research Organization
CR	Complete response
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTLA4	Cytotoxic T-lymphocyte-associated protein 4
Cr	Creatinine
DCR	Disease control rate
DoR	Duration of response
DMARD	Disease-modifying antirheumatic drug
EC	Ethics committee
ECOG PS	Eastern Cooperative Oncology Group Performance Status
eCRF	Electronic case report form
ECG	Electrocardiogram
EDC	Electronic data capture

Abbreviations	Full Name
EGFR	Epidermal growth factor receptor
EORTC QLQ-C30	European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30
FAS	Full analysis set
FBG	Fasting blood glucose
FT3	Free triiodothyronine
FT4	Free thyroxine
GCP	Good Clinical Practice
γ-GT	γ-glutamyltransferase
HBcAb	Hepatitis B core antibody
HBeAb	Hepatitis B e antibody
HBeAg	Hepatitis B e antigen
HBsAb	Hepatitis B surface antibody
HBsAg	Hepatitis B surface antigen
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
HGB	Hemoglobin
HR	Hazard ratio
ICF	Informed consent form
ICPi	Immune Checkpoint inhibitor
iDMC	Independent Data Monitoring Committee
Ig	Immunoglobulin
INR	International normalized ratio
irAE	Immunity-related adverse event
ITT	Intention to treat
IV	Intravenous
IWRS	Interactive Web Response System
LCSS	The Lung Cancer Symptom Scale
MRI	Magnetic resonance imaging
NAb	Neutralizing antibody
NGS	Next-generation sequencing
NSAIDS	Nonsteroidal anti-inflammatory drugs

Abbreviations	Full Name
NSCLC	Non-small-cell lung cancer
NYHA	New York Heart Association
ORR	Objective response rate
OS	Overall survival
PD	Progressive disease
PD-1	Programmed cell death protein 1
PD-L1	Programmed cell death ligand 1
PD-L2	Programmed cell death ligand 2
PEX	Physical Examination
PFS	Progression free survival
PK	Pharmacokinetics
PLT	Platelet
PPS	Per-protocol set
PR	Partial response
PT	Prothrombin time
RBC	Red blood cell count
RECIST	Response Evaluation Criteria in Solid Tumors
SAE	Serious adverse event
SAP	Statistical analysis plan
SOC	System Organ Class
SD	Stable disease
SS	Safety set
TCR	T-cell receptor
TBIL	Total bilirubin
TEAE	Treatment-emergent adverse event
TKI	Tyrosine kinase inhibitor
TP	Total protein
TPS	Tumor Proportion Score
TSH	Thyroid stimulating hormone
TTR	Time to response
ULN	Upper limit of normal
UGLU	Urine glucose
UPRO	Urine protein

Abbreviations	Full Name
URBC	Urine red blood cell
UREA	Urea
UWBC	Urine white blood cell
VEGF	Vascular endothelial growth factor
WBC	White blood cell count

1 Background

1.1 Disease Background

Malignant tumors pose a serious threat to the health of humans. Esophageal cancer, occurs primarily in developing countries and ranks 8th in morbidity and 6th in mortality worldwide[1]. The incidence of different histological types of esophageal cancer varies among different regions of the world. It is estimated that in 2017 the number of newly diagnosed esophageal cancer cases is about 16,940 in the US, with approximately 15,690 deaths. The 5-year overall survival rates of esophageal cancer are 18.4% and 12% in the US and EU, respectively. China has the largest number of esophageal cancer cases in the world, with both a higher morbidity and mortality rate than that seen globally. It was estimated that in 2015, the number of new cancer cases in China has reached 4.29 million, and the number of new cancer deaths was 2.81 million[2]. In China, esophageal cancer ranks 4th in morbidity (478,000 cases) and 4th in mortality (375,000 cases)[2]. Despite some progress in the field of esophageal cancer treatment in recent years, there is still a huge unmet medical need.

Esophageal cancer refers to a malignant tumor derived from the esophageal epithelium between the hypopharynx and esophagogastric junction. It has two dominant histologic types: esophageal adenocarcinoma and esophageal squamous cell carcinoma (ESCC). ESCC accounts for about 90% of all esophageal cancers in China, while less than 30% in the US, Europe, Australia and many other western countries [3].

The treatment patterns for patients with ESCC in Asia and western countries are similar. Surgery is the main treatment for early- and mid-stage esophageal cancer. More advanced disease (node positive or T3-4 disease) is treated with neoadjuvant chemoradiation followed by surgery or by definitive chemoradiation therapy. Patients who are not surgical candidates are offered definitive chemoradiation therapy. A statistical report of 1510 patients with esophageal cancer treated in Shanxi Provincial Cancer Hospital showed that the 1-, 5-, and 10-year cumulative survival rates after surgery were 78%, 38%, and 30%, respectively, with an overall median survival of 2.68 years[4]. Patients who develop recurrent disease following neoadjuvant therapy/surgery or chemoradiation and those who present with distant metastases typically receive palliative chemotherapy. First-line chemotherapy includes cisplatin with paclitaxel or a fluoropyrimidine, these two regimens shown comparable outcomes in the treatment of ESCC in a retrospective analysis, with a median survival about 1 year [5]. There are few randomized controlled trials in subjects with advanced esophageal cancer, and these trials usually involve subjects with both adenocarcinoma of the esophagogastric junction and gastric cancer. First-line treatment is mainly

platinum-based chemotherapy, involving a combination of two or three drugs[6-12]. A randomized controlled Phase 3 clinical trial evaluated the efficacy of capecitabine, fluorouracil, oxaliplatin, and cisplatin for first-line treatment of advanced gastric and esophageal cancer (REAL-2). A total of 1002 subjects were randomly assigned to ECF (epirubicin + cisplatin + fluorouracil), ECX (epirubicin + cisplatin + capecitabine), EOF (epirubicin + oxaliplatin + fluorouracil), or EOX (epirubicin + oxaliplatin + capecitabine) in a 1:1:1:1 ratio. The proportion of esophageal cancer cases in each treatment arm was 30–40%, of which, ESCC accounted for approximately 10%. For the ECF, ECX, EOF, and EOX arms, respectively, the median survival was 9.9, 9.9, 9.3, and 11.2 months, and the 1-year survival was 37.7%, 40.8%, 40.4%, and 46.8%[6]. In a randomized controlled Phase 3 clinical study comparing EOX with or without panitumumab (REAL-3) in patients with adenocarcinoma of the esophagus, gastroesophageal junction, and stomach, panitumumab failed to prolong survival. In this study, a total of 275 subjects were allocated to the EOX arm. Forty percent (40%) of these patients had esophageal cancer, 99% adenocarcinoma. The overall survival (OS) in the EOX arm was 11.3 months[7].

A limited number of small studies have been conducted in patients with squamous cell carcinoma of the esophagus. A single-arm Phase 2 clinical study evaluating the efficacy of paclitaxel in combination with cisplatin and fluorouracil for the treatment of advanced esophageal cancer enrolled 61 subjects, 31 subjects had ESCC. The ORR was 48% (48% for adenocarcinoma and 50% for ESCC) and OS was 10.8 months[8]. In a randomized controlled trial comparing cisplatin in combination with fluorouracil with or without cetuximab for the treatment of esophageal cancer, 30 subjects received cisplatin in combination with fluorouracil. The ORR was 13%, disease control rate (DCR) was 57%, PFS was 3.6 months, and OS was 5.5 months[9]. A single-arm study in China evaluating paclitaxel in combination with cisplatin enrolled 39 subjects. The ORR was 48.6% and OS was 13 months [10].

Although targeted therapy has significantly improved the prognosis of various types of solid tumors, so far, no drug has shown definitive efficacy in treating ESCC[11, 12]. In the past decade, there was increased development of cancer immunotherapy. Many clinical studies have demonstrated the efficacy of immune checkpoint inhibitors and adoptive immunotherapy in solid and hematologic tumors. Based on this research, immunotherapy has the potential to offer a new approach to the treatment of ESCC, and several studies have been initiated.

In a Phase 1b clinical study evaluating pembrolizumab in subjects with advanced esophageal cancer (PD-L1 expression > 1%) who failed or were intolerant to first-line systemic treatment (KEYNOTE-028), the ORR was 30% (95%CI, 13–53)[13]. In a Phase 2 clinical study evaluating

nivolumab in subjects with advanced esophageal cancer who failed or were intolerant to first-line systemic treatment, the ORR was 17.2% and mOS was 12.1 months[14]. Based on the treatment effect observed in earlier trials, Phase 3 trials comparing nivolumab[15] or pembrolizumab[16] vs. chemotherapy alone for second-line treatment of esophageal cancer are currently ongoing. A randomized controlled trial comparing pembrolizumab in combination with chemotherapy vs. chemotherapy alone for first-line treatment of esophageal cancer is also currently underway (KEYNOTE-590, Checkmate 648). [17, 19]

Some studies examining PD-L1 expression in esophageal cancer demonstrated the relationship between PD-L1 expression level and prognosis. Interestingly, results vary in each trial. In an analysis of 288 subjects with ESCC, the percentage of PD-L1-positive subjects was 50.7%. The study demonstrated that the correlation between PD-L1 expression and prognosis varied depending on tumor stage and the presence of lymph node metastases. PD-L1 expression had a negative correlation with PFS and OS in subjects with stage I–II disease without lymph node metastasis, but no correlation was shown in subjects with stage III–IV disease.[21] In another study involving 162 cases of esophageal cancer, there was a higher percentage of PD-L1-expression in subjects with stage IV disease, lymph node metastases, or local treatment failure. Here, PD-L1-positive subjects responded poorly to treatment and had a worse prognosis.[22] In a report involving 41 cases of esophageal cancer, PD-L1 expression was associated with a poor prognosis and had strong correlation with a later stage of disease.[23] This variability in the relationship between PD-L1 expression and outcome may, in part, be explained by the use of prior therapy. PD-L1 expression can be dynamically variable in esophageal cancer. In a study comparing PD-L1 expression before and after neoadjuvant therapy in 28 subjects with esophageal cancer (19 cases of concurrent chemoradiotherapy, 9 cases of chemotherapy), PD-L1 expression increased significantly after neoadjuvant concurrent chemoradiotherapy and decreased significantly after neoadjuvant chemotherapy.[1] Therefore, PD-L1 expression and its relationship with treatment efficacy in ESCC after multiple lines of treatment may be different from the relationship in subjects receiving first-line treatment or in treatment-naive subjects.

1.2 Investigational Drug (Sintilimab)

1.2.1 Mechanism of action

Immune checkpoints are a type of immune inhibitory molecule, whose physiological function is to regulate the intensity and extent of the immune response and to avoid damage and destruction of normal tissues. Cancer cells often manipulate these immune checkpoints to escape immune surveillance. The efficacy of drugs designed to block the actions of immune checkpoints such as,

CTLA-4 and PD-1/PD-L1, has been validated clinically.

PD-1, the receptor primarily expressed on activated T-cells, has two ligands, PD-L1 and PD-L2. PD-L1 is the main ligand that is expressed on activated T-cells, antigen-presenting cells, and tumor cells. The binding of PD-1 with PD-L1 plays an important role in regulating T cell activation and maintaining peripheral immune tolerance. When T cells do not express PD-1, they interact with antigen-presenting cells to enable the activation and proliferation of T cells as well as the secretion of activated cytokines, which can kill tumor cells. Activated T cells begin to express PD-1. After PD-1 binds to the ligand PD-L1 expressed on the surface of antigen-presenting cells or tumor cells, the inhibitory signal transmitted by PD-1 inhibits the proliferation of T cells and the secretion of activated cytokines, thus weakening the function of T cells. Most tumor cells evade the attack from immune cells through this mechanism. The activity of T cells and their ability to kill cancer cells can be restored by blocking the PD-1/PD-L1 interaction with drugs.[26]

The US FDA has currently approved 6 PD-1/PD-L1 products, 3 are anti-PD-1 antibodies, including nivolumab (brand name: Opdivo), pembrolizumab (brand name: Keytruda), and cemiplimab (brand name: Libtayo). The other 3 are anti-PD-L1, including atezolizumab (brand name: Tecentriq), avelumab (brand name: Bavencio), and durvalumab (brand name: Imfinzi). These antibodies are indicated for advanced melanoma, advanced non-small-cell lung cancer (NSCLC), advanced classical Hodgkin's lymphoma, advanced renal cell carcinoma and urothelial carcinoma, advanced head and neck cancer, MSI-H/dMMR cancer, and Merkel cell carcinoma. Many additional indications are currently being studied in phase III clinical trials or have been submitted for approval.

Sintilimab is a recombinant fully human IgG4 anti-PD-1 monoclonal antibody (R&D code: IBI308). Multiple preclinical in vitro trials have demonstrated the ability of sintilimab to block the PD-1 pathway. The anti-tumor activity of murine analogs of sintilimab has also been validated in various murine tumor models.

1.2.2 Clinical study results of sintilimab

A Phase 1a dose-escalation trial was initiated in Sep. 2016 to evaluate 4 dose levels (1 mg/kg, 3 mg/kg, 200 mg, and 10 mg/kg) of sintilimab. The preliminary pharmacokinetic (PK) results of sintilimab in subjects (n = 3) with multiple tumors showed that: a single dose of sintilimab at 1 mg/kg reached the maximum drug exposure immediately after completion of the single-dose infusion. The drug distribution was rapid after reaching peak concentration, followed by a slow elimination ($t_{1/2} \approx 17.3$ d), which is typical of the two-compartment PK characteristics of a

monoclonal antibody. The elimination half-life is similar to the physiological half-life of IgG4.

The pharmacodynamic (PD) results showed that: a dose of sintilimab at 1 mg/kg rapidly (24 h) saturated peripheral PD-1 (95.8 ± 2.3%) and maintained the receptor occupancy with decreasing concentrations throughout the study. It is estimated that steady state can be reached after 84 days with 6 continuous doses of sintilimab 1 mg/kg administered Q2W. If there is no significant change in drug clearance, the minimum concentration at steady state will be around 13 μg/mL and peripheral PD-1 receptor occupancy will be maintained. The Phase 1a trial has enrolled 9 subjects (3 for each arm) in 3 treatment arms (1 mg/kg, 3 mg/kg, and 200 mg), and evaluated the dose-limiting toxicities specified in the protocol for each arm. No dose-limiting toxicities were observed.

Following completion of the dose escalation trial, clinical studies of sintilimab for the treatment of lymphomas and solid tumors were subsequently conducted. A total of 595 Chinese subjects and 36 US subjects received ≥ 1 dose of sintilimab, of which 534 Chinese subjects and 36 US subjects received sintilimab monotherapy, and 61 Chinese subjects received sintilimab in combination with chemotherapy. Over 93% of the subjects completed at least 2 cycles of treatment, 83.5% completed at least 3 cycles of treatment, 73.6% completed at least 4 cycles of treatment, and 65.9% completed at least 5 cycles of treatment. The median treatment duration for subjects that received 200mg Q3W was 24.29 weeks (range: 9.57~57.86 weeks).

Overall, a total of 77.3% of Chinese subjects (460/595) experienced a treatment-related adverse events (TRAE), the three most common (≥10%) TRAE including fever (15.0%), hypothyroidism (14.1%), and increased AST (13.6%). A total of 18.7% (111/595) of subjects had TRAE ≥ grade 3, among which the most common (incidence ≥ 1%) were decreased platelet count (1.2%), decreased neutrophil count (1.0%), and decreased lymphocyte count (1.0%). A total of 55.6% of US subjects (20/36) experienced sintilimab-related adverse events (TRAE), the most common (≥ 10%) included fatigue (16.7%), nausea (13.9%), and diarrhea (13.9%).

A total of 29.4% of Chinese subjects (175/595 subjects) experienced treatment-emergent SAEs during the study. The most common treatment-emergent SAEs included lung infection (4.0%), pneumonia (2.5%), and pulmonitis (2.5%). A total of 36.1% of US subjects (13/36 subjects) experienced treatment-emergent SAEs during the study. The most common treatment-emergent SAEs included urinary tract infection (8.3%), pleural effusion (5.6%), and hypotension (5.6%). The overall safety profile of sintilimab is comparable with current globally marketed PD-1/PD-L1 products.

Based on the safety data above, an ongoing multicenter randomized, open-label, Phase 2 study

comparing the efficacy and safety of sintilimab with paclitaxel or irinotecan in the treatment of subjects with advanced/metastatic ESCC who failed first-line therapy (ORIENT-2) is being conducted.

1.3 Risk/Benefit Assessment

1.3.1 Potential risks

Considering the mechanism of action and the clinical safety information available for IBI308, the additional adverse events (AEs) in the sintilimab arm that occur during this clinical trial are expected to be the immune-related inflammatory response resulting from the activation of immune system, e.g. pneumonitis, colitis, hepatitis, renal insufficiency, and endocrine events. According to the available clinical data, anti-PD-1 monoclonal antibodies are well-tolerable despite a high incidence of adverse reactions. Treatment discontinuation due to adverse reactions only occurs in a small number of subjects, and most events resolve after appropriate interventions. As early symptoms of immune-related adverse events (irAEs) vary, the investigators should pay extra attention to early signs and symptoms of irAEs during the trial, make decisions promptly, adjust the dose according to Section 5.2 in the protocol, and provide effective treatment measures to reduce the subject's risk.

Adverse events due to the administration of cytotoxic chemotherapy, cisplatin, paclitaxel, and 5-fluorouracil, are expected to occur in both arms. These include nausea, vomiting, infusion reactions, cytopenias, mucositis, diarrhea, neurotoxicity, and renal insufficiency.

1.3.2 Potential benefits

Subjects in this study will be treated with cisplatin plus either paclitaxel (TP regimen) or 5-FU (CF regimen) as per investigator's choice. Both regimens are recognized worldwide as effective first-line chemotherapy for advanced esophageal cancer. Therefore, subjects in both the sintilimab and placebo arms will receive a standard of care treatment that is potentially effective. The test arm will additionally receive the investigational drug, sintilimab. Pharmacological and safety data from a Phase 1a clinical trial showed that sintilimab has clear pharmacological activity and good tolerability in subjects with advanced cancers. Similar drugs have shown significant anti-tumor activity in subjects with advanced esophageal cancer, supporting the conduct of clinical trials in subjects with advanced esophageal cancer.

2 Study Objectives

2.1 Primary Objectives

- To compare OS of sintilimab vs. placebo, in combination with chemotherapy, as first-line treatment in subjects with unresectable, locally advanced, recurrent or metastatic ESCC;
- To compare OS of sintilimab vs. placebo, in combination with chemotherapy, as first-line treatment in subjects with PD-L1 positive (CPS ≥10, i.e., combined positive score), unresectable, locally advanced, recurrent or metastatic ESCC.

2.2 Secondary Objectives

- To compare progression-free survival (PFS), objective response rate (ORR), disease control rate (DCR), and duration of response (DoR) between two treatment arms in the overall ITT population;
- To compare objective response rate (ORR), progression-free survival (PFS), disease control rate (DCR), and duration of response (DoR) between two treatment arms in subjects with PD-L1 positive (CPS ≥10) ESCC;
- To compare safety between the two treatment arms.

2.3 Exploratory Objectives:

- To compare the changes in quality of life between the two treatment arms;
- To study the pharmacokinetic (PK) characteristics of sintilimab in combination with chemotherapy in subjects with unresectable, locally advanced, recurrent or metastatic ESCC;
- To evaluate the correlation between biomarkers in tumor tissue and efficacy, including PD-L1 expression level.

3 Study Design

3.1 Overall Design

This is a multi-regional, double-blind, randomized Phase 3 clinical trial evaluating the efficacy and safety of sintilimab vs. placebo, in combination with chemotherapy, as first-line treatment in subjects with unresectable, locally advanced, recurrent or metastatic ESCC.

An open-label phase is added to the protocol after completion of enrollment in the randomization phase of the study.

In the randomization phase, subjects with unresectable, locally advanced, recurrent or metastatic ESCC will be randomly assigned to the sintilimab arm or placebo arm in a 1:1 ratio. A total of 676 subjects will be enrolled, of which 338 subjects will be in the sintilimab arm and the other 338 subjects will be in the placebo arm. Stratification factors include the Eastern Cooperative Oncology Group Performance Status (ECOG PS) score (0 or 1), hepatic metastasis (positive or negative), chemotherapy regimens (TP or CF), and PD-L1 expression (TPS < 10% or ≥ 10%). Chemotherapy regimen and PD-L1 expression status must be determined before randomization or before the first dose administration for the open-label phase. Specifically, approximately 250 subjects will be PD-L1 subjects expressing TPS ≥10% (TPS is defined as the proportion of positive tumor cells).

Subjects will be treated with sintilimab (weight < 60 kg: 3 mg/kg IV on Day 1 Q3W; weight ≥ 60 kg: 200 mg IV on Day 1 Q3W) or placebo, in combination with investigator's choice of cisplatin (75 mg/m^2 IV on Day 1 Q3W) plus either paclitaxel (Cycle 1: 87.5 mg/m^2 IV on Day 1 and Day 8 Q3W; from Cycle 2: 175 mg/m^2 IV on Day 1 Q3W) (referred as TP regimen) or fluorouracil (800 mg/m^2 IV continuous infusion over 24 hours daily on Days 1-5 Q3W) (CF regimen). The treatment will repeat every 3 weeks until progressive disease (PD), intolerable toxicity, initiation of new anti-tumor therapy, withdrawal of informed consent, lost to follow-up, completion of therapy, death, or any other investigator-determined reasons for treatment discontinuation (whichever occurs first). A maximum of 6 cycles is recommended for TP regimen and CF regimen, and if tolerated by the subject, the duration of chemotherapy will be determined by the investigator. Treatment with sintilimab or placebo will be infused for a maximum period of up to 24 months (starting from the first dose). Sintilimab/placebo can be used alone if chemotherapy is intolerable. Chemotherapy will not be allowed to switch between the TP and CF regimens during the study.

Tumor imaging evaluations will be performed by investigator per RECIST V1.1. Subjects will undergo imaging assessment once Q6W (± 7 days) for 48 weeks during the initial study dosing period, then once Q12W (± 7 days) until disease progression, start of new antineoplastic therapy, withdrawal of consent, lost to follow-up, death, or study termination, whichever occurs first. After the completion or discontinuation of the study treatment, safety follow-up and survival follow-up will be performed. The primary endpoints of the trial are the OS in the intention-to-treat (ITT) population and PD-L1 positive (CPS ⩾10) subjects.

An interim analysis of OS will be performed at least once and no more than twice during the trial. The results and report will be submitted to the independent Data Monitoring Committee

(iDMC). The iDMC will determine whether the treatment effect crossed the efficacy boundaries then provide advice to the sponsor on whether the trial data can be submitted and the trial can be discontinued early.

Open-label Phase:

As of April 9, 2021, a total of 659 subjects have been randomized, with 640 subjects in China and 19 subjects outside of China. Based on the interim analysis conducted by the iDMC in the overall population and PD-L1 positive population, sintilimab in combination with chemotherapy significantly prolonged the overall survival of subjects compared with placebo in combination with chemotherapy. In order to further evaluate the efficacy and safety of sintilimab in combination with chemotherapy in subjects representing the Western population with advanced esophageal squamous cell carcinoma, when the randomization of 676 subjects is completed then randomization will be stopped and an open-label assignment of experimental arm therapy will continue in regions outside of China. The open-label usage is referred to as the 'open-label phase within this protocol. An additional 70 subjects will be treated in this open-label phase. Assignment to the open-label phase will follow the same inclusion/exclusion criteria as specified in the protocol.

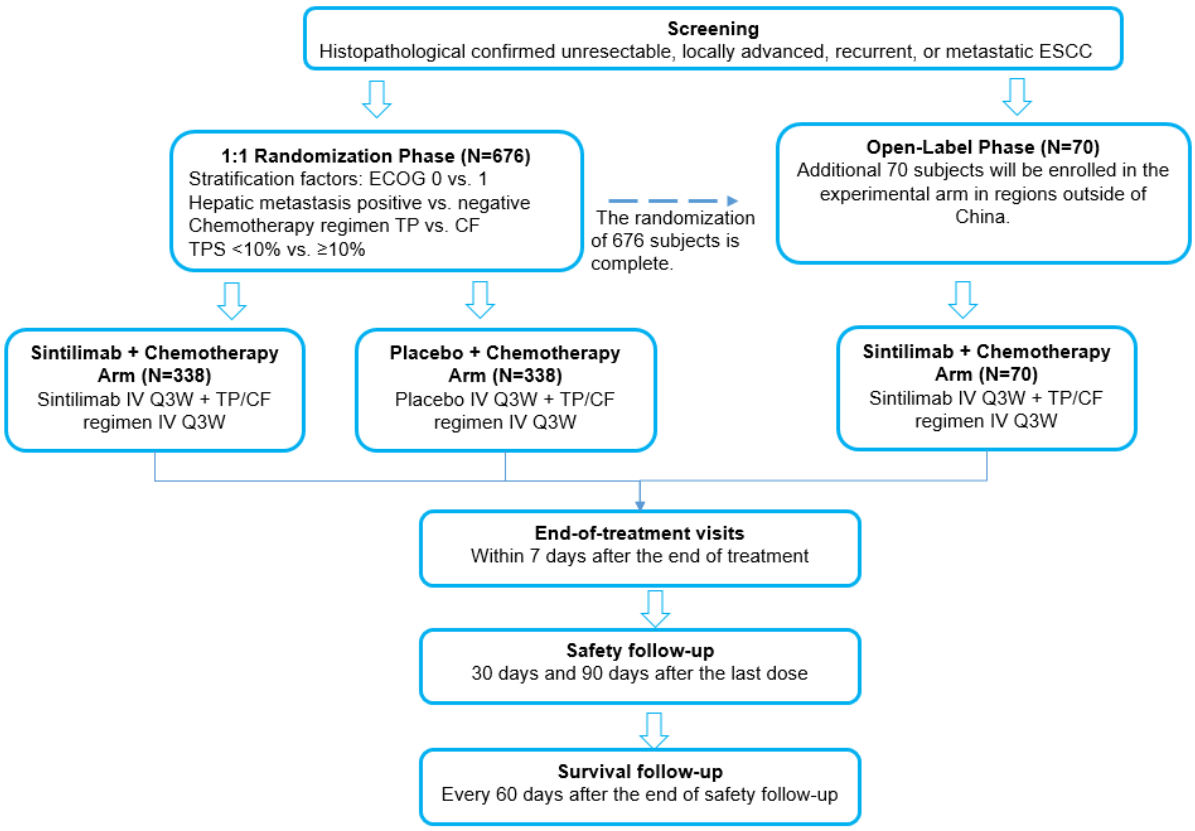

Figure 1 Schematic of CIBI308A301 study design and administration

3.2 Design Principles

3.2.1 Rationale for a double-blind and 1:1 ratio study design

Anti-PD-1 mAb has shown its unique efficacy in a variety of tumors including some efficacy in advanced gastrointestinal (GI) tract tumors. However, considering that there is no exact efficacy data for anti-PD-1 antibody in combination with chemotherapy for the first-line treatment of esophageal cancer, this study will use a 1:1 ratio for central randomization and blinding to control the dropout rate. PD-1 antibodies have been used in clinical practice for many years and the adverse event profile is well-described. The primary endpoint, OS, is unlikely to be affected by unintentional unblinding.

3.2.2 Rationale for pre-determining the proportion of subject population with PD-L1 expression TPS≥10%

Current studies on PD-1 monoclonal antibodies commonly use immunohistochemistry to detect the expression level of PD-L1. Due to different assays, the definition of positive cut-off value varies. For example, pembrolizumab uses 22C3 reagent for PD-L1 positive detection, and TPS of 1%, 10% or 50% is selected as the definition of PD-L1 positive.

The results of early PD-L1 detection in our phase II study (ORIENT-2) comparing sintilimab with chemotherapy for second-line treatment of esophageal squamous cell carcinoma showed that the proportion of subjects with TPS ≥ 10% was approximately 30%. The ATTRACTION-3 study, a phase III study comparing nivolumab with chemotherapy for second-line treatment of esophageal squamous cell carcinoma, showed that of the 419 subjects, 121 (29%) had PD-L1 expression TPS ≥ 10%[29]. Based on the above detection results of PD-L1 expression, it has been pre-determined that subjects with PD-L1 expression TPS ≥ 10% will account for approximately 36% (approximately 250) of the overall population.

3.2.3 Rationale for selecting CPS≥10 as the definition for PD-L1 positive population

The definition of PD-L1 expression level has been one of the focus issues in PD-1/PD-L1 therapy. Defining PD-L1 expression levels with TPS was first introduced into PD-1/PD-L1 studies. Pembrolizumab was approved as a second-line treatment for PD-L1-positive (TPS > 1%) advanced lung cancer on February 2015 (KEYNOTE-001 study). On October 2016, pembrolizumab was approved for first-line treatment of PD-L1-positive (TPS > 50%) advanced

lung cancer (KEYNOTE-024 study). At the same time, nivolumab has also explored the relationship between PD-L1 expression levels and efficacy in the evaluation of PD-L1 expression levels by TPS in different tumor types. Although as of May 2017, pembrolizumab was approved for patients with advanced urothelial cancer (KEYNOTE-045 trial) and patients with positive PD-L1 expression were defined by CPS ≥ 10 for the first time in the study, the sample size of studies using CPS to define PD-L1 positivity in esophageal cancer was not large. Studies such as KEYNOTE-028[30] and KEYNOTE-180[31] studies were phase Ib and phase II studies, and thus, the efficacy of using CPS to define PD-L1 positive expression and PD-1 monoclonal antibody is uncertain. Combining the detection of PD-L1 expression at that time and the data from the phase II study of sintilimab and chemotherapy for second-line treatment of esophageal squamous cell carcinoma (ORIENT-2), we chose to define positive PD-L1 expression as TPS ≥ 10%.

However, in recent years, more and more clinical studies have shown that the definition of positive PD-L1 expression by CPS may be more related to the efficacy of PD-1 monoclonal antibody, and the definition of positive PD-L1 expression by CPS is also used for population screening of more tumor types. These include:

The results of the study of pembrolizumab in first-line treatment of advanced urothelial carcinoma (KEYNOTE-052) showed that the OS benefit was significantly better in the population with PD-L1 expression CPS ≥ 10 than in the population with CPS < 10 (mOS 18.5 m vs 9.7 m) [32]. It was reported in the 2020 ASCO-GI meeting that pooling the results of Pembrolizumab in the first-line treatment study (KEYNOTE-062), second-line treatment study (KEYNOTE-061), and third-line treatment study (KEYNOTE-059 Cohort 1) of advanced gastric cancer showed that pembrolizumab had a significant effect on the population with PD-L1 expression CPS ≥ 10, with a mOS of 7.9 months for pembrolizumab in the third-line treatment of gastric cancer with PD-L1 expression CPS ≥ 10, 10.4 months for gastric cancer with PD-L1 expression CPS ≥ 10 in the second-line treatment (mOS of 8.0 months vs. chemotherapy, HR of 0.64), and 17.4 months for gastric cancer with PD-L1 expression CPS ≥ 10 in the first-line treatment (mOS of 10.8 months vs. chemotherapy, HR of 0.69) [33]. The results of the study of pembrolizumab in first-line treatment of recurrent or metastatic head and neck squamous cell carcinoma (KEYNOTE-048) showed that both pembrolizumab and pembrolizumab in combination chemotherapy could prolong OS compared with cetuximab in the population with

PD-L1 expression CPS ≥ 20 and CPS ≥ 1. The mOS was 14.9 months for pembrolizumab in the population with PD-L1 expression CPS ≥ 20, 10.8 months for pembrolizumab in combination chemotherapy, with a HR of 0.61. The mOS was 14.7 months for pembrolizumab plus chemotherapy versus 11.1 months for cetuximab plus chemotherapy with a HR of 0.62, 12.3 months for pembrolizumab versus 10.4 months for cetuximab plus chemotherapy with a HR of 0.74, 13.6 months for pembrolizumab plus chemotherapy versus 10.6 months for cetuximab plus chemotherapy with a HR of 0.64 [34] in the population with PD-L1 expressing CPS ≥ 1. The results of the study of pembrolizumab in second-line and above treatment of advanced cervical cancer (KEYNOTE-158 Cohort E) showed that the population with PD-L1 expression CPS ≥ 1 could achieve good efficacy, with an ORR of 14.3%[35].

Similar results were obtained in some studies of PD-1 monoclonal antibody in esophageal cancer, and PD-1 monoclonal antibody showed better clinical benefit for the population with PD-L1 expression CPS ≥ 10. KEYNOTE-181 was a phase III study comparing pembrolizumab with chemotherapy in the second-line treatment of advanced esophageal cancer. The study results showed that there were 401 subjects with esophageal squamous cell carcinoma, of which 167 subjects had PD-L1 expression CPS ≥ 10, accounting for 42% of the esophageal squamous cell carcinoma population. The mOS was 10.3 months in the pembrolizumab group and 6.7 months in the chemotherapy group, with a HR of 0.64 (95% CI 0.46-0.90). The mOS was 7.3 months in the pembrolizumab group and 7.5 months in the chemotherapy group, with a HR of 0.88 (95% CI 0.66-1.16). The mOS was 8.2 months in the Pembrolizumab group and 7.1 months in the chemotherapy group, with a HR of 0.78 (95% CI 0.63-0.96) [36]. KEYNOTE-590 was a phase III study comparing pembrolizumab combined with chemotherapy (pembrolizumab and 5-fluorouracil) with chemotherapy in the first-line treatment of advanced esophageal cancer. The interim analysis results (ESMO in 2020) showed that there were 548 subjects with esophageal squamous cell carcinoma, of which 286 subjects had PD-L1 expression CPS ≥ 10, accounting for 52% of the esophageal squamous cell carcinoma population. The mOS was 13.9 months in the pembrolizumab combined with chemotherapy group and 8.8 months in the chemotherapy group, with a HR of 0.57 (95% CI 0.43-0.75). The mOS was 12.6 months in the pembrolizumab combined with chemotherapy group and 9.8 months in the chemotherapy group, with a HR of 0.72 (95% CI 0.60-0.88) [37]. At the same time, the results of ATTRACTION-3 and ESCORT studies of two other PD-1 monoclonal antibody studies compared with chemotherapy for second-

line treatment of esophageal squamous cell carcinoma showed that the clinical benefit of PD-1 monoclonal antibody for the population with PD-L1 expression TPS ≥ 10% was not exact. In the ATTRACTION-3 study, a phase III study comparing nivolumab with chemotherapy as second-line treatment for advanced esophageal squamous cell carcinoma, the HR for OS was 0.69 (95% CI 0.46-1.04) [29]for PD-L1 expressing TPS ≥ 10%. In the ESCORT study, which was a phase III study comparing camrelizumab with chemotherapy as second-line therapy for advanced ESCC, the HR for OS was 0.60 (95% CI 0.32-1.08) [38] for PD-L1 expressing TPS ≥ 10%. The upper limit of the 95% CI of the HR of OS ≥ 10% for TPS in these two studies was greater than 1, indicating that the OS benefit of PD-1 monoclonal antibody for the population with PD-L1 expression TPS ≥ 10% was not definite.

In summary, compared with TPS, the definition of PD-L1 positivity by CPS criteria may screen for a population that is more suitable for PD-1 monoclonal antibody therapy, so CPS ≥ 10 was selected to define PD-L1 expression positivity, and OS of PD-L1 positive population was used as one of the primary study endpoints.

3.2.4 Rationale for selecting cisplatin plus paclitaxel or fluorouracil as the chemotherapy regimen

The treatment of esophageal cancer varies according to different tumor stages. Such treatment includes surgery, chemotherapy, and radiotherapy. Systemic chemotherapy is the main treatment of metastatic, advanced, recurrent, unresectable esophageal cancer. The data for systemic chemotherapy for esophageal cancer are mostly derived from clinical studies involving gastric and gastroesophageal junction adenocarcinoma. The incidence of esophageal cancer differs between China and western countries. The majority of esophageal cancer is ESCC in China, while it is mainly adenocarcinoma in western countries. Therefore, it is very important to find an effective treatment for ESCC. Currently, the choice of chemotherapy regimens is mainly based on the performance status and comorbidities of a subject. Available first-line chemotherapy regimens include fluorouracil (5-FU or capecitabine) alone or in combination with cisplatin or oxaliplatin, taxanes (paclitaxel or docetaxel) alone or in combination with platinum-based agents, and irinotecan in combination with 5-FU[27]. The ORRs of these first-line chemotherapies for ESCC are reported to range from 20% to 48%, the 5-year survival rate is less than 30%. There is still no consensus on the optimal first-line chemotherapy regimen, and combination chemotherapy is a common choice. In 2016, Liu et al published the largest retrospective study of ESCC (398 cases), which showed that the efficacy of TP regimen (paclitaxel plus cisplatin) is

similar to CF regimen and that the toxicities were manageable. [5]

3.3 iDMC

In this study, iDMC is set to conduct at least one but not more than two interim analysis of the primary efficacy endpoints (OS) and to provide periodic analyses of safety. The data analysis report for the iDMC will be provided by an independent statistician. The iDMC will evaluate the treatment effect at the interim analysis and will determine whether this has crossed the efficacy boundaries and provide advice to the sponsor on whether the trial can be discontinued early. The iDMC charter will be finalized and approved by the iDMC and sponsor prior to the interim analysis. Refer to the iDMC charter for the detailed information concerning the members, responsibilities, and procedures of the iDMC.

3.4 Definition of Study Completion

The subject is considered to have completed the study if the survival follow-up is completed or the subject withdraws consent.

The trial is completed if the last subject has completed the survival follow-up, been treated for 24 months, or the sponsor decides to discontinue the trial early based on the advice from the iDMC and/or the agreement between sponsor and health authority.

3.5 Criteria for Study Discontinuation

This study may be interrupted temporarily or discontinued prematurely if there are sufficient reasons to do so. The party who discontinues or interrupts the study should provide written notification to the subjects, investigators, funding agencies, and regulatory authorities, with documented reasons for interruption or discontinuation. If the study is discontinued prematurely or interrupted at a single site, the principal investigator should notify the subjects, Ethics Committee (EC), and sponsor immediately, and provide the reasons for discontinuation or interruption. Where applicable, the investigators should contact the subjects and inform them of the changes in the visit schedule.

Reasons for study discontinuation or interruption include but are not limited to:

- Unexpected, significant, or unacceptable risks to the subjects are identified;
- The study is discontinued or interrupted based on overwhelming efficacy at the time of the interim analysis;
- The subjects are unable to meet protocol requirements for compliance;

- The data is incomplete and/or insufficient for evaluation;
- The primary endpoint has been met.

The study may be resumed only if the safety, protocol compliance, and data quality issues have been addressed, and the requirements of the sponsor, EC, National Medical Product Administration (NMPA), and US Food and Drug Administration are met.

4 Study Population

4.1 Inclusion Criteria

1. Histopathologically confirmed unresectable, locally advanced, recurrent or metastatic ESCC (excluding mixed adenosquamous carcinoma and other histological subtypes).
2. Aged ≥ 18.
3. ECOG PS of 0 or 1.
4. Subject must be unsuitable for definitive treatment, such as definitive chemoradiotherapy and/or surgery. For subjects who have received (neo)adjuvant or definitive chemotherapy/radiochemotherapy, time from the completion of last treatment to disease recurrence must be > 6 months.
5. Could provide archival or fresh tissues for PD-L1 expression analysis with obtainable results.
6. Have at least one measurable lesion per RECIST v1.1.
7. Adequate organs and bone marrow functions, as defined below:
   1) Complete blood count: absolute neutrophil count (ANC) ≥ 1.5×10^9/L, platelet (PLT) count ≥ 100×10^9/L, hemoglobin (HGB) ≥ 9.0 g/dL. Note: Subjects cannot receive blood transfusion, erythropoietin (EPO), or granulocyte-colony stimulating factor (GSF) within 7 days prior to the blood collection.
   2) Hepatic function: total bilirubin (TBIL) ≤ 1.5 × upper limit of normal (ULN), alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ≤ 2.5 × ULN in subjects without hepatic metastasis; TBIL ≤ 1.5 × ULN, ALT and AST ≤ 5 × ULN in subjects with hepatic metastasis.
   3) Renal function: urine protein < 2+ from random sample or < 1 g from 24-hour urine collection, and creatinine clearance rate (Ccr) ≥ 60 mL/min by Cockcroft-Gault formula:

$$\text{Female: } Ccr = \frac{(140-age)\times \text{weight(kg)}\times 0.85}{72\times \text{serum creatinine(mg/dL)}}$$

$$\text{Male: } Ccr = \frac{(140-age)\times \text{weight(kg)}\times 1.00}{72\times \text{serum creatinine(mg/dL)}}$$

Note: for subjects aged ≥ 65 or with Ccr < 60 mL/min by Cockcroft-Gault formula but normal serum creatinine, the Ccr can be recalculated from 24-hour urine collection by the formula[28]:

$$Ccr = \frac{urine\ creatinine(\mu mol/L) \times urine\ volume\ per\ minute(mL/min)}{\text{serum creatinine}(\mu\text{mol/L})}$$

The calculations of Ccr for one subject must use the same formula throughout the entire study.

4) Adequate coagulation function, defined as international normalized ratio (INR) ≤ 1.5 or prothrombin time (PT) ≤ 1.5 × ULN; if the subject is receiving anticoagulant therapy, the results of coagulation tests need to be within the acceptable range for anticoagulants.

8. Expected survival ≥ 12 weeks.
9. Subject (female subjects of childbearing age or male subjects whose partners are of childbearing age) must take effective contraceptive measures during the entire course of the trial and until 180 days after the last dose (see Section 4.3).
10. Signed the informed consent form (ICF) and be able to comply with the scheduled follow-up visits and related procedures required in the protocol.

4.2 Exclusion Criteria

1. ESCC with endoscopy-confirmed near-complete obstruction requiring interventional therapy.
2. Post stent implantation in the esophagus or trachea with risks of perforation.
3. Received systemic treatment for advanced or metastatic ESCC.
4. Received a cumulative dose of cisplatin ≥ 300 mg/m^2 and the last cisplatin dose was within 12 months of randomization or first dose of study treatment in the open-label phase.
5. High risk of hemorrhage or perforations due to tumor invasion in adjacent organs (aorta or trachea), or have fistula formation.
6. Hepatic metastasis > 50% of the total liver volume.
7. Received treatment with an anti-PD-1, anti-PD-L1, anti-PD-L2, anti-CD137, or anti-CTLA-4 antibody, or any other antibody or drug that specifically targets T-cell co-stimulation or immune checkpoint pathways.

8. Enrolled in another interventional clinical study, unless only involved in an observational study (non-interventional) or in the follow-up phase of an interventional study.
9. Received palliative therapy for local lesion within 2 weeks prior to the first dose.
10. Received systemic treatment with Chinese traditional medicines with anti-cancer indications or immunomodulators (including thymosins, interferons, and interleukins) within 2 weeks prior to the first dose of study treatment.
11. Received systemic immunosuppressants within 2 weeks prior to randomization or first dose of study treatment in the open-label phase, excluding local use of glucocorticoids administered by nasal, inhaled, or other routes, and systemic glucocorticoids at physiological doses (no more than 10 mg/day of prednisone or equivalents), or glucocorticoids to prevent allergies to contrast media.
12. Received a live attenuated vaccine within 4 weeks prior to the first dose of study treatment or be scheduled to receive live attenuated vaccine during the study period.

    Note: Seasonal inactivated influenza virus vaccines within 4 weeks prior to the first dose of study treatment are permitted, but attenuated influenza vaccines are not.
13. Received major surgery (craniotomy, thoracotomy, or laparotomy) within 4 weeks prior to the first dose of study treatment or is scheduled to receive major surgery during the course of the trial.
14. Any toxicity (excluding alopecia, events that are not clinically significant, or asymptomatic laboratory abnormalities) due to prior anti-tumor therapy that has not yet resolved to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) v5.0 grade 0 or 1 prior to the first dose of study treatment.
15. Known symptomatic central nervous system (CNS) metastasis or carcinomatous meningitis. Subjects with brain metastases who have received prior treatment can be enrolled if the disease is stable (no imaging evidence of PD for at least 4 weeks prior to the first dose of study treatment), there is no evidence of new brain metastases or progression of the existing metastatic lesion(s) upon repeated imaging, and corticosteroids have not been required for at least 14 days prior to the first dose of study treatment. Patients with carcinomatous meningitis are ineligible, regardless of whether the disease is clinically stable or not.
16. Clinically significant ascites, including ascites that could be detected on physical examination, has been treated with a prior procedure, or currently requires treatment. Asymptomatic subjects with a small amount of ascitic fluid demonstrated by imaging can be enrolled.
17. Moderate bilateral pleural effusion or large unilateral pleural effusion, or effusion resulting in respiratory dysfunction and requiring drainage.

18. Subjects with bone metastases at risk of paraplegia.
19. Known active autoimmune disease requiring treatment or previous disease history within 2 years (subjects with vitiligo, psoriasis, alopecia, or Graves' disease not requiring systemic treatment, hypothyroidism only requiring thyroid replacement, or type I diabetes only requiring insulin can be enrolled).
20. Known history of primary immunodeficiency diseases.
21. Known active pulmonary tuberculosis.
22. Known history of allogeneic organ transplantation or allogeneic hematopoietic stem cell transplantation.
23. Known allergy to any monoclonal antibody or any formulation or excipient of chemotherapy agents (e.g. paclitaxel, fluorouracil, or cisplatin) in that the subjects is inappropriate to receive TP or CF regimen.
24. HIV-infected subjects (positive anti-HIV antibody).
25. Active or poorly controlled serious infections.
26. Symptomatic congestive heart failure (NYHA Class II–IV) or symptomatic or poorly controlled arrhythmia.
27. Uncontrolled hypertension (systolic blood pressure ≥ 160 mmHg or diastolic blood pressure ≥ 100 mmHg) despite standard treatment.
28. Any arterial thromboembolic event within 6 months prior to enrollment, including myocardial infarction, unstable angina, cerebrovascular accident, or transient cerebral ischemic attack.
29. Significant malnutrition, such as those requiring continuous parenteral nutrition ≥7 days; excluding those having received intravenous treatment for malnutrition for more than 4 weeks before the first dose of study treatment.
30. History of deep venous thrombosis, pulmonary embolism, or other serious thromboembolic events within 3 months prior to enrollment (implantable port or catheter-related thrombosis, or superficial venous thrombosis are not considered as "serious" thromboembolisms).
31. Uncontrolled metabolic disorders, non-malignant organ or systemic diseases, or cancer-related secondary diseases that may lead to higher medical risks and/or survival evaluation uncertainties.
32. Severe pulmonary dysfunction.
33. Hepatic encephalopathy, hepatorenal syndrome, or cirrhosis with Child-Pugh Class B or C.

34. Bowel obstruction or history of the following diseases: inflammatory bowel disease, extensive bowel resection (partial colectomy or extensive small intestine resection accompanied with chronic diarrhea), Crohn's disease, or ulcerative colitis.
35. Known acute or chronic active hepatitis B (positive HBsAg and HBV DNA viral load $\geq 10^3$ copies/mL or $\geq$ 200 IU/mL), or acute or chronic active hepatitis C (positive HCV antibody and positive HCV RNA).
36. History of gastrointestinal (GI) perforation and/or fistula within 6 months prior to the enrollment, excluding gastrostomy or enterostomy.
37. Interstitial lung disease requiring corticosteroids.
38. History of other primary malignant tumors, excluding:
    - Malignant tumors that achieved a complete response (CR) at least 2 years prior to enrollment and expected to require no treatment during the trial.
    - Adequately treated nonmelanoma skin cancer or lentigo maligna with no sign of disease recurrence.
    - Adequately treated carcinoma in situ with no sign of disease recurrence.
    - Prostate cancer under active surveillance.
39. Pregnant or breastfeeding female subjects.
40. Acute or chronic diseases, psychiatric disorders, or laboratory abnormalities that may lead to the following consequences: increased investigational drug-related risks, interference with interpretation of trial results, or considered ineligible for participating in the trial by the investigators.
    - If there are any uncertainties regarding the inclusion/exclusion, please contact the sponsor immediately and provide a complete medical history of the subject. The sponsor and principal investigator will discuss and determine the eligibility of the subject.

4.3 Restrictions During the Study

For women of childbearing potential who are sexually active with male partners who have not undergone sterilization, and men who have not undergone sterilization and are sexually active with women of childbearing potential, the subjects and their partners must use one of the acceptable methods of contraception listed in **Table 2** during the entire course of the trial and until 180 days after the last dose of study treatment. Periodic abstinence, a calendar-based method, and withdrawal are not acceptable forms of contraception. Women of childbearing potential are defined as females who have experienced menarche, have not undergone surgical

sterilization (bilateral tubal ligation, bilateral salpingectomy, or panhysterectomy), and are not postmenopausal.

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

- Females ≥ 50 years old who have at least 12 months of amenorrhea after stopping hormone replacement therapy and whose luteinizing hormone and follicle stimulating hormone levels are within the postmenopausal range are considered menopausal;
- Females < 50 years old who have at least 12 months of amenorrhea after stopping hormone replacement therapy, who have undergone radiation-induced ovariectomy or chemotherapy-induced amenorrhea, and whose luteinizing hormone and follicle stimulating hormone levels are within the postmenopausal range are considered menopausal.

Table 2 Effective methods of contraception

Single method (must use one)	Double barrier (must use two)
Intrauterine device	Condom
Contraceptive implant	Diaphragm/cervical cap with spermicide
	Hormonal contraceptives including: Oral contraceptive, contraceptive patch, contraceptive ring

4.4 Criteria for Discontinuation/Withdrawal

4.4.1 Treatment discontinuation

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

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

- Disease progression as per RECIST v1.1
- Treatment discontinuation required by the subject or his/her legal representative;

- Occurrence of an AE that requires discontinuation due to protocol-specified reasons (refer to Section 5.2);
- Onset of another malignant tumor that requires active treatment;
- Onset of a concurrent disease that interferes further treatment;
- Positive serum pregnancy test results;
- Poor compliance of the subject;
- Inappropriate to continue participating in the study when continued participation would result in unacceptable risk to the subject, as determined by the investigator and/or sponsor;
- Completion of 24-month of treatment with the study drugs.

All the visits and procedures presented in the study schedule (**Table 1**) should be completed for subjects who discontinued treatment but continue to be followed.

4.4.2 Subject withdrawal

A subject has the right to withdraw from the study at any time for any reasons. A subject must withdraw from the study if the subject or his/her legal representative withdraws informed consent.

A subject can withdraw from the study for the following:

- Screen failures;
- A subject or his/her legal representative withdraws informed consent;
- Death;
- Lost to follow-up;
- Study completion.

A subject who withdraws from the study will no longer receive the treatment and protocol-specified follow-up visits. However, the investigator should make every effort to persuade him / her to complete all the examinations specified for the end-of-treatment visit.

The reasons for withdrawal should be documented in the electronic case report forms (eCRFs). A subject who has signed the ICF and received any study interventions cannot be replaced after withdrawal or treatment discontinuation.

4.4.3 Lost to follow-up

A subject is considered lost to follow-up when he/she fails to return to the study site for 2 consecutive scheduled visits and the site personnel are unable to contact the subject.

The following actions must be taken if a subject does not return to the study site for a scheduled visit:

- The study site should try to contact the subject, reschedule the missed visits, reiterate the importance of complying with the schedule of visits, and confirm whether he/she is willing and/or should continue to participate in the study.
- Before a subject is considered lost to follow-up, the investigator or designee should make every effort to recontact the subject (at least 2 phone calls should be made; if the subject is still out of contact, a letter should be mailed to the subject's last known address). These attempts to contact the subject should be documented in the subject's medical records or study documents.

The subject is considered lost to follow-up and determined to have withdrawn from the study if the subject is still unable to be contacted.

5 Study Drugs and Other Treatments

The study drugs include sintilimab, placebo, paclitaxel, and cisplatin. The first dose of study treatment should start on the day of randomization or first day of the open-label phase, following screening (Day 1 of Cycle 1) and an acceptable delay should be no later than 48 h. The sponsor should be notified if the first dose is not administered within 48 h after randomization. Every effort should be made to start the study treatment on the day of randomization or on the first day of the open-label phase. For the rest of the treatment cycles, treatment can be delayed for up to 1 week if the administration day is on a holiday or if the subject cannot visit the site due to non-safety reasons.

Table 3 Dosage and administration

Study Drug	Dose	Frequency	Route	Treatment Cycle	Treatment Arm
Sintilimab[1]	Weight < 60 kg: 3 mg/kg	Q3W	IV infusion	on Day 1, every 21 days	Sintilimab arm
	Weight ≥ 60 kg: 200 mg	Q3W	IV infusion	on Day 1, every 21 days	Sintilimab arm
Placebo[1]	Weight < 60 kg:	Q3W	IV	on Day 1, every 21 days	Placebo arm

Study Drug	Dose	Frequency	Route	Treatment Cycle	Treatment Arm
	3 mg/kg		infusion		
	Weight ≥ 60 kg: 200 mg	Q3W	IV infusion	on Day 1, every 21 days	Placebo arm
Paclitaxel[2, 3]	87.5 mg/m^2	Q3W	IV infusion	on Day 1 and Day 8 for Cycle 1	Sintilimab/placebo arm
	175 mg/m^2	Q3W	IV infusion	on Day 1, starting from Cycle 2, every 21 days	Sintilimab/placebo arm
Cisplatin[3]	75 mg/m^2	Q3W	IV infusion	on Day 1, every 21 days	Sintilimab/placebo arm
5-FU[3,4]	800 mg/m^2	Q3W	IV infusion	continuous infusion over 24 hours daily on Days 1-5, every 21 days	Sintilimab/placebo arm

1. Sintilimab/placebo should be infused prior to the chemotherapy. For subjects < 60 kg, every dose of sintilimab/placebo should be calculated based on the actual weight. Allow at least a 1 hour interval between sintilimab/placebo and chemotherapy administration.
2. Paclitaxel administration should be administered 87.5 mg/m^2 IV D1, D8 Q3W for Cycle 1, then 175 mg/m^2 IV D1 Q3W from Cycle 2 onwards.
3. If the weight fluctuation is less than 10% compared to baseline (the day of the first dose), use the baseline weight to calculate the body surface area, and then calculate the chemotherapy dose based on the body surface area. Otherwise, use the weight on the scheduled day of administration to calculate the chemotherapy dose. For convenience, the protocol allows for a deviation of ± 5% of the total infusion dose each time.
4. The cumulative dose of 5-fluorouracil in a single cycle is 4000 mg/m^2, and other clinically acceptable modes of administration can also be used, such as 1000 mg/(m^2 · d) given on days 1 to 4. Cumulative dosing time in a single cycle allows for a 20% adjustment range (i.e., 4 to 6 days of continuous dosing). If necessary, the investigator was allowed to adjust the cumulative dose between 3200 and 4000 mg/m^2 in a single cycle based on the subject's tolerability.

All the study drugs in **cannot visit** the site due to non-safety reasons.

Table 3 are provided by the sponsor, and the product/batch numbers of all procured drugs are accessible. The local labs are responsible for recording the batch numbers, manufacturers, and expiration dates.

5.1 Treatment Regimens of Study Drugs

5.1.1 Sintilimab

The main active ingredient of sintilimab is the recombinant fully human anti-PD-1 monoclonal antibody at a concentration of 10 mg/mL. This product is a clear, colorless or light yellow liquid free of foreign matter. The excipients include 30.06 mg/L mannitol, 3.73 mg/L histidine, 5.88 mg/L dihydrate sodium citrate, 2.92 mg/L sodium chloride, 0.0075 mg/L disodium edetate (ethylenediaminetetraacetic acid disodium salt), and 0.2 mg/mL polysorbate 80, with a pH of 6.0.

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

The preparation and administration of sintilimab is as follows:

1. Calculate the required dose of sintilimab (weight < 60 kg: 3 mg/kg IV Q3W; weight ≥ 60 kg: 200 mg IV Q3W).
2. Calculate the volume of 0.9% (weight/volume) sodium chloride solution needed to dilute the sintilimab. The final concentration should be between 1.5 and 5 mg/mL. Then, calculate the redundant volume in the 0.9% (weight/volume) sodium chloride solution containing IV infusion bag, draw and discard the redundant volume.
3. Warm the vial of sintilimab injection to room temperature (25℃) and draw the required dose of sintilimab (step 1) completely and transfer it into the IV infusion bag in step 2 at one time. Record the time when the preparation process starts.
4. Gently invert the IV bag to mix the solution, ensuring the 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.
5. Administer with a 0.2-0.5 μm in-line filter (infusion time is 30–60 min). Document the start and stop time of infusion.

Note: Before preparation, make sure that the sintilimab injection is clear without any quality

issues such as turbidity or precipitation. To avoid medication errors and to ensure sterility, make sure that the required dose of sintilimab is drawn and transferred into the IV infusion bag at one time. Do not draw and transfer several times. Make sure that the time from sintilimab drawing to the end of infusion is no more than 6 h. The prepared solution can be stored for 24 h at 2-8℃ protected from light, and can be stored up to 6 h at 20 -25℃ under indoor lighting (including the duration of dosing). Avoid mixing with other drugs. Do not administer as an IV push.

5.1.2 Other study drugs

5.1.2.1 Placebo

All the personnel and subjects at the study sites as well as the sponsor are blinded. Placebo will be administered according to the guidelines for sintilimab administration in Section 5.1.1.

5.1.2.2 Cisplatin

Cisplatin is provided by the sponsor after re-labeling. The study site should store, prepare, and administer the drug according to the approved prescribing information as well as institutional guidelines.

To prevent cisplatin-induced nephrotoxicity, adequate hydration is required. Cisplatin should be administered with 3-days of hydration. Potassium chloride, mannitol, and furosemide are suggested concurrently to maintain a daily urine output of 2000–3000 mL. Cisplatin is a highly emetogenic chemotherapeutic agent. It is recommended to initially use an NK-1 receptor antagonist (such as aprepitant) in combination with a 5-HT3 receptor antagonist for antiemetic treatment. Other antiemetics including dopamine receptor antagonists (such as metoclopramide) and antihistamines (such as phenergan and diphenhydramine) may also be used. Chronic use of glucocorticoids for chemotherapy-induced nausea and emesis is not recommended.

5.1.2.3 Paclitaxel

Paclitaxel is provided by the sponsor after re-labeling. The study site should store, prepare, and administer the drug according to the approved prescribing information as well as institutional guidelines. The following information is for reference.

Refer to the prescribing information and local clinical practices for details regarding premedication before paclitaxel. The following table provides recommendations for chemotherapy premedication.

Table 4 Recommendations for premedication before chemotherapy

Paclitaxel	
Dexamethasone	10 mg IV 30 minutes before chemotherapy
Diphenhydramine	50 mg intramuscular injection 30–60 min before chemotherapy (or equivalent dose of other similar drugs)
Cimetidine or Ranitidine	Cimetidine (300 mg) or ranitidine (50 mg) IV 30–60 min before chemotherapy

5.1.2.4 5-FU

5-FU is provided by the sponsor after re-labeling. The study site should store, prepare, and administer the drug according to the approved prescribing information as well as clinical conventions.

5.2 Dose Adjustments

5.2.1 General principles

- The subject's hematologic, hepatic, and renal function must meet the requirements for study drug administration prior to Day 1 of each cycle. All the toxicities related to the study drug must resolve to NCI CTCAE v5.0 grade 0 – 1 or baseline levels, excluding the following cases:
  - Alopecia
  - Grade 2 fatigue
  - Hemoglobin (HGB) ≥ 8.0 g/dL
  - Decrease of Ccr due to cisplatin administration (calculated with the same formula as the baseline)*
  - Grade 2 neurotoxicities*
  - Grade 2 weight loss*
- All the dose adjustments should be documented, including the reasons and actions taken.
- The investigator should discuss with the sponsor to determine administration for any further concerns.

* refer to section 5.2.4 for more details

Some important overlapping toxicities of cytotoxic chemotherapy and sintilimab include nephrotoxicity, neuropathy and diarrhea. In evaluating these toxicities, Investigators should consider factors such as (but not limited to): 1) baseline creatinine and maintenance of hydration prior to and following the administration of cisplatin in the evaluation of nephropathy, 2) cumulative dose of cisplatin or paclitaxel in the evaluation of neuropathy, and 3) the timing of the onset of diarrhea.

- If the Investigator determines that a toxicity is clearly due to cytotoxic chemotherapy, the Investigator should follow the dose modifications outlined in Sections 5.2.4.1 and 5.2.4.2 as well as usual clinical practice at their institution. If treatment is delayed or discontinued due to cisplatin-, paclitaxel- or 5-FU-related toxicities, sintilimab/placebo can be administered alone.
- If the Investigator determines that a toxicity is clearly due to sintilimab, the Investigator should follow the criteria for temporary interruption of sintilimab in Section 5.2.2. If sintilimab/placebo administration is delayed due to immune-related toxicities, cisplatin, paclitaxel, or 5-FU should also be delayed until the toxicities resolve to the levels acceptable for administration, synchronized with sintilimab/placebo. If the resumption of chemotherapy, prior to sintilimab (during corticosteroid tapering) is considered, the investigator should first discuss this with the sponsor.
- If the Investigator determines that a toxicity could be related to cytotoxic chemotherapy or to sintilimab, dosing of all agents should be held until resolution to Grade 0-1. Upon resumption of dosing and if indicated (based on the toxicity seen), a reduced dose of cytotoxic chemotherapy should be administered. If the resumption of chemotherapy, prior to sintilimab (during corticosteroid tapering) is considered, the investigator should first discuss this with the sponsor.

5.2.2 Sintilimab dose adjustments

Dose adjustments for sintilimab/placebo are not permitted during the entire course of the study (except for subjects < 60 kg whose sintilimab doses are calculated based on weight, which is not considered as dose adjustments). Attached below is the reference table for sintilimab/placebo dose adjustments (only for sintilimab-related AEs determined by the investigator). If the administration delay occurs in a 3-week treatment cycle for sintilimab, all the subsequent administration should be delayed to ensure a dosing interval of 21 ± 3 days.

Sintilimab administration under special circumstances:

- An administration delay is not required for grade 3 lymphopenia.
- An administration delay is not required for any drug-related Grade 3 amylase or lipase abnormalities if it is not related to symptoms or clinical manifestations of pancreatitis.
- Administration can be continued for grade 3–4 drug-related endocrine AEs, such as adrenocortical insufficiency, hypophysitis, hyperthyroidism, hypothyroidism, and type I diabetes, that are adequately controlled with physiologic hormone replacement therapy (corticosteroids or thyroid hormone).

Table 5 Sintilimab dose adjustments

Drug-Related Toxicities	**Severity**	**Management**
1. Skin Toxicities		
Rash/Inflammatory Dermatitis	Grade 1	Continue, consider topical emollients and/or mild-moderate potency topical corticosteroids
	Grade 2	Consider interruption, treat with topical emollients, oral antihistamines, and medium- to high-potency topical corticosteroids, consider initiating prednisone 1 mg/kg, tapering over ≥ 4 weeks
	Grade 3	Interrupt and consult a dermatologist to decide whether and when to resume the treatment, treat with topical emollients, oral antihistamines, and high-potency topical corticosteroids, initiate (methyl)prednisolone or equivalent 1-2 mg/kg/d, tapering over ≥ 4 weeks
	Grade 4	Interrupt and consult a dermatologist to decide whether and when to resume the treatment after resolving and prednisone requirement ≤ 10 mg/day, Initiate (methyl)prednisolone or equivalent 1-2 mg/kg with slow tapering when toxicity resolves, Initiate topical therapies recommended by a dermatologist
Bullous Dermatosis	Grade 1	Interrupt and consult a dermatologist to decide whether and when to resume the treatment
	Grade 2–3	Interrupt and consult a dermatologist to decide whether and when to resume the treatment. For Grade 2 toxicity, initiate class 1 high-potency topical corticosteroid (eg, clobetasol, betamethasone or equivalent) and reassess every 3 days for progression or improvement

Drug-Related Toxicities	Severity	Management
		and Low threshold to initiate treatment with prednisone (or equivalent) at 0.5-1 mg/kg dosing and taper over at least 4 weeks; For Grade 3 toxicity, administer IV (methyl) prednisolone (or equivalent) 1-2 mg/kg, tapering over at least 4 weeks. If bullous pemphigoid is diagnosed, it may be possible to avoid long-term use of systemic corticosteroids and treat with rituximab, as an alternative approach to treating the irAE.
	Grade 4	Permanently discontinue. Administer IV (methyl) prednisolone (or equivalent) 1-2 mg/kg with tapering over at least 4 weeks when the toxicity resolves. If bullous pemphigoid is diagnosed, it may be possible to avoid long-term use of systemic corticosteroids and treat with rituximab as an alternative approach to treating the irAE.
Serious Skin Adverse Reactions: SJS, TEN, AGEP, and DRESS	Grade 1 (not applicable)	/
	Grade 2	Interrupt and consult a dermatologist to decide whether and when to resume the treatment. Initiate therapy with topical emollients, oral antihistamines, and medium- to high strength topical corticosteroids. Consider initiation of prednisone (or equivalent) 0.5-1 mg/kg tapered over at least 4 weeks
	Grade 3	Interrupt and consult a dermatologist to decide whether and when to resume the treatment. Treat skin with topical emollients and other petrolatum emollients, oral antihistamines, and high-strength topical corticosteroids; dimethicone may also be offered as an alternative to petrolatum. Administer IV (methyl)prednisolone (or equivalent) 0.5-1 mg/kg and convert to oral corticosteroids on response, wean over at least 4 weeks
	Grade 4	Permanently discontinue. Initiate IV (methyl)prednisolone (or equivalent) 1-2 mg/kg, tapering when toxicity resolves to normal IVIG or cyclosporine may also be considered in severe or corticosteroid unresponsive cases
2. GI Toxicities		

Drug-Related Toxicities	**Severity**	**Management**
Colitis	Grade 1	Continue, or interrupt until resolve to grade 0–1
	Grade 2	Interrupt until resolve to grade 1. Administer corticosteroids, unless diarrhea is transient, starting with initial dose of 1 mg/kg/day prednisone or equivalent when symptoms improve to G1 or less, taper corticosteroids over at least 4-6 weeks before resuming treatment, although resuming treatment while on low-dose corticosteroid may also be an option after an evaluation of the risks and benefits
	Grade 3	Interrupt until resolve to grade 1. Administer corticosteroids (initial dose of 1-2 mg/kg/d prednisone or equivalent). If symptoms persist ≥ 3-5 days or recur after improvement, consider administering IV corticosteroid or noncorticosteroid (eg, infliximab).
	Grade 4	Permanently discontinue. Administer 1-2 mg/kg/d methylprednisolone or equivalent until symptoms improve to G1, and then start taper over 4-6 weeks. Consider early infliximab 5-10 mg/kg if symptoms refractory to corticosteroid within 2-3 days
Hepatitis	Grade 1	Continue and monitor
	Grade 2	Interrupt, resume after resolving to grade 0–1 and prednisone requirement ≤ 10 mg/day. For grade 2 hepatic toxicity with symptoms, may administer corticosteroid 0.5-1 mg/kg/d prednisone or equivalent if the abnormal elevation persists with significant clinical symptoms in 3-5 days. In follow-up, may resume ICPi treatment followed by taper only when symptoms improve to G1 or less and corticosteroid ≤ 10 mg/d; taper over at least 1 month
	Grade 3–4	Permanently discontinue. Immediately start corticosteroid 1-2 mg/kg methylprednisolone or equivalent. Corticosteroid taper can be attempted around 4-6 weeks; re-escalate if needed; If corticosteroid refractory or no improvement after 3 days, consider mycophenolate mofetil or azathioprine (if using azathioprine should test for thiopurine methyltransferase deficiency).

Drug-Related Toxicities	Severity	Management
3. Pulmonary Toxicities		
Pneumonitis	Grade 1	Interrupt if exacerbation confirmed by imaging
	Grade 2	Interrupt until resolve to grade 0–1 Prednisone 1-2 mg/kg/d and taper by 5-10 mg/wk over 4-6 weeks.
	Grade 3–4	Permanently discontinue. Empirical antibiotics; (methyl)prednisolone IV 1-2 mg/kg/d; no improvement after 48 hours, may add infliximab 5 mg/kg or mycophenolate mofetil IV 1 g twice a day or IVIG for 5 days or cyclophosphamide; taper corticosteroids over 4-6 weeks
4. Endocrine Toxicities		
Primary Hypothyroidism	Grade 1	Continue and monitor closely
	Grade 2	Continue and monitor closely
	Grade 3–4	Continue, consult an endocrinologist, and symptom management
Hyperthyroidism	Grade 1	Continue and monitor closely
	Grade 2	Continue and monitor closely
	Grade 3–4	Continue, consult an endocrinologist, and symptom management
Primary Adrenocortical Insufficiency	Grade 1–2	Continue and monitor closely. For Grade 1, replacement therapy with prednisone (5-10 mg daily) or hydrocortisone (10-20 mg orally every morning, 5-10 mg orally in early afternoon). May require fludrocortisone (0.1 mg/d) formineralocorticoid replacement in primary adrenal insufficiency. For Grade 2, initiate outpatient treatment at two to three times maintenance. (if prednisone, 20 mg daily; if hydrocortisone, 20-30 mg in the morning, and 10-20 mg in the afternoon) to manage acute symptoms. Taper stress-dose corticosteroids down to maintenance doses over 5-10 days

Drug-Related Toxicities	Severity	Management
		Maintenance therapy as in G1.
	Grade 3–4	Continue, consult an endocrinologist, and symptom management. emergency department referral for normal saline (at least 2 L) and IV stress-dose corticosteroids on presentation (hydrocortisone 100 mg or dexamethasone 4 mg. Taper stress-dose corticosteroids down to maintenance doses over 7-14 days after discharge. Maintenance therapy as in G1
Hypophysitis	Grade 1–2	Continue, monitor closely, and hormonal supplementation
	Grade 3–4	Continue, consult an endocrinologist, hormonal supplementation and initial pulse dose therapy with prednisone 1-2 mg/kg oral daily (or equivalent) tapered over at least 1-2 weeks
Diabetes	Grade 1	Continue and monitor closely
	Grade 2	Continue and monitor closely
	Grade 3–4	Continue and consult an endocrinologist to determine whether to resume the treatment
5. Musculoskeletal Toxicities		
Inflammatory Arthritis	Grade 1	Continue
	Grade 2	Interrupt until the symptoms are controlled and prednisone requirement is ≤ 10 mg/day. If inadequately controlled by NSAIDS, initiate prednisone or prednisolone 10-20 mg/d or equivalent for 4-6 weeks. If improvement, slow taper according to response during the next 4-6 weeks; if no improvement after initial 4-6 weeks, treat as G3. If unable to lower corticosteroid dose to 10 mg/d after 3 months, consider DMARD Consider intra-articular corticosteroid injections for large joints.

Drug-Related Toxicities	**Severity**	**Management**
	Grade 3–4	Interrupt, consult a rheumatologist to decide whether to resume the treatment after resolving to grade 0–1. Initiate oral prednisone 0.5-1 mg/kg. If failure of improvement after 4 weeks or worsening in meantime, consider synthetic or biologic DMARD. Synthetic: methotrexate, leflunomide. Biologic: consider anticytokine therapy such as TNF-α or IL-6 receptor inhibitors. (Note: As caution, IL-6 inhibition can cause intestinal perforation; while this is extremely rare, it should not be used in patients with colitis.) Test for viral hepatitis B, C, and latent/active TB test prior to DMARD treatment.
Myositis	Grade 1	Continue
	Grade 2	Interrupt until the symptoms are controlled and CK is normal. If CK is elevated three times or more, initiate prednisone or equivalent at 0.5-1 mg/kg.
	Grade 3–4	Interrupt until resolve to grade 0–1 without immunosuppression; permanently discontinue if there are signs of myocardial involvement. Initiate prednisone 1 mg/kg or equivalent. Consider 1-2 mg/kg of methylprednisolone IV or higher-dose bolus if severe compromise (weakness severely limiting mobility, cardiac, respiratory, dysphagia). Consider plasmapheresis. Consider IVIG therapy. Consider other immunosuppressant therapy, such as methotrexate, azathioprine, or mycophenolate mofetil, if symptoms and CK levels do not improve or worsen after 4-6 weeks.
Polymyalgia Rheumatica-Like Syndrome	Grade 1	Continue
	Grade 2	Consider interruption until symptoms are controlled. prednisolone < 10 mg;

Drug-Related Toxicities	Severity	Management
	Grade 3–4	Interrupt, consult a rheumatologist to decide whether to resume the treatment after resolving to grade 0–1. Initiate prednisone 20 mg/d or equivalent. If no improvement or need for higher dosages for prolonged time, may offer a corticosteroid-sparing agent, such as methotrexate or IL-6 inhibition with tocilizumab.
6. Nephrotoxicities		
Nephritis	Grade 1	Consider interruption, make judgment based on other possible causes and the baseline renal function.
	Grade 2	Interrupt, administer 0.5-1mg/kg/d prednisone equivalents. If worsening or no improvement: 1 to 2 mg/kg/d prednisone equivalents and permanently discontinue treatment. If improved to G1 or less, taper corticosteroids over 4-6 weeks.
	Grade 3	Permanently discontinue. Initiate 1 to 2 mg/kg/d prednisone equivalents.
	Grade 4	Permanently discontinue, Consult a nephrologist. Administer corticosteroids (initial dose of 1-2mg/kg/d prednisone or equivalent).
Symptomatic Nephritis: Follow-Up	Grade 1	Resume routine creatinine monitoring if resolve to baseline values.
	Grade 2	If resolve to grade 1, taper glucocorticoid dose for at least 3 weeks; If elevations persist. 7 days or worsen and no other cause found, treat as G3.
	Grade 3–4	If resolve to grade 1, taper glucocorticoid dose for at least 4 weeks. If elevations persist >3-5 days or worsen, consider additional immunosuppression (eg, mycophenolate).
7. Neurotoxicities		
Myasthenia Gravis	Grade 1 (not applicable)	/
	Grade 2	Interrupt until resolve. Administer corticosteroids (prednisone, 1-1.5 mg/kg orally daily) if symptoms G2; wean based on symptom

Drug-Related Toxicities	**Severity**	**Management**
		improvement.
	Grade 3–4	Permanently discontinue. Continue corticosteroids and initiate IVIG 2 g/kg IV over 5 days (0.4 g/kg/d) or plasmapheresis for 5 days.
Guillain-Barré Syndrome	Grade 1 (not applicable)	/
	Grade 2–4	Permanently discontinue. Start IVIG (0.4 g/kg/d for 5 days for a total dose of 2 g/kg) or plasmapheresis. Or methylprednisolone 2-4 mg/kg/d, followed by slow corticosteroid taper. Or pulse corticosteroid dosing (methylprednisolone 1 g/d for 5 days) for G3-4 along with IVIG or plasmapheresis.
Peripheral Neurotoxicity	Grade 1	Lower the criteria for interruption and monitor the symptoms for 1 week; closely monitor the symptoms if continue the treatment.
	Grade 2	Interrupt until resolve to grade 0–1. Initial observation OR initiate prednisone 0.5-1 mg/kg (if progressing from mild).
	Grade 3–4	Permanently discontinue. Initiate IV methylprednisolone 2-4 mg/kg and proceed as per Guillain-Barre´syndrome management.
Autonomic Neuropathy	Grade 1	Lower the criteria for interruption and monitor the symptoms for 1 week; closely monitor the symptoms if continue the treatment.
	Grade 2	Interrupt until resolve to grade 0–1. Initial observation OR initiate prednisone 0.5-1 mg/kg (if progressing from mild).
	Grade 3–4	Permanently discontinue. Initiate methylprednisolone 1 g daily for 3 days followed by oral corticosteroid taper.
Aseptic Meningitis	Grade 1–4	Permanently discontinue. Once bacterial and viral infection are negative, may closely monitor off corticosteroids or consider oral prednisone 0.5-1 mg/kg or IV methylprednisolone 1mg/kg if moderate/severe symptoms.
Encephalitis	Grade 1–4	Permanently discontinue. Once bacterial and viral infection are negative, trial of methylprednisolone 1-2 mg/kg.

Drug-Related Toxicities	Severity	Management
		If severe or progressing symptoms or oligoclonal bands present, consider pulse corticosteroids methylprednisolone 1 g IV daily for 3-5 days plus IVIG 2 g/kg over 5 days. If positive for autoimmune encephalopathy antibody and limited or no improvement, consider rituximab or plasmapheresis in consultation with neurology.
Transverse Myelitis	Grade 1–4	Permanently discontinue. Give methylprednisolone 2 mg/kg Strongly consider higher doses of 1 g/d for 3-5 days and IVIG.
8. Hematotoxicities		
Autoimmune Hemolytic Anemia	Grade 1	Continue and monitor closely
	Grade 2	Interrupt and consider permanently discontinuing. Administer 0.5-1 mg/kg/d prednisone equivalents
	Grade 3–4	Permanently discontinue, IV prednisone corticosteroids 1-2 mg/kg/d. If no improvement or if worsening while on corticosteroids or severe symptoms on presentation, initiate other immunosuppressive drugs, such as rituximab, IVIG, cyclosporine A, and mycophenolate mofetil
Acquired Thrombotic Thrombocytopenic Purpura	Grade 1–4	Interrupt. Administer 0.5-1 mg/kg/d prednisone for Grade 1-2. For Grade 3-4, administer methylprednisolone 1 g IV daily for 3 days, with the first dose typically administered immediately after the first PEX
Hemolytic Uremic Syndrome	Grade 1–2	Continue and monitor closely
	Grade 3–4	Permanently discontinue. Begin therapy with eculizumab therapy 900 mg weekly for four doses, 1,200 mg week 5, the 1,200 mg every 2 weeks
Aplastic Anemia	Grade 1–2	Interrupt, treat with growth factors, and monitor closely. For Grade 2, administer ATG + cyclosporine
	Grade 3–4	Interrupt, treat with growth factors, horse ATG plus cyclosporine and monitor daily. If no response, repeat immunosuppression with rabbit ATG plus

Drug-Related Toxicities	**Severity**	**Management**
		cyclosporine, cyclophosphamide
Lymphopenia	Grade 1	Continue
	Grade 2–3	Continue and monitor the complete blood count and CMV weekly
	Grade 4	Interrupt
Immune Thrombocytopenia	Grade 1	Continue and monitor closely
	Grade 2–4	Interrupt, resume the treatment after resolving to grade 1. For Grade 2, administer prednisone 1 mg/kg/d (dosage range, 0.5-2 mg/kg/d) orally for 2-4 weeks after which time this medication should be tapered over 4-6 weeks to the lowest effective dose. For Grade 3-4, Prednisone 1-2 mg/kg/d (oral or IV depending on symptoms). If worsening or no improvement, 1-2 mg/kg/d prednisone equivalents and permanently discontinue treatment IVIG used with corticosteroids when a more-rapid increase in platelet count is required If IVIG is used, the dose should initially be 1 g/kg as a one-time dose. This dosage may be repeated if necessary. If previous treatment with corticosteroids and/or IVIG unsuccessful, subsequent treatment may include rituximab, thrombopoietin receptor agonists, or more-potent immunosuppression.
Acquired Hemophilia	Grade 1–2	Interrupt. For Grade 1, administer 0.5-1 mg/kg/d prednisone; For Grade 2, administer 1 mg/kg/d prednisone 6 rituximab (dose, 375 mg/m2 weekly for 4 weeks) and/or cyclophosphamide (dose, 1-2 mg/kg/d); choice of rituximab v cyclophosphamide is patient specific and should be done with assistance of hematology consult; prednisone, rituximab, and cyclophosphamide should be given for at least 5 weeks
	Grade 3–4	Permanently discontinue. Prednisone 1-2 mg/kg/d (oral or IV depending on symptoms) 6 rituximab (dose, 375 mg/m^2 weekly for 4 weeks) and/or (dose, 1-2 mg/kg/d). If worsening or no improvement add cyclosporine or immunosuppression/immunoadsorption

Drug-Related Toxicities	Severity	Management
9. Cardiovascular Toxicities		–
Myocarditis, Pericarditis, Arrhythmia, Ventricular Insufficiency with Heart Failure and Vasculitis	Grade 1	Interrupt
	Grade 2–4	Permanently discontinue. High-dose corticosteroids (1-2 mg/kg of prednisone) initiated rapidly (oral or IV depending on symptoms). In patients without an immediate response to high-dose corticosteroids, consider early institution of cardiac transplant rejection doses of corticosteroids (methylprednisolone 1 g every day) and the addition of either mycophenolate, infliximab, or antithymocyte globulin.
Venous Thromboembolism	Grade 1–3	Continue
	Grade 4	Permanently discontinue
10. Ocular Toxicities		
Uveitis/Iritis	Grade 1	Continue
	Grade 2	Interrupt until after consulting an ophthalmologist. Topical corticosteroids, cycloplegic agents, systemic corticosteroids. May resume ICPi treatment once off systemic corticosteroids, which are purely indicated for ocular adverse effects or once corticosteroids for other concurrent systemic irAEs are reduced to ≤ 10 mg; continued topical/ocular corticosteroids are permitted when resuming therapy to manage and minimize local toxicity. Re-treat after return to G1 or less.
	Grade 3–4	Permanently discontinue. Emergent ophthalmology feferral. Systemic corticosteroids (IV prednisone 1-2 mg/kg or methylprednisolone 0.8-1.6 mg/kg) and intravitreal/periocular/topical corticosteroids per ophthalmologist opinion.
Episcleritis	Grade 1	Continue
	Grade 2	Interrupt and consult an ophthalmologist. Topical corticosteroids,

Drug-Related Toxicities	Severity	Management
		cycloplegic agents, systemic corticosteroids.
	Grade 3–4	Permanently discontinue. Urgent ophthalmology referral. Systemic corticosteroids and topical corticosteroids with cycloplegic agents.
Blepharitis	No grades available	Continue, unless the symptoms are persistent and serious.

SJS: Stevens-Johnson syndrome; TEN: toxic epidermal necrolysis; AGEP: acute generalized exanthematous pustulosis; DRESS: drug rash with eosinophilia and systemic symptoms; NSAIDs: Non-Steroidal Anti-Inflammatory Drug; DMARD: Disease-modifying antirheumatic drug; IVIG: Intravenous Immunoglobulin; CK: Creatine Kinase; PEX: Physical Examination; ATG: Antithymocyte Globulin; ICPi: Immune Checkpoint inhibitor.

Sintilimab treatment is allowed to be held for up to 12 weeks. If the symptoms do not resolve and treatment cannot be resumed within 12 weeks, the subject must permanently discontinue sintilimab treatment and enter the follow-up phase of the study except for the following two cases:

- Sintilimab hold > 12 weeks due to glucocorticoid taper while treating immune-related adverse events (irAEs): Consult the sponsor's medical manager prior to resuming sintilimab. Tumor imaging evaluation for efficacy shall not be affected by treatment interruption and will be performed as scheduled.
- Sintilimab hold > 12 weeks due to AEs unrelated to sintilimab: Consult the sponsor's medical manager prior to resuming sintilimab. Tumor imaging evaluation for efficacy shall not be affected by treatment interruption and will be performed as scheduled.

5.2.3 Management of sintilimab-related infusion reactions

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

Table 6 Guidelines for the management of sintilimab-related infusion reactions

NCI CTCAE Grades	Treatments	Premedications for Subsequent Infusions
Grade 1 Mild reaction; infusion interruption not indicated; intervention not indicated	Monitor the subject, including vital signs, closely until the subject is stable as determined by the investigator.	Not applicable.
Grade 2 Treatment or infusion interruption required, but responds promptly to timely symptomatic treatment (e.g. antihistamines, nonsteroidal anti-inflammatory drugs [NSAIDS], anesthetics, IV fluids); prophylactic medications indicated for ≤ 24 h	**Stop the infusion and monitor symptoms.** Other appropriate treatments include but are not limited to: IV fluids Antihistamines NSAIDS Acetaminophen Consider bronchodilators Consider corticosteroids Monitor the subject, including vital signs, closely until the subject is stable as determined by the investigator. If symptoms resolve within 1 h after interrupting the infusion, then the infusion will be resumed at 50% of the original infusion rate (e.g. from 100 mL/h to 50 mL/h). If symptoms recur with resumption of the infusion, discontinue further treatment at that visit. Monitor the subject closely until the subject is stable. If symptoms resolve in > 1 h, discontinue the treatment at that visit.	Premedications should be given for subsequent infusions. The following premedications are recommended within 1.5 h (± 30 min) prior to sintilimab infusion: Diphenhydramine 50 mg PO (or equivalent antihistamines) Acetaminophen 500–1000 mg PO (or equivalent antipyretics) **If grade 2 toxicities occur despite of adequate premedications, the study drugs should be permanently discontinued.**
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	**Discontinue the infusion.** Other appropriate treatments include but are not limited to: Epinephrine** IV fluids Antihistamines	Not applicable. **The study drugs should be permanently discontinued.**

NCI CTCAE Grades	Treatments	Premedications for Subsequent Infusions
clinical sequelae (e.g. renal impairment, pulmonary infiltration) Grade 4 Life threatening; pressors or ventilatory support indicated	NSAIDS Acetaminophen Oxygen Bronchodilators Pressors Corticosteroids Monitor the subject, including the vital signs, closely until the subject is stable as determined by the investigator. Hospitalization may be indicated. **Epinephrine should be used immediately for allergic reactions.	
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 v5.0 (http://ctep.cancer.gov).		

5.2.4 Dose adjustments of chemotherapy

5.2.4.1 Dose adjustments for chemotherapy-related hematotoxicities

Treatment for the next cycle can only begin if ANC is $\geq 1.5 \times 10^9$/L and PLT is $\geq 75 \times 10^9$/L. Treatment can be delayed due to toxicities for up to 6 weeks (e.g., the longest interval between two consecutive cycles of treatment is 9 weeks).

Different dose levels of chemotherapy are shown below. Up to two levels of dose reduction are allowed. If treatment-related toxicity persists after two dose reductions, the chemotherapy should be discontinued.

Table 7 Dose adjustments of chemotherapy

	Initial Dose (100%)	-1 Dose Level (75%)	-2 Dose Level (50%)
Cisplatin	75 mg/m^2	56 mg/m^2	40 mg/m^2
Paclitaxel	175 mg/m^2	130 mg/m^2	90 mg/m^2

	Initial Dose (100%)	-1 Dose Level (75%)	-2 Dose Level (50%)
5-FU	800 mg/m^2	600 mg/m^2	400 mg/m^2

Table 8 Dose adjustments for chemotherapy-related hematotoxicities in previous cycle

Toxicities	First occurrence			Reoccurrence		
	Paclitaxel	Cisplatin	5-FU	Paclitaxel	Cisplatin	5-FU
Grade 2 Platelet count decreased	Initial dose	Initial dose	Initial dose	-1 dose level	-1 dose level	-1 dose level
Grade 3 Platelet count decreased	-1 dose level	-1 dose level	-1 dose level	-2 dose level	-2 dose level	-2 dose level
Grade 4 Platelet count decreased	-2 dose level	-2 dose level	-2 dose level	Discontinue	Discontinue	Discontinue
Grade 3 Neutrophil count decreased	Initial dose	Initial dose	Initial dose	-1 dose level	-1 dose level	-1 dose level
Grade 3 Febrile neutropenia (temperature ≥38.5℃)	-1 dose level	-1 dose level	-1 dose level	-2 dose level	-2 dose level	-2 dose level
Grade 4 Neutrophil count decreased	-1 dose level	-1 dose level	-1 dose level	-2 dose level	-2 dose level	-2 dose level
Grade 3 Febrile neutropenia (temperature ≥38.5℃ and life-threatening sepsis)	-2 dose level	-2 dose level	-2 dose level	Discontinue	Discontinue	Discontinue

Note: If > Grade 3 neutrophil decrease or febrile were observed in the previous treatment cycle, prophylactic G-CSF can be applied in the following cycles.

5.2.4.2 Recommended dose adjustments for chemotherapy-related non-hematotoxicities

Table 9 Dose adjustments for chemotherapy-related non-hematological toxicities in

previous the cycle

Toxicities	CTCAE Grading	Cisplatin	Paclitaxel	5-FU
Grade 3 or 4 nausea or vomiting	First occurrence	-1 dose level	-1 dose level	-1 dose level
	Reoccurrence	-2 dose level	-1 dose level	-2 dose level
Grade 3 or 4 diarrhea	First occurrence	-1 dose level	-1 dose level	-1 dose level
	Reoccurrence	-1 dose level	-1 dose level	-2 dose level
Neurotoxicities (excluding ototoxicity)	Grade 2	-1 dose level	-1 dose level	Initial dose
	Grade 3 or 4	Discontinue	-2 dose level	Initial dose
Ototoxicity	Grade 2	-2 dose level	Initial dose	Initial dose
	Grade 3 or 4	Discontinue	Initial dose	Initial dose
Transaminase increased	Grade 3	-1 dose level	-1 dose level	-1 dose level
	Grade 4	-2 dose level	-2 dose level	-2 dose level
Nephrotoxicities (Ccr decreased)	51-59 mL/min	-1 dose level	Initial dose	Initial dose
	41-50 mL/min	-2 dose level	Initial dose	Initial dose
	≤ 40 mL/min	Discontinue	Initial dose	Initial dose
Mucositis oral	Grade 3	Initial dose	-1 dose level	-1 dose level
	Grade 4	Initial dose	-2 dose level	-2 dose level
Dermal toxicity/hand-foot syndrome	Grade 2	Initial dose	Initial dose	-1 dose level
	Grade 3 or 4	Initial dose	Initial dose	-2 dose level
Cardiotoxicity	Grade 2	Initial dose	-1 dose level	Discontinue if attribute to 5-FU
	Grade 3	Initial dose	-2 dose level	Discontinue if attribute to 5-

Toxicities	CTCAE Grading	Cisplatin	Paclitaxel	5-FU
				FU
Weight loss	Grade 2	-1 dose level	-1 dose level	-1 dose level
	Grade 3	-2 dose level	-2 dose level	-2 dose level
Grade 3 or 4 other non-hematological toxicities	First occurrence	-1 dose level	-1 dose level	-1 dose level
	Reoccurrence	-2 dose level	-2 dose level	-2 dose level
Multiple ≤grade 3 hematological toxicities	First occurrence	-1 dose level	-1 dose level	-1 dose level
	Reoccurrence	-2 dose level	-2 dose level	-2 dose level

Note: Supportive treatment can be given by investigators according to the clinical guidelines and prophylactic treatment can be used in future chemotherapy cycles.

5.2.4.3 Paclitaxel-induced allergic reactions/hypersensitivity

When an allergic reaction reoccurs in a subject with a history of mild to moderate hypersensitivity, prophylaxis for hypersensitivity (see below) and close monitoring of vital signs are recommended.

If a subject experiences a grade 3 or higher allergic reaction to paclitaxel in Cycle 1, the subject should be actively treated and treatment with all study drugs should be discontinued.

- Mild symptoms: complete paclitaxel infusion. Closely monitor. No treatment indicated.
- Moderate symptoms: Interrupt paclitaxel infusion, administer diphenhydramine 25–50 mg and dexamethasone 10 mg via intravenous infusion. Once symptoms have resolved, resume paclitaxel infusion at a slower rate (20 mL/hour for 15 min, then at 40 mL/h for 15 min, and if no further symptoms develop, continue at original rate until infusion is complete). If symptoms reoccur, interrupt the paclitaxel infusion and permanently discontinue all subsequent paclitaxel infusions.
- Severe and life-threatening symptoms: Interrupt the infusion, administer diphenhydramine and dexamethasone via intravenous infusion (as above). Use epinephrine or bronchodilators if indicated. Permanently discontinue all subsequent chemotherapy infusions.

  Note:

1. An allergic reaction may occur during cisplatin infusion. The severity and incidence is lower than those of paclitaxel. If an allergic reaction occurs, treat it the same way as for paclitaxel.
2. If infusion interruption is indicated for a subject during the first paclitaxel infusion, the subject should withdraw from the study.

5.3 Principles for Managing Immune Checkpoint Inhibitor Toxicities

The mechanism of sintilimab is to stimulate T-cell activation and proliferation, which may lead to autoimmune disease involving multiple systems. Autoimmune AEs such as immune-related pneumonitis, diarrhea/enterocolitis, renal insufficiency, rash, hepatitis, endocrine disorders, and peripheral or central neuritis have been observed with checkpoint inhibitors including ipilimumab, nivolumab, pembrolizumab, and atezolizumab. If subjects experienced the irAEs described above, the signs and symptoms should be monitored, relevant examinations should be performed, and the cause should be identified. If an alternative cause is not found (such as PD, concomitant medications, or infections) and glucocorticoids and/or other immunosuppressants are required, then any AE described above is considered related to sintilimab-induced immune hyperfunction, which should be diagnosed as an irAE. Endocrine events such as hyperthyroidism/hypothyroidism, hypophysitis, type I diabetes, and adrenal insufficiency may not require immunosuppressants, but are still considered as immune-related events.

See **Table 5**, **Table 6** and other standard treatment, such as the latest National Comprehensive Cancer Network (NCCN) guidelines, American Society of Clinical Oncology (ASCO) guidelines, etc for management of immune-related toxicity in cancer immunotherapy for dose adjustments and management of toxicity.

5.4 Concomitant Treatments

5.4.1 Prohibited treatments

The following treatments are prohibited throughout the trial:

- Any systemic chemotherapy or biotherapy (except for cytokine drugs to treat chemotherapy-induced AEs), as well as herbal and proprietary Chinese medicines, with anti-tumor effects other than sintilimab, paclitaxel, and cisplatin;
- Immunomodulators, including but not limited to non-specific immunomodulators (such as thymosin, interferon, interleukin, immunoglobulin, and gamma globulin) as well as herbal and proprietary Chinese medicines with immunomodulating effects;

- Radiotherapy to control tumors (Except palliative radiotherapy to relieve pain of bone metastasis and brain metastasis, and the radiotherapy target area cannot contain target lesion);
- Inoculation with live vaccine within 30 days prior to the first dose of study treatment and throughout the trial. Live vaccines include but are not limited to measles, mumps, rubella, chicken pox, yellow fever, rabies, Bacillus Calmette Guerin, and typhoid (oral) vaccines; Seasonal inactivated influenza virus vaccines are permitted, but live attenuated influenza vaccines are not;
- Corticosteroids. Inhaled steroids for subjects with asthma or chronic obstructive pulmonary disease (COPD) are permitted; temporary use of corticosteroids for dyspnea are permitted; corticosteroids are permitted for the treatment of immune-related AEs; corticosteroids as a pretreatment for chemotherapy; corticosteroids to prevent contrast allergy; corticosteroids of physiologic dose are permitted after consulting the sponsor.

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

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

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

5.4.2 Permitted treatments

- Medications that meet the protocol requirements, as determined by the investigator (e.g. concomitant medication used for disease-related symptoms and treatment-related AEs);
- Subjects with underlying diseases such as hypertension and diabetes requiring chronic medications can continue these treatments;

- Local surgery or radiotherapy used for isolated lesions (excluding target lesions);
- Supportive care for relieving tumor-related symptoms, such as bisphosphonate treatment for bone metastases;
- Use of corticosteroids by topical administration, such as dermal, ocular, nasal, and inhaled;
- Prophylactic antiviral therapy is permitted for hepatitis B carriers. Refer to treatment guidelines for dosage and administration.
- If a grade 3 or higher neutropenia occurs, prophylactic treatment with a granulocyte colony-stimulating factor is permitted starting from the next cycle.

5.4.3 Drug-drug interactions

- Sintilimab: No interaction information is currently available.
- Paclitaxel:
  - Paclitaxel is metabolized by cytochrome P450 isoenzyme CYP2C8 and CYP3A4. When used concomitantly with known CYP2C8 and CYP3A4 substrates, inducers (e.g. rifampicin, carbamazepine, phenytoin, efavirenz, and nevirapine), and inhibitors (e.g. erythromycin, fluoxetine, and gemfibrozil), the pharmacokinetics of paclitaxel will change and caution should be used.
  - The interactions between paclitaxel and CYP3A4 substrates, as well as protease inhibitors (ritonavir, saquinavir, indinavir, and nelfinavir) which are CYP3A4 substrates/inhibitors, have not been confirmed by clinical studies.
  - Many drugs (ketoconazole, verapamil, diazepam, quinidine, dexamethasone, cyclosporine, teniposide, etoposide, and vincristine) can inhibit paclitaxel from metabolizing to 6α-hydroxypaclitaxel in vitro at concentrations which exceed the therapeutic doses. Testosterone, 17 α-ethinyl estradiol, retinoic acid, and a specific CYP2C8 inhibitor quercetin, also inhibit the formation of 6 α-hydroxypaclitaxel *in vitro*.
- Cisplatin:
  - Concomitant use of aminoglycosides, amphotericin B, or cefotaxime with cisplatin increases the risk of nephrotoxicity;
  - The concomitant use of probenecid and cisplatin may result in hyperuricemia.

- Chloramphenicol, furosemide, and ethacrynate sodium may increase the risk of cisplatin-induced ototoxicity;
- Antihistamines can mask the symptoms of cisplatin-induced tinnitus and vertigo.

Study treatment is given at the study sites. Treatment compliance is monitored by medication dispensing and returning records, medical records, and eCRFs.

- 5-FU:
  - Elevated coagulation times have been reported in subjects taking fluorouracil concomitantly with warfarin. While pharmacokinetic data are not available to assess the effect of fluorouracil administration on warfarin pharmacokinetics, the elevation of coagulation times that occurs with the fluorouracil prodrug, capecitabine, is accompanied by an increase in warfarin concentrations. Thus, the interaction may be due to inhibition of cytochrome P450 2C9 by fluorouracil or its metabolites.

5.5 Drug Management

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

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

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

Used sintilimab/placebo should be stored under the same storage conditions before verification by the clinical research associate (CRA), who will then arrange for the study drugs to be recycled.

5.5.1 Dispensation

This trial uses stratified randomization. The randomization list will be generated by statisticians

with SAS. After confirming that the subject meets all of the inclusion and exclusion criteria, the study site will log in the Interactive Web Response System (IWRS) and enter the subject information into the IWRS. The IWRS will allocate a random number to the subject and provide the subject with a medication number.

5.5.2 Return and destruction

In this trial, the containers of used sintilimab/placebo should be returned, and those of the chemotherapeutic agents can be destroyed on-site according to the appropriate guidelines and operating procedures established by the study sites and local agencies.

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

5.6 Study Drug Records

The designee of the study sites should keep accurate and complete records for receiving, dispensing, using, storing, returning, and destroying study drugs in accordance with the relevant regulations and guidelines and the operational requirements of this study.

6 Study Procedure

6.1 Enrollment and Randomization

6.1.1 Enrollment and randomization

The investigator will enroll subjects using the following steps during the randomization and open-label phase:

1. Obtain the ICF signed by the subjects prior to any study-related procedures;
2. Confirmation of the subjects' eligibility by the principal investigator or trained designee after reviewing the inclusion/exclusion criteria;
3. Chemotherapy regimen and PD-L1 expression status must be determined before randomization or before the first dose administration for the open-label phase;
4. Randomize the subjects through the IWRS in a 1:1 ratio stratifying for ECOG PS score (0 or 1), hepatic metastasis (positive or negative), chemotherapy regimens (TP or CF), and PD-L1 expression (TPS < 10% or ≥ 10%).

Subjects who do not meet the criteria (screen failures) may be re-screened. If re-screening is considered, the investigator must contact the sponsor's medical manager. Each subject can be re-

screened once. The subject must sign the ICF again and be assigned a new identification number when re-screening.

6.1.2 Enrollment error handling

The inclusion/exclusion criteria must be followed strictly. If an ineligible subject is enrolled, the sponsor's medical manager and investigator must discuss whether the subject is allowed to continue the study and whether the subject can be treated with the study drugs. If it is determined by the investigator that allowing the subject to continue the study is medically appropriate and this is agreed to by the sponsor's medical monitor, then the subject will continue the study and receive the study drugs. On the other hand, if the medical monitor does not agree, the subject should not continue the study (regardless of receiving the study drugs or not). The investigator may not allow the improperly enrolled subject to continue with the study until they receive the written approval from the sponsor.

6.2 Study Plan and Schedule

6.2.1 Screening

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

- Signing the ICF
- Confirming the inclusion/exclusion criteria
- Recording the demographics, medical history, and prior medications
- Recording the vital signs, height, and weight
- Physical examination
- ECOG PS
- 12-lead ECG (within 7 days prior to the first dose)
- Complete blood count/blood biochemistry/routine urinalysis (within 7 days prior to the first dose)
- Coagulation function (within 7 days prior to the first dose)
- Pregnancy test (within 3 days prior to the first dose)
- Thyroid function (results obtained within 28 days prior to randomization or before the first dose of study treatment in the open-label phase are also accepted)

- HIV antibody, hepatitis B panel (test HBV DNA for subjects with positive HBsAg), and HCV antibody (test HCV RNA for subjects with positive HCV antibodies). Results obtained within 28 days prior to randomization or before the first dose of study treatment in the open-label phase are also accepted.
- AE evaluation
- Concomitant medications
- Tumor imaging evaluation
- Archival or fresh tumor tissue

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

6.2.1.1 Medical history

A medical history should be obtained by the investigator or qualified designee. It includes all active diseases and diseases diagnosed within the past 10 years that are clinically significant, as determined by the investigator, including but not limited to history of cigarette use, alcohol use, surgery, and drug allergy. Detailed disease information regarding esophageal cancer should be documented separately but not listed as a part of the disease history. All autoimmune diseases should be documented, regardless of the date of onset.

6.2.1.2 Prior medications

All medications (including over-the-counter supplements) used within 30 days prior to the first dose of study treatment, including any washout requirements specified in the protocol, will be reviewed by the investigator or qualified designee and should be documented.

6.2.1.3 Concomitant medications

The investigator or qualified designee will document all the medications used throughout the trial (from the signing of the ICF to the safety follow-up), including all concomitant medications up to 30 days post dose (the first safety follow-up visit), and all concomitant medications for AE from 30 days post dose (the first safety follow-up visit) to 90 days post dose (the second safety follow-up visit). Within 90 days post dose (the 2nd safety follow-up visit), if a subject starts a new anti-tumor therapy, only concomitant medications taken for irAE and study drug or study procedure-related SAEs will be recorded after the new anti-tumor therapy. Concomitant medication taken for SAEs related to sintilimab or to the procedure 90 days post dose will be recorded.

6.2.2 Baseline (prior to Day 1 of Cycle 1)

- IWRS randomization (only used for the randomization phase, the first dose must be administered within 48 h after randomization)
- Recording the vital signs
- Weight
- ECOG PS
- AE evaluation
- Concomitant medications
- EQ 5D-5L
- EORTC QLQ-C30
- EORTC QLQ-OES18
- PK sampling (if applicable)
- Immunogenicity
- Survival status

6.2.3 Treatment visits

- Recording the vital signs
- Weight. If the weight fluctuation is less than 10% compared to baseline (the day of the first dose), use the baseline weight to calculate the chemotherapy dose (except for sintilimab). Otherwise, use the weight on the scheduled day of administration to calculate the chemotherapy dose.
- Physical examination
- ECOG PS
- 12-lead ECG
- Complete blood count/blood biochemistry/routine urinalysis
- Thyroid function
- Urine pregnancy test
- HBV DNA and/or HCV RNA (if applicable)

- AE evaluation
- Concomitant medications
- Tumor imaging evaluation (if applicable)
- Administration of study drugs (tumor imaging evaluation should be performed prior to administration)
- EQ 5D-5L (if applicable)
- EORTC QLQ-C30 (if applicable)
- EORTC QLQ-OES18 (if applicable)
- PK sampling (if applicable)
- Immunogenicity (if applicable)
- Survival status

Refer to **Table 1** for the study schedule during the treatment.

Refer to Sections 7.1, 7.2, 7.3, and 7.4 for details regarding tumor imaging evaluation, safety evaluation, immunogenicity sampling, and PK sampling, respectively.

6.2.4 End-of-treatment visits

The following should be completed within ± 7 days after confirming the end of treatment:

- Recording the vital signs
- Physical examination
- Weight
- ECOG PS
- 12-lead ECG
- Complete blood count/blood biochemistry/routine urinalysis
- Coagulation function
- Thyroid function
- Pregnancy test
- Tumor imaging evaluation (if applicable)
- AE evaluation

- Concomitant medications
- Survival status
- EQ 5D-5L
- EORTC QLQ-C30
- EORTC QLQ-OES18
- Subsequent anti-tumor therapy

6.2.5 Safety follow-up

The safety follow-up will be performed at the 30th day (± 7 days) and 90th day (± 7 days) after the last dose and will include the following procedures:

- Recording the vital signs
- Physical examination
- Weight (only for the first safety follow-up)
- ECOG PS
- 12-lead ECG (only for the first safety follow-up)
- Complete blood count/blood biochemistry/routine urinalysis (only for the first safety follow-up)
- AE evaluation
- Concomitant medications
- Document subsequent anti-tumor therapy
- Survival status
- EQ 5D-5L (only for the first safety follow-up)
- EORTC QLQ-C30 (only for the first safety follow-up)
- EORTC QLQ-OES18(only for the first safety follow-up)
- PK sampling (only for the first safety follow-up)
- Immunogenicity (only for the first safety follow-up)

If the safety follow-up is less than 7 days after the end-of-treatment visit, then the safety follow-up may be replaced by the end-of-treatment visit and does not need to be repeated. However,

immunogenicity sampling should be obtained.

If the subject initiates a new anti-tumor therapy within 30 days after the last dose, then the safety follow-up must be performed before initiation of the new therapy.

6.2.6 Survival follow-up

After completing the safety follow-ups, the subject should be contacted (telephone visits are allowed) once every 60 days (± 7 days) to obtain the survival information, any subsequent systemic anti-tumor therapy, and PD information. Long-term follow-up should be continued until death or end of study.

6.2.7 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 the subject initiates a new anti-tumor therapy within 30 days after the last dose, then the safety follow-up must be performed before initiation of the new therapy.

The subject should be followed for survival after initiation of a new anti-tumor therapy. Refer to Section 6.2.6 for details regarding survival follow-up.

6.2.8 Unscheduled visits

Unscheduled visits may be performed if requested by the subject or investigator. The investigator will carry out relevant examinations based on the subject's status, which includes but is not limited to the vital signs, targeted physical examination, ECOG PS, complete blood count/blood biochemistry/routine urinalysis, and tumor imaging evaluation. Test results from the unscheduled visits should be documented in the eCRFs.

7 Study Evaluation

7.1 Efficacy Evaluation

Tumor evaluations will be performed based on RECIST v1.1. Refer to Appendix 3 for the evaluation methods.

All the decisions made during the study will be based on the imaging evaluations by the local investigators, subject's clinical status, and relevant examination results.

7.1.1 Tumor imaging and disease evaluations

Tumor imaging examinations usually include contrast-enhanced CT or MRI of the neck, chest, abdomen, and pelvis. Contrast-enhanced MRI should also be performed on the brain at baseline for subjects with signs and symptoms of CNS metastasis. The imaging method should be consistent for a given subject during the trial.

During the screening, the investigator of the study site will confirm the presence of measurable lesions based on RECIST v1.1 to determine the eligibility of the subject. According to RECIST v1.1, a maximum or 5 lesions in total and 2 lesions per organ will be recorded.

7.1.2 Tumor imaging during the study

The imaging method used for the evaluation of tumor burden during each visit should be the same as the one used at baseline. Other affected sites should be examined based on the signs and symptoms of each subject. Baseline evaluation will be conducted within 28 days prior to the first dose of the study treatment, which means the investigator can evaluate the imaging results within 28 days prior to the enrollment.

After the first dose of study treatment, tumor imaging evaluation will initially be performed once Q6W (± 7 days) for 48 weeks, then once Q12W (± 7 days) until initiation of a new anti-tumor therapy, PD, withdrawal of informed consent, lost to follow-up, death, or completion of the study (whichever comes first).

Patients who have radiographic PD will discontinue treatment, treatment beyond disease progression is not allowed. For certain cases which PD cannot be determined, especially on those with equivocal non-target lesions enlargement or equivocal new lesions, the treatment may be continued until signs of clinical instability develop or when PD is confirmed by the investigator in the next scheduled scan. Once PD is confirmed, the disease progression date will be recorded as the date when the suspected PD was initially observed. Definition of clinical stability is as

follows:

- Absence of clinically significant signs and symptoms suggesting PD (including worsening laboratory values);
- No reduction in ECOG PS score;
- No rapid PD;
- Absence of rapid progression of disease or progressive tumor at critical anatomical sites (e.g. spinal cord compression) that requires urgent medical interventions.

Tumor evaluations should be performed as scheduled and should not be delayed due to treatment delays, holidays, or any other reasons.

Further tumor evaluations are not required for subjects who discontinue the treatment due to radiographic PD.

For subjects who discontinue the treatment for reasons other than radiographic PD, tumor evaluation should be performed Q6W (± 7 days) for 48 weeks, then once Q12W (± 7 days) until one of the followings occurs: start of new anti-tumor therapy, PD, withdrawal of informed consent, or death. A scan at the end of the treatment is not mandatory if it were less than 4 weeks after the last tumor evaluation.

If the subject has confirmed or suspected bone metastatic lesion(s) present at baseline, an additional bone scan should be performed within 28 days prior to the first dose. If bone metastasis is present at baseline, bone scan is recommended every 12 weeks or as clinically indicated.

7.2 Safety Evaluation

The investigator or qualified designee should evaluate each subject, as specified in the schematic of the study design, to identify the potential new or worsening AEs. Safety evaluations can be performed more frequently if clinically indicated. AEs are graded and documented according to NCI CTCAE v5.0 during the study and follow-up. Toxicities will be characterized by severity grade, causality, and actions taken with the study treatment.

All AEs with unknown causes after exposure to the study treatment must be evaluated to determine whether the event is potentially immune-related.

Refer to Sections 8.2 and 8.3 for details regarding AE evaluation and documentation.

Refer to the schedule of visits in **Table 1** for the timing of the evaluations. Refer to Appendix 2

for ECOG PS criteria.

7.2.1 Physical Examination

7.2.1.1 Comprehensive physical examination

A comprehensive physical examination will be performed by the investigator or designee during the screening, including the respiratory tract, cardiovascular system, abdomen, skin, head and neck (including ears, eyes, nose, and throat), lymph nodes, thyroid, musculoskeletal system (including spine and limbs), genitalia/anus, and nervous system. All the clinically significant abnormalities should be documented in the disease history. After the first dose of study treatment, any new clinically significant abnormalities should be documented as AEs.

7.2.1.2 Targeted physical examination

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

7.2.1.3 ECOG PS

The investigator or qualified designee will evaluate PS during screening, prior to administration on Day 1 of each treatment cycle, during the end-of-treatment visit, and during safety follow-up in accordance with the instructions in the Schedule of Visits.

7.2.1.4 Vital signs

Vital signs will be examined in accordance with the schedule of visits in **Table 1**, including temperature, pulse, respiratory rate, and blood pressure. Blood pressure and pulse are measured in the supine position after resting for at least 5 min. The time and date of measurement should be documented in the appropriate section of the eCRF. Temperature, pulse, respiratory rate, and blood pressure should be measured prior to the administration of study drugs.

Additional monitoring of vital signs is allowed based on standard clinical practice or clinical need, and should be documented in the eCRF when an AE/SAE occurs (if applicable). The time and date of measurement should be documented in the appropriate section of the eCRF.

7.2.1.5 12-lead ECG

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

The subject must be resting in a supine position for at least 5 min prior to 12-Lead ECG. All the 12-lead ECG results should be recorded in the supine position. Further ECGs (or other related tests) should be performed if clinically indicated, such as a cardiac AE. The investigator should review the ECG on the day it is performed, and document the results on the ECG. The evaluation method should be consistent throughout the trial.

The investigator should evaluate all the ECGs as either normal, clinically significant abnormalities, or clinically insignificant abnormalities. If it is a clinically significant abnormality(s), the investigator should document an AE in the eCRF.

7.2.2 Routine laboratory safety evaluations

See below for the specific laboratory procedures/evaluations. Refer to the Procedure Manual for the total amount of blood/tissues extracted/collected throughout the trial (from pre-trial to post-trial visits), including the amount of each subject's blood/tissues extracted/collected for each specimen type during each visit. Refer to the section on laboratory evaluations in the Schedule of Visits.

7.2.2.1 Laboratory safety evaluation (complete blood count, routine urinalysis, and blood biochemistry)

Refer to **Table 10** for laboratory tests including complete blood count, routine urinalysis, and blood biochemistry.

Table 10 Routine laboratory safety evaluation

Complete blood count	RBC, HGB, WBC, PLT, LYM, and ANC
Blood Biochemistry	TBIL, ALT, AST, γ-GT, ALP, ALB, TP, LDH, UREA/BUN, Cr, Na, K, Cl, Mg, Ca, P, amylase, AMY and FBG
Routine Urinalysis	PH, UWBC, UPRO, URBC, and UGLU
Thyroid Function	FT3, FT4, and TSH
Coagulation Function	PT and INR
Viral Serological Test	HBsAg, HBsAb, HBcAb, HBeAg, HBeAb, HBV DNA, HCV antibody, HCV RNA, and HIV antibody

ALB = albumin; ALP = alkaline phosphatase; ALT = alanine aminotransferase; AMY=amylase; ANC = absolute neutrophil count; AST = aspartate aminotransferase; BUN= blood urea nitrogen; Cr = serum creatinine; FBG = fasting blood glucose; FT3 = free triiodothyronine; FT4 = free thyroxine; γ-GT = γ-glutamyltransferase; HBcAb = hepatitis B core antibody; HBeAb = hepatitis B e antibody; HBeAg = hepatitis B e antigen; HBsAb = hepatitis B surface antibody; HBsAg = hepatitis B surface antigen; HBV = hepatitis B virus; HCV = hepatitis C virus; HGB = hemoglobin; HIV = human immunodeficiency virus; INR = international normalized ratio; LDH = lactate dehydrogenase; LYM = lymphocyte count; PH = pH; PLT = platelet; PT = partial thromboplastin time; TBIL = total bilirubin; TP = total protein; TSH = thyroid stimulating hormone; RBC = red blood cell; UGLU = urine glucose; UPRO = urine protein; URBC = urine red blood cell; UREA = urea; UWBC = urine white blood cell; WBC = white blood cell.

7.2.2.2 Pregnancy test

Serum β-human chorionic gonadotropin (β-hCG) pregnancy tests should be performed in women of childbearing potential (refer to Section 4.3 for definition) within 3 days prior to the first dose of study treatment and at the end-of-treatment visit. At each cycle a urine pregnancy test should be performed only in women of childbearing potential. If the result of urine β-hCG is positive or inconclusive, then serum β-hCG pregnancy test should be performed. Result of the serum pregnancy test is determinative. If the serum β-hCG result is positive, the subject is not eligible and must be excluded from the study.

7.3 Immunogenicity

Immunogenicity samples will be collected within 1 hour prior to sintilimab/placebo infusion in Cycles 1/2/4/8/12/16, then every 8 cycles (Cycle 24, 32, and so on) thereafter, and during the 30-day safety follow-up. If an infusion-related reaction occurs during sintilimab/placebo administration, blood samples should be taken near the start of the event, end of event, and around 30 days after the reaction, for immunogenicity analysis. Blood samples are analyzed at the central laboratory.

Each subject should be tested for anti-drug antibody (ADA) titer and ADA-positive specimens will be further tested for neutralizing antibodies (NAbs). For ADA and NAb analysis, 5 mL of whole blood will be collected using vacutainers with clot activator and serum will be separated and frozen in aliquots. Refer to the Laboratory Manual provided by the sponsor's designated central laboratory for sampling methods, sample storage, transportation, and analysis.

7.4 PK

PK samples will be collected at the following time points: within 1 h before, immediately after (+ 5 min), any point within 2-24 h after, any point within 144-192 h after sintilimab/placebo infusion in Cycle 1, within 1 h before sintilimab/placebo infusion in Cycle 2/4/8, immediately after (+ 5 min), any point within 2-24 h after, any point within 144-192 h after sintilimab/placebo infusion in Cycle 12, within 1 h before sintilimab/placebo infusion in Cycle 13 and 16, then 1 h before sintilimab/placebo infusion every 8 cycles (e.g. Cycle 24, 32, etc.), and at the first safety follow-up.

For PK analysis, 3.5 mL of whole blood will be collected using vacutainers with clot activator. Serum is then separated and frozen in aliquots. Refer to the Laboratory Manual provided by the sponsor's designated central laboratory for sampling methods, sample storage, transportation, and analysis.

7.5 Quality of Life Evaluation

Quality of life evaluation will be performed on the day of the first dose, during each imaging evaluation, and during the first safety follow-up as per EQ 5D-5L, EORTC QLQ-C30, and EORTC QLQ-OES18. Refer to Quality of Life Evaluation Manual provided by the sponsor for detailed evaluation scales and requirements.

EuroQol 5 Dimensions scale (EQ-5D-5L) is a multi-dimensional scale that measures health-related quality of life, which consists of a questionnaire and a visual analogue scale. The system is comprised of 5 dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension consists of 5 levels: no problems, slight problems, moderate problems, severe problems, and extreme problems. A total of 3125 possible combination of health states can be measured.

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

EORTC QLQ-OES18 is a supplement to the EORTC QLQ-C30 core questionnaire, which contains 18 items for measuring symptoms and adverse drug reactions related to esophageal cancer and consists of 4 scales (dysphagia, eating restriction, reflux, and pain) and six single items.

7.6 Biomarker Analysis

All eligible subjects must provide tumor tissues during screening. Acceptable tumor tissues include archival specimens or at least 5 unstained, 4–5 μm sections from a fresh specimen (tissue should have a surface area of 25 mm^2 containing greater than 20% of tumor cells) for evaluating PD-L1 expression. Subjects who are successfully screened could optionally provide 5 additional tumor tissue sections from the same paraffin block for a supplemental test for detecting PD-L1 expression.

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

7.7 Storage and Destruction of Biological Samples

If needed, certain analysis such as selectivity with incurred sample, parallelism with incurred sample, in-study cut point determination, et al., using pooled or individual samples which are necessary for further evaluation and validation of analytical methods may also be performed. Results of these analysis may be included in the CSR or published separately from the CSR.

Incurred samples reanalysis will be assessed simultaneously with the biological samples. The results of these evaluations will not be recorded in the CSR, but will be presented separately in a biological analysis report.

After all necessary analysis, subject information will be desensitized (including anonymized and pooled) and then disposed or destroyed.

8 Safety Reports and AE Management

8.1 Definition of AEs

An AE is defined as any adverse medical event that occurs since the signing of the informed consent form, regardless of whether or not it is considered as related to the study drugs. AEs include but are not limited to the followings:

- Deterioration of pre-existing (prior to enrollment) medical conditions/diseases (including symptoms, signs, and laboratory abnormalities);
- Any new adverse medical conditions (including symptoms, signs, and newly diagnosed diseases);
- Clinically significant laboratory abnormalities, changes in the vital signs, ECG abnormalities, and findings on physical examination.

8.2 Evaluating Adverse Events

An investigator who is a qualified physician will evaluate all adverse events. Any adverse event should be evaluated the relationship with study therapy. Any adverse event should be evaluated according to the NCI Common Terminology for Adverse Events (CTCAE), version 5.0. All adverse events regardless of CTCAE grade must also be evaluated for seriousness.

Table 11 Detailed rules of AE evaluation

CTCAE 5.0 Grade	**Grade 1**	**Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; medical intervention not indicated**
	Grade 2	**Moderate; minimal, local or non-invasive intervention required; limiting age-appropriate instrumental activities of daily living**
	Grade 3	**Severe or medically significant but not immediately life-threatening; hospitalization or prolonged hospitalization indicated; disabling; limiting self-care activities of daily life, but not bedridden**
	Grade 4	**Life-threatening consequences; urgent intervention indicated**
	Grade 5	**AE-related deaths**
Seriousness	A serious adverse event is any adverse event occurring at any dose or during any use of Sponsor's product that:	
	† **Results in death** (excluding those death due to PD);	
	† **Is life threatening;** or, places the subject, in the view of the investigator, at immediate risk of death from the event as it occurred (Note: This does not include an adverse event that, had it occurred in a more severe form, might have caused death.);	
	† **Results in a persistent or significant disability/incapacity;** (substantial disruption of one's ability to conduct normal life functions); or	
	† **Results in or prolongs an existing inpatient hospitalizatio**n; (hospitalization is defined as an inpatient admission, regardless of length of stay) (Note: Hospitalization for an elective procedure to treat a pre-existing condition that has not worsened is not a serious adverse event. A pre-existing condition is a clinical condition that is diagnosed prior to the use of a Innovent product and is documented in the patient's medical history.); or	
	† **Is a congenital anomaly/birth defect** (in offspring of subject taking the product regardless of time to diagnosis); or	
	Other important medical events that may not result in death, not be life threatening, or not require hospitalization may be considered a serious adverse event when, based upon 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 Sponsor's product to be discontinued?	

Relationship to Sponsor's Product	Did the Sponsor's product cause the adverse event? The determination of the likelihood that the Sponsor's product caused the adverse event will be provided by an investigator who is a qualified physician. 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 initialed 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 Sponsor's product and the AE;** the greater the correlation with the components and their respective elements (in number and/or intensity), the more likely the Sponsor's product caused the adverse event (AE):	
	Exposure	Is there evidence that the subject was actually exposed to the Sponsor's product such as: reliable history, acceptable compliance assessment (pill count, diary, etc.), expected pharmacologic effect, or measurement of drug/metabolite in bodily specimen?
	Time course	Did the AE follow in a reasonable temporal sequence from administration of the Sponsor's product? Is the time of onset of the AE compatible with a drug-induced effect (applies to trials with investigational medicinal product)?
	Possible causes	Is the AE not reasonably explained by another etiology such as underlying disease, other drug(s)/vaccine(s), or other host or environmental factors?
	Dechallenge	Was the Sponsor's product discontinued or dose/exposure/frequency reduced? If yes, did the AE resolve or improve? If yes, this is a positive dechallenge. If no, this is a negative dechallenge. (Note: This criterion is not applicable if: (1) the AE resulted in death or permanent disability; (2) the AE resolved/improved despite continuation of the Sponsor's product; or (3) the trial is a single-dose drug trial); or (4) Sponsor's product(s) is/are only used one time.)
	Rechallenge Tests	Was the subject re-exposed to the Sponsor's product 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 trial is a single-dose drug trial); or (3) Sponsor's product(s) is/are used only one time).
	Consistency	Is the clinical/pathological presentation of the AE consistent with previous knowledge regarding the Sponsor's product

	with Trial Treatment Profile	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.		
Record one of the following		**Use the following scale of criteria as guidance (not all criteria must be present to be indicative of a Sponsor's product relationship).**
Yes, there is a reasonable possibility of Sponsor's product relationship.		There is evidence of exposure to the Sponsor's product. The temporal sequence of the AE onset relative to the administration of the Sponsor's product is reasonable. The AE is more likely explained by the Sponsor's product than by another cause.
No, there is not a reasonable possibility of Sponsor's product Relationship		Subject did not receive the Sponsor's product OR temporal sequence of the AE onset relative to administration of the Sponsor's product is not reasonable OR the AE is more likely explained by another cause than the Sponsor's product.

8.3 AE Documentation

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

8.3.1 Collection and time of AEs

The investigator should use non-leading questions when asking the subjects about AEs.

All AEs including SAEs and irAEs will be collected within 90 days after the last dose if new anti-tumor therapy has not been initiated. Only irAEs and study treatment- or procedure-related SAE will be collected if a new anti-tumor therapy has been initiated.

After 90 days since the last dose, investigator should report sintilimab-related or procedure-related SAEs.

8.3.2 Follow-up of AEs

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

8.3.3 Contents of AE documentation

The investigator must document all the AEs, including the diagnosis (document signs and symptoms including the laboratory abnormalities if there is no diagnosis), time and date of occurrence (if applicable), CTCAE grade and changes in severity, whether it is an SAE, irAE or not, measures taken for the study drugs, treatment for the AE and outcome of the event, and relationship between the event and study drugs.

For an SAE, the investigator should also provide the date when the AE meets the criteria for an SAE, the date when the investigator is informed of the SAE, the reason that it is considered an SAE, date of hospitalization, date of hospital discharge, possible cause of death, date of death, whether an autopsy has been performed, causality assessment (the drug being investigator or other drugs included in the regimen), and other possible causes of the SAE. The investigator should provide their rationale for the causality and a description of the SAE. In the SAE description, the following should also be included: the subject number, age, gender, height, and

weight; indication for receiving the investigational drug, cancer staging, and overall condition; SAE occurrence, development, outcome, and result; laboratory results related to the SAE (the time of the examination, units, and normal ranges must be provided); medical history, onset and duration of concurrent diseases related to the SAE; medication history and initiation, duration, and dosage of concomitant medications related to the SAE; initiation, duration, and dosage of the study drugs.

Descriptions of the AE are as follows:

Diagnosis, signs, and symptoms

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

AEs secondary to other events

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

Ongoing or recurrent AEs

An ongoing AE refers to an event that does not resolve and is ongoing between two assessment time points. These AEs should only be documented once in the eCRFs.

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

Laboratory abnormalities

Any abnormal laboratory finding that is clinically significant should be reported as an AE. The investigator is responsible for reviewing all the laboratory abnormalities and determine whether the findings should be reported as AEs.

Death

During the entire course of the study, all deaths (including those that occur before Day 90) after the last dose should be documented in the Mortality Report Form of the eCRFs and reported to the sponsor in a timely manner, regardless of the causality with the study drugs.

If the cause of death is known, record the cause of death as an AE and the outcome of the event as a death and submit an SAE report; if the cause of death is unclear, the AE should be recorded as Death of Unknown Cause in the AE form, and submit the SAE report as Death of Unknown Cause. The exact cause of the death should be further investigated.

If the cause of death is confirmed to be PD, then the event may not be documented or reported as an SAE, but the event should be documented in the Mortality Report Form of the eCRF and reported to the sponsor timely.

If the subject initiates a new anti-tumor therapy within the 90 days after the last dose, the death after the initiation of new therapy should not be reported as an SAE, unless the death is believed to be related to study drugs or study procedures.

Pre-existing medical conditions

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

Hospitalization, prolonged hospitalization, or surgery

Any AE that results in hospitalization or prolonged hospitalization should be documented and reported as an SAE, except for the following situations:

- Hospitalization or prolonged hospitalization as required by study protocol (such as for dose administration or efficacy evaluation).
- Hospitalization due to a pre-existing medical condition that remains stable, e.g. elective surgery/therapy scheduled prior to the study.

However, elective surgery/therapy required because of the exacerbated condition during the study (e.g. surgery/therapy required earlier than scheduled) should be considered as an AE.

Progressive disease

A PD is defined as the worsening of subject condition caused by the primary tumor that the study drug is targeting, the appearance of new lesions, or the progression of the primary lesion. PD will not be reported as an AE. Any life-threatening events, hospitalization or prolonged

hospitalization, permanent or significant disability/incapacity, congenital anomaly/birth defects, or other important medical events caused by PD will not be reported as an SAE.

Overdose

An overdose is the administration of a drug at more than 20% of the dose specified in the study protocol. All the occurrences of overdose must be documented in the eCRF. Any adverse events resulting from the overdose should be recorded. If the adverse events met the serious criteria, it should be reported as a SAE.

New anti-tumor therapy

All irAEs and study treatment- or procedure-related SAEs occurred within 90 days after the last dose are required to be documented and reported if a new anti-tumor therapy has been initiated.

8.4 Expedited Reporting of SAEs and Pregnancy

SAE reporting:

All the SAEs that occur from the signing of ICF through Day 90 (inclusive) after the last dose must be reported within 24 hours. The investigator must fill out the SAE Report Form provided by the sponsor, regardless of whether it is the initial report or a follow-up report. Besides, the investigator must report the SAE to the sponsor (drugsafety@innoventbio.com) by the time within 24 hours after noticing the event. In accordance with the laws and regulations of corresponding regions and countries, the investigator should also report the SAE to the regulatory authorities and EC/IRB

For SAEs occurring beyond the above period, those considered related to sintilimab should also be reported.

The investigator must submit the completed SAE report form to the sponsor within 24 h after noticing the event. The investigator should urgently collect all missing information and provide a complete SAE report. The investigator should also notify the regulatory authorities and EC in accordance with the regulations.

Pregnancy

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

During the study, if a female subject exposed to the study drugs becomes pregnant, she must be excluded from the study. The investigator must report the sponsor within 24 h of noticing the

event and submit the Innovent Clinical Study Pregnancy Report/Follow-Up Form.

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

The investigator must continuously monitor and visit on the outcome of the pregnancy until the 8th week after the subject gives birth. The outcome should be reported to the sponsor.

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

If the subject also experienced an SAE during the pregnancy, the event should be reported according to SAE procedures.

8.5 Abnormal Hepatic Function

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

Table 12 Liver injuries required to be reported as SAEs

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

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

Other than repeated AST and ALT tests, albumin, creatine kinase, TBIL, direct and indirect bilirubin, γ-GT, PT/INR, and ALP should also be tested. Detailed medical history includes history of alcohol, acetaminophen, soft drugs, various supplements, traditional Chinese

medicine, chemical drug exposure, family diseases, occupational exposure, sexual behavior, travel, contact with subjects with jaundice, surgery, blood transfusion, hepatic diseases or allergies, cardiac diseases, and immune diseases. Further tests may include the detection of acute hepatitis A, B, C and E, hepatic imaging (such as biliary tract), autoantibodies, and echocardiography. If a retest showed consistency with the criteria outlined in **Table 12** and there is no other possible cause, the possibility of drug-induced liver injury should be considered before all the results of etiological tests are accessible. These potential drug-induced liver injuries should be reported as SAEs. Additional dosing with the study drugs should follow the Dose Modification Criteria included in Section 5.2.2.

8.6 Management of Drug-Related Toxicities

During the course of the trial, the sponsor will conduct blinded safety review for the irAE regularly.

8.6.1 irAEs

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. Refer to the latest guideline for Management of Immunotherapy-Related Toxicities for a detailed guide on irAE management.

Sponsors will continue to collect irAEs until 90th day after the last dose. An irAE should be followed up until it resolves to Grade 0-1 or baseline level, or investigators decide not to follow up anymore with acceptable reasons (e.g. cannot fully recover or getting better).

8.7 Unblinding

8.7.1 Emergency unblinding

This is a randomized, double-blind study followed by an open-label phase. During the randomization phase, subjects are randomized to either sintilimab or placebo arm in a double-blind form. The investigators, subjects, medical personnel and assistants, as well as the sponsor and designee do not know the exact drug given other than the chemotherapy.

During the study, if there is a need for unblinding such as occurrence of an SAE, the responsible investigator will submit a request, then the sponsor and principal investigator will decide

together whether to unblind. If emergency unblinding is required, the investigator can discuss with the sponsor and submit a request to unblind. After approval, the subject's treatment allocation will be known through the IWRS.

For safety reasons, the sponsor's medical monitor may unblind certain subjects through the IWRS during the study. The investigator, subject, and other personnel of the sponsor should not be unblinded unless the information is necessary for the safety consideration of the subject.

8.7.2 Accidental unblinding

Every effort should be made to ensure that the subjects and investigators remain blinded to treatment allocation. However, unblinding may take place accidentally. The unblinding to the investigators, study personnel performing evaluations at the study sites, or subjects will not be an adequate reason to discontinue the study treatment for the subject or exclude the subject from safety or efficacy analyses (the reason may be an exciting cause).

9 Statistics

9.1 Statistical Analysis Plan

A detailed statistical analysis plan (SAP) will begin after the first enrollment and will be finalized prior to database locking and unblinding. The SAP should contain details of all analyses and the presentation of results.

9.2 Hypothesis and Sample Size Calculation

This is a superiority trial. The primary efficacy endpoints are the OS in the overall population and in the PD-L1-positive population. The hypotheses of superiority are:

Null hypothesis H0: HR ≥ 1

Alternative hypothesis Ha: HR < 1

This is a Phase 3 trial with OS as the primary endpoint. The overall type I error of the hypothesis testing on the two populations for the efficacy endpoint of OS was strongly controlled by initially assigning a one-sided α of 0.0125 to the overall population OS hypothesis and a one-sided α of 0.0125 to the PD-L1 positive population OS hypothesis.

For OS in the overall population, assuming that the hazard ratio (HR) of sintilimab to placebo, in combination with chemotherapy, is 0.75 [the median OS (mOS) is 13.3 and 10 months, respectively], 500 OS events are required to provide approximate 83% power (one-sided α for OS in the overall population is 0.0125, which accounts for one interim analysis). It is estimated that approximately 55% of the overall population is PD-L1 positive (CPS⩾10%). For OS in the PD-L1 positive population, assuming that the HR of sintilimab to placebo, in combination with chemotherapy, is 0.65 (the mOS is 15.4 and 10 months, respectively), 240 OS events are required to provide approximate 86% power (one-sided α level of 0.0125, which accounts for one interim analysis).

It is estimated that 676 subjects need to be enrolled to observe the 500 OS events required for the randomization phase in this study.

For the open-label phase, only descriptive statistics will be provided for both efficacy and safety endpoints. A sample size of 70 subjects will be adequate for descriptive summaries.

This study is designed to have at least 1 and no more than 2 interim analyses. Details of the interim analysis are described in detail in Section 9.4.5.

9.3 Statistical Analysis Population

Intention-to-treat set (ITT): all enrolled subjects who are randomized. Treatment arms are analyzed based on results of the randomization.

Safety analysis set (SS): includes all randomized subjects who received at least one dose of study treatment during the randomization phase and all enrolled subjects who received at least one dose of sintilimab during the open-label phase. Subjects are analyzed based on the actual treatment received during the study. The SS is used for all the safety evaluations. Treatment arms are analyzed based on the actual allocations.

Per-protocol set (PPS): A subset of ITT, refers to subjects who do not have major protocol violations that affect the efficacy evaluation. The PPS is used for the sensitivity analyses of primary efficacy endpoints and key secondary efficacy endpoints.

9.4 Statistical Analysis Methods

For the randomization phase, see Section 9.4.1 and 9.4.2 for analyses of primary and secondary endpoints. For the open-label phase, descriptive statistics will be provided for all the applicable endpoints that are described in the randomization phase. During the open-label phase, for any time-to-event endpoints, date of first dose of investigational medical product (IMP) will be used instead of randomization date in the definitions when start date and censored date need to be specified.

9.4.1 General statistical analysis

Continuous data will be summarized using mean, standard deviation, median, maximum, and minimum. Categorical data will be described using frequency and percentage.

All the statistical analyses will be performed with SAS 9.2 (or higher).

Efficacy results that are deemed to be statistically significant after consideration of the Type-I error control strategy are described in Section 9.4.7. Nominal p-values will be computed for primary and key secondary efficacy endpoints other than those presented in Section 9.4.1.1 and 9.4.1.2 but should be interpreted with caution due to potential issues of multiplicity.

9.4.1.1 Analysis of primary efficacy endpoints

The primary efficacy endpoints are OS in the overall and PD-L1-positive population.

- OS-overall population or OS-PD-L1-positive population: from randomization to the date of death. At the end of the study, subjects who are alive will be censored at the "last known alive date".

A stratified log-rank test will be used to compare the OS between treatment arms. The HR and corresponding 95% CI will be estimated with a stratified Cox proportional hazards model where

the stratifications used are stratification factors used for randomization. The adjusted confidence interval using actual risk will also be provided for HR if required by the regulatory authorities. The mOS and corresponding 95% CIs will be estimated via the Kaplan-Meier method, and survival curves will be plotted.

Sensitivity analyses with OS endpoint also include max-combo test.

9.4.1.2 Analysis of key and other secondary efficacy endpoints

The key secondary efficacy endpoints are ORR and PFS in the overall and PD-L1-positive populations. The other secondary efficacy endpoints are DCR and DoR in the overall and PD-L1-positive populations.

- ORR: the proportion of subjects in the ITT analysis set who have achieved Investigator-determined CR or PR per RECIST v1.1.

The ORRs and corresponding 95% CIs of the sintilimab arm and placebo arm will be estimated using normal approximation. The difference and corresponding 95% CI of ORRs between the treatment arms will also be computed based on Miettinen-Nurminen methods for stratified data where the stratification factors will be identical to those in the primary analysis of OS.

- PFS will be analyzed using the ITT analysis set.

PFS is the time from randomization to first date of investigator-determined progression (by imaging), or to death due to any cause. Subjects who neither progress nor die will be censored at the date of their last tumor imaging evaluation. Subjects who do not have any tumor imaging evaluation after baseline will be censored on the date of randomization.

A stratified log-rank test will be used to compare the PFSs between treatment arms. The HR and corresponding 95% CI will be estimated with a stratified Cox proportional hazards model where stratifications are the same as those used for the OS analysis. The mPFS and corresponding 95% CI will be estimated via the Kaplan-Meier method, and survival curves will be plotted.

- DCR: the proportion of subjects in the ITT analysis set who have achieved Investigator-determined CR or PR or stable disease (SD).

The DCRs and corresponding 95% CIs of the sintilimab arm and placebo arm will be estimated. The difference and corresponding 95% CI of DCRs between the treatment arms will also be computed.

- DoR: subjects who have achieved CR or PR: from first date of investigator-determined response to investigator-determined PD or death; subjects who neither progress nor die: be censored at the date of their last tumor imaging evaluation.

The mDoR will be estimated via the Kaplan-Meier method and survival plots will be presented.

9.4.2 Safety analysis

The safety analysis will use the SS. Safety parameters include AEs, laboratory tests, vital signs, ECG, immunogenicity, etc. Unless otherwise stated, all the safety analyses will be summarized by treatment arm.

9.4.2.1 Drug exposure

The amount of drug exposure and duration of treatment (number of treatment cycles) will be summarized.

9.4.2.2 AEs

All the AEs will be coded according to MedDRA.

The incidence (frequency) of AEs, TEAEs, TRAEs, irAEs, SAEs, AEs resulting in treatment discontinuation, and AEs resulting in death will be summarized. The severity distribution of TEAEs, TRAEs, and irAEs will be summarized using NCI CTCAE v5.0 presented by SOC/PT.

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

9.4.2.3 Laboratory tests

Abnormalities in hematology and biochemistry will be assessed through laboratory parameters. Each laboratory test result will be graded according to NCI CTCAE v5.0. The number of subjects with laboratory abnormalities at baseline will be presented by severity grade. Laboratory parameters measured on the day of first dose of study treatment (Day 1 of Cycle 1) will be considered as baseline measurements. The treatment phase for all laboratory parameters begins after Day 1 of study treatment.

The frequency of laboratory abnormalities of each subject during the treatment phase will be summarized by severity grade. The worst grade (most severe) for each subject will be used if the same laboratory parameter was found to be abnormal more than once. All the laboratory parameters will be summarized by the worst NCI grade.

Shift tables describing changes in frequency of any given laboratory parameter before and after treatment based on NCI grades will be provided.

Lists of subjects with laboratory abnormalities ≥ grade 3 will be provided.

For any given laboratory parameter, a subject is considered evaluable if at least one measurement is available.

Routine urinalysis: A shift table is used to describe changes between normalities and abnormalities before and after the treatment.

9.4.2.4 ECG

Descriptive statistics are used for ECG and changes from baseline. A shift table is used to describe ECG changes in PR and QTc from baseline before and after the treatment and data lists will be provided for other abnormalities.

9.4.2.5 Vital signs, physical examinations, and other safety-related examinations

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

Abnormal changes from baseline in physical examination will be listed.

9.4.2.6 Immunogenicity

Immunogenicity data will be presented with descriptive statistics. The numbers and percentages of subjects with ADAs and NAbs will be summarized.

9.4.3 Compliance

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

The proportion of subjects administered study drugs of doses between 80–110% of the dose specified in the protocol, who complete the study in accordance with study protocol, and who complete different number of treatment cycles will also be summarized.

9.4.4 Baseline characteristics and concomitant medications

Subjects' demographics (sex, race, ethnicity and age), tumor diagnosis information (pathological diagnosis, tumor staging, prior treatment), baseline tumor evaluation (target lesion, number of non-target lesions, sites, total diameter, etc), and other baseline information [height and weight (BMI, BSA), vital signs, laboratory tests, past/concomitant medications] will be analyzed using descriptive statistics.

Other important baseline information such as region, choice of chemotherapies and time of

enrollment (prior or after protocol Version 3.0) will also be summarized.

9.4.5 Interim analysis

This study is designed to have at least 1 and no more than 2 interim analyses. OS will be statistically tested separately for the overall population and the PD-L1-positive population (CPS ≥ 10) at the interim analysis for the randomization phase. Considering that the time to reach the preset events may be different between the overall population and the PD-L1-positive population, the final number of interim analyses will be determined according to the estimated time to reach the preset number of OS events in each population in a blind manner just before planned interim analysis timepoint. This decision was made prior to unblinding of the first interim analysis and the number of prespecified interim analyses would not be modified afterwards.

The type I error boundary for the interim analysis was determined using the Lan-DeMets spending function in combination with the O'Brien-Fleming boundary in both populations. The analysis time points for each population are: interim analysis of OS in the overall population at approximately 70% (350) OS events; interim analysis of OS in the PD-L1-positive population at approximately 70% (168) OS events. Assuming that at the time of the first OS analysis for the PD-L1-positive population, the number of OS events in the overall population is far below the preset 350 (less than approximately 310, 62% of the overall number of events), 3 OS analyses will be performed for the overall population, that is, an interim analysis will be performed based on the actual number of OS events in the overall population when the prespecified number of OS events in the interim analysis for PD-L1-positive population is reached; a second interim analysis of OS in the overall population will be performed when the preset number of OS events in approximately 70% of the overall population occurs; and a final OS analysis will be performed when approximately 500 OS events in the overall population occur. As mentioned above, the decision on whether to add an interim analysis or not must be made before the first interim analysis event, based on the blind data, and using the same preset O'Brien-Fleming spending function. The alpha boundary under the different scenarios of number of interim analyses is shown in the table below.

Table 13 Boundary under different OS interim analysis strategies

PD-L1 positive (CPS ≥ 10) Subgroup			
Number of events	Nominal alpha Boundary	Type I error	HR Boundary
168 (70%)	0.0028	0.0028	0.652
240 (final analysis)	0.0116	0.0097	0.746

Overall Population (1 time Interim Analysis)			
Number of events	Nominal alpha Boundary	Type I error	HR Boundary
350 (70%)	0.0028	0.0028	0.744
500 (final analysis)	0.0116	0.0097	0.816
Overall Population (2 times Interim Analysis: Scenario 1)			
Number of events	Nominal alpha Boundary	Type I error	HR Threshold
310 (62%)	0.0015	0.0015	0.714
350 (70%)	0.0024	0.0013	0.740
500 (final analysis)	0.0116	0.0097	0.816
Overall Population (2 times Interim Analysis: Scenario 2)			
Number of events	Nominal alpha Boundary	Type I error	HR Boundary
290 (58%)	0.0010	0.0010	0.697
350 (70%)	0.0025	0.0018	0.741
500 (final analysis)	0.0116	0.0097	0.816

If the interim analysis under the actually applied interim analysis strategies does not reach statistical significance, and the actual number of events at the time of final analysis is different from the preset number of events, the boundary for the last analysis will be adjusted using the Hwang-Shih-DeCani spending function based on the actual number of events.

Refer to Section 9.4.7 for specific methods for controlling type I error in the analysis described above.

The interim analysis will be submitted to the iDMC. Refer to Section 3.3 for details regarding the iDMC.

9.4.6 Subgroup analysis

Subgroup analysis is based on stratification factors, subjects' baseline characteristics, and other potential clinically significant factors.

9.4.7 Multiple comparisons and adjustments

For OS, the overall type I error rate is maintained by pre-specifying the α used for evaluating the overall population and the PD-L1-positive population separately. At both interim analysis and

final analysis, OS in overall population and OS in PD-L1 positive population will be tested. If at either interim analysis or at final analysis, any test evaluating a particular population reaches statistical significance, all α allocated to that population will be transferred to the other population according to **Figure 2** . After the change in α for a population, the same O'Brien-Fleming spending function will be used to further calculate the α distributed to the interim and final analysis for that population. When applicable, the updated interim analysis boundary will also be used to conduct a retrospective comparison on the occurred interim analysis statistical test results after the completion of α value transfer. If the original analysis is found to be statistically significant compared to the updated boundary, then it will be statistically confirmed that the endpoint has reached statistical significance in the previous interim analysis.

If required by regulatory requirement per specific regions or countries, key secondary endpoints will also be tested under significant levels subject to multiplicity adjustment. Specifically, if the primary analyses for both populations are statistically significant, the fixed sequence of testing secondary endpoints will be ORR in overall population → PFS in overall population → ORR in PD-L1 positive population → PFS in PD-L1 positive population. Formal testing of key secondary endpoints for each respective population will only be conducted once at the first interim analysis for the respective population.

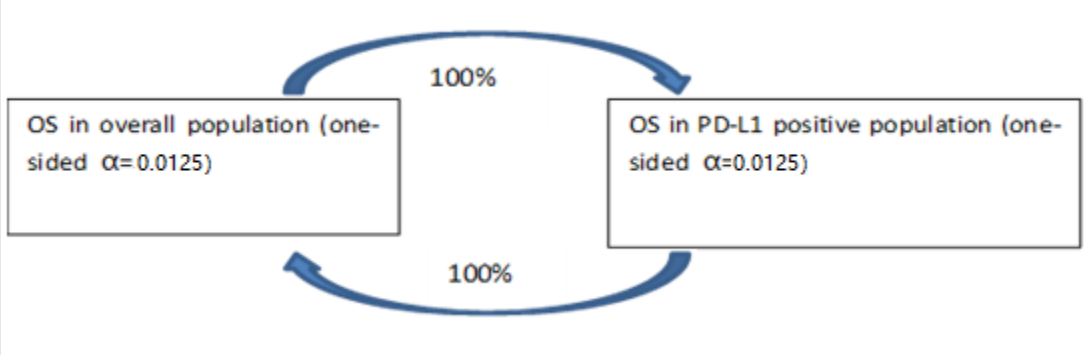

Figure 2 Alpha transfer for OS endpoint between two populations

9.4.8 Exploratory analysis

Compare the changes in quality of life between the two randomized treatment arms;

Study the PK characteristics of sintilimab in combination with chemotherapy in subjects with unresectable locally advanced, recurrent, or metastatic ESCC; will include, but is not limited to, descriptive summary statistics of sintilimab trough concentrations;

Evaluate the correlation between biomarkers in tumor tissue and efficacy, including PD-L1

expression level.

9.5 Methods for Controlling Bias

9.5.1 Randomization and blinding

The investigators, subjects, and sponsor must remain blinded to the treatment allocations during the randomization phase of the study. Refer to Section 8.7 if unblinding is required due to AEs.

Randomization will be implemented in the IWRS, stratified by ECOG PS score (0 or 1), hepatic metastasis (positive or negative), chemotherapy regimens (TP or CF), and PD-L1 expression (TPS < 10% or ≥ 10%). The investigator or qualified designee will log in to the IWRS through their respective passwords. The system will assign each subject a unique randomization number and the corresponding treatment arm: sintilimab + chemotherapy or placebo + chemotherapy. Subjects allocated to the sintilimab + chemotherapy arm will receive sintilimab in combination with TP/CF regimen; subjects allocated to the placebo + chemotherapy arm will receive placebo in combination with TP/CF regimen.

The independent statistician responsible for randomization will use the blocked randomization to generate a random assignment table (subjects' random numbers), in accordance with the ratio of sintilimab + chemotherapy arm: placebo + chemotherapy arm = 1:1. The sponsor's study drug supply team will package the study drug according to the list of study drug random number.

For this study, subjects who meet the exclusion criteria are allowed to be re-screened. Subjects who are re-screened will be identified in the IWRS. Each subject can only undergo randomization once. Forced randomization is not allowed in this study.

In this study, the stratification factor of PD-L1 expression (TPS < 10% or ≥ 10%) requires approximately 250 PD-L1 positive subjects expressing TPS ≥10% in the overall population.

9.5.2 Blinding maintenance evaluation

Other than situations that require emergency unblinding as outlined in Section 8.7, the investigators, subjects, and sponsor must remain blinded to the treatment allocations during the randomization phase of the study.

In this study, iDMC is used for the interim analysis. The iDMC will receive blind and unblinded reports from independent statisticians. The investigators, subjects, and sponsor must remain blinded during this process.

Data that may lead to unblinding, such as drug concentration, will not be accessible by the investigators, subjects, and sponsor's research team in this study.

10 Quality Assurance and Quality Control

In accordance with the Good Clinical Practice (GCP), the sponsor is responsible for the implementation and maintenance of quality assurance and quality control systems as per appropriate standard operating procedures, to ensure 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.

Each study site will implement internal quality management of the study process, data and biological sample collection, documentation, and completion. Particular quality management plans should be developed for each study site.

10.1 Clinical Monitoring

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

Before the study begins, the monitor will assess the competency of each study site, and report issues related to facilities, technical equipment, and medical personnel to the sponsor. During the course of the study, the monitor is responsible for the monitoring of whether the written ICF from all subjects have been obtained and whether the data records are correct and complete. The monitor should compare the data recorded in the eCRFs with the raw data, and inform the investigator of any errors or omissions. Besides, the monitor should also control the compliance of the protocol and study procedures for each study site, arrange for the supply of study drugs, and ensure that the drugs are kept under proper conditions.

The monitoring visits should be conducted in accordance with relevant laws and regulations. From the time the subjects are enrolled, each center shall receive regular visits for the purpose of monitoring. After each visit to the investigator, the monitor should submit a written report to the sponsor.

10.2 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, source records, and source data.

11 Data Management and Record Keeping

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

Data entry into the eCRFs should be completed as soon as possible during or after visiting. The eCRFs should be updated at any time to ensure that they reflect the latest 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, then evaluate the completeness and consistency by comparing them with the source document especially the 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 an inquiry in the EDC for suspicious data. The study site personnel are responsible for dealing with such inquiry. The EDC system will record the audit trail of the inquiry, 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.). Permanent copies of study visit records will be considered as source documents which is used to record the data of enrolled subjects. Data in the eCRFs should be retrieved from the source documents and consistent with source data.

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 are 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.

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

The study documents should be properly kept for future reviews or data tracking. Security and environmental risks should be considered for keeping documents.

No study documents can be destroyed without the written consent from the sponsor and investigator. The investigator/study site may transfer the study documents to other parties or another location that comply with the record-keeping requirements only after notifying the sponsor and obtaining the written consent.

12 Ethics

12.1 EC

The sponsor or designee will prepare the relevant documents including the trial 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 in 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 correspond 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.

12.2 Implementation of Ethics

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

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 violations must be reported to the EC, sponsor, or regulatory authorities.

12.3 Informed Consent

Before the start of any study process, the ICF is introduced to explain the risks and benefits of this study to potential participants, 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 inquiries, and has sufficient time for consideration. Written consent must be obtained from the subject. All signed ICFs must be kept in the investigator's files or in the subject's folder.

The investigator is responsible for the interpretation of the ICF of the subject, obtaining informed and dated ICF from the subject prior to the start of the study. After signing, the investigator should send the subject a copy of the signed ICF. The investigator is required to document the process of ICF in the source study document.

12.4 Protection of Subjects' Data

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

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

12.5 Protocol Deviations

Protocol deviation refers to any non-compliance with the study protocol, the International Conference on Harmonization Good Clinical Practice (ICH GCP), or operating manual. Non-compliance may come from the subjects, investigators, or study site personnel. Corrective actions shall be taken and completed in a timely manner in response to the deviation.

13 Publishing of Study Data

All the data generated in this study is the confidential information owned by the sponsor. The sponsor has the right to publish the study results. Information about the publishing policies between the sponsor and investigator will be described in the clinical trial agreement.

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

The sponsor has the right to announce or publish information or data related to the trial or to report it to the drug administration. The sponsor must obtain the consent of the investigator if the name of the investigator would be included in the content of the announcement, publication, or advertisements.

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15 Appendix

Appendix 1: Signature Page for Investigator

Protocol Title: A Multicenter, Double-Blind, Randomized Phase 3 Clinical Trial Evaluating the Efficacy and Safety of Sintilimab vs. Placebo, in Combination with Chemotherapy, for First-Line Treatment of Unresectable, Locally Advanced, Recurrent, or Metastatic Esophageal Squamous Cell Carcinoma (ORIENT-15)

Protocol Number: CIBI308A301

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

Instructions for investigators: please sign and date this page, print the name of the investigator, position, and study site, and return the signed form to Innovent Biologics (Suzhou) Co., Ltd..

I have read the entire content of this study protocol and will perform the study as required:

Signature of Investigator: _____ Date: _____

Name (Print): _____

Title of Investigator: _____

Study Site/Address: _____

_____

_____

Appendix 2: ECOG PS

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

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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, tumour lesions/lymph nodes will be categorized measurable or non-measurable as follows:

1.1.1 Measurable

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

- 10 mm by CT scan (CT scan slice thickness no greater than 5 mm)
- 10 mm 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:

- 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;
- 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.
- Blastic bone lesions are non-measurable.

Cystic lesions:

- 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;
- 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.

Tumor markers: Tumor markers alone cannot be used to assess objective tumor response. If markers are initially above the upper normal limit, however, they must normalize for a subject to be considered in complete response. Because tumor markers are disease-specific, instructions for their measurement should be incorporated into protocols on a disease specific basis. Specific guidelines for both CA-125 response (in recurrent ovarian cancer) and PSA response (in

recurrent prostate cancer), have been published. In addition, the Gynecologic Cancer Intergroup has developed CA-125 progression criteria which are to be integrated with objective tumor assessment for use in first-line trials in ovarian cancer.

Cytology, histology: These techniques can be used to differentiate between PR and CR in rare cases if required by protocol (for example, residual lesions in tumor types such as germ cell tumors, where known residual benign tumors can remain). When effusions are known to be a potential adverse effect of treatment (e.g. with certain taxane compounds or angiogenesis inhibitors), the cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment can be considered if the measurable tumor has met criteria for response or stable disease in order to differentiate between response (or SD) and PD.

2. Tumor Response Evaluation

2.1 Assessment of Overall Tumor Burden and Measurable Disease

To assess objective response or future progression, it is necessary to estimate the overall tumor burden at baseline and use this as a comparator for subsequent measurements. Only subjects with measurable disease at baseline should be included in protocols where objective tumor response is the primary endpoint. Measurable disease is defined by the presence of at least one measurable lesion. In studies where the primary endpoint is tumor progression (either time to progression or proportion with progression at a fixed date), the protocol must specify if entry is restricted to those with measurable disease or whether subjects having non-measurable disease only are also eligible.

2.2 Baseline Documentation of Target and Non-Target Lesions

When more than one measurable lesion is present at baseline all lesions up to a maximum of five lesions total (and a maximum of two lesions per organ) representative of all involved organs should be identified as target lesions and will be recorded and measured at baseline (this means in instances where subjects have only one or two organ sites involved a maximum of two and four lesions respectively will be recorded).

Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, but in addition should be those that lend themselves to reproducible repeated measurements. On occasion, the largest lesion does not lend itself to

reproducible measurement in which circumstance the next largest lesion which can be measured reproducibly should be selected.

Lymph nodes merit special mention since they are normal anatomical structures which may be visible by imaging even if not involved by tumor. Pathological nodes which are defined as measurable and may be identified as target lesions must meet the criterion of a short axis of ≥ 15 mm by CT scan. Only the short axis of these nodes will contribute to the baseline sum. The short axis of the node is the diameter normally used by radiologists to judge if a node is involved by solid tumor. Nodal size is normally reported as two dimensions in the plane in which the image is obtained (for CT scan this is almost always the axial plane; for MRI the plane of acquisition may be axial, saggital or coronal). The smaller of these measures is the short axis. For example, an abdominal node which is reported as being 20 mm × 30 mm has a short axis of 20 mm and qualifies as a malignant, measurable node. In this example, 20 mm should be recorded as the node measurement. Nodes with short axis ≥ 10 mm but < 15 mm should not be considered target lesions. Nodes that have a short axis < 10 mm are considered non-pathological and should not be recorded or followed.

A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. If lymph nodes are to be included in the sum, then as noted above, only the short axis is added into the sum. The baseline sum diameters will be used as reference for baseline level of disease.

All other lesions including pathological lymph nodes should be identified as non-target lesions and should also be recorded at baseline. These lesions should be followed as "present", "absent", or in rare cases "unequivocal progression". Multiple target lesions involving the same target organ may be recorded as a single item (e.g. "multiple enlarged pelvic lymph nodes" or "multiple liver metastases").

2.3 Response Criteria

2.3.1 Evaluation of target lesions

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.

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).

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.

2.3.2 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.

2.3.3 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.

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

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

2.3.4 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.

2.3.5 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.

2.4 Evaluation of Best Overall Response

The best overall response is the best response recorded from the start of the study treatment until the end of treatment taking into account any requirement for confirmation. On occasion a response may not be documented until after the end of therapy so protocols should be clear if post-treatment assessments are to be considered in determination of best overall response. Protocols must specify how any new therapy introduced before progression will affect best response designation. The subject’s best overall response assignment will depend on the findings of both target and non-target disease and will also take into consideration the appearance of new lesions. Furthermore, it depends on the nature of the study, protocol requirements, and results. Specifically, in non-randomized trials where response is the primary endpoint, confirmation of PR or CR is needed to deem either one the "best overall response".

2.4.1 Time point response

It is assumed that at each protocol specified time point, a response assessment occurs. **Table 14** provides a summary of the overall response status calculation at each time point for subjects who have measurable disease at baseline.

When subjects have non-measurable (therefore non-target) disease only, **Table 15** is to be used.

2.4.2 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. This would be most likely to happen in the case of PD. For example, if a subject had a baseline sum of 50 mm with three measured lesions and at follow-up only two lesions were assessed, but those gave a sum of 80 mm, the subject will have achieved PD status, regardless of the contribution of the missing lesion.

2.4.3 Best overall response: all time points

The best overall response is determined once all the data for the subject is known.

Best response determination in trials where confirmation of complete or partial response is not required: Best response in these trials is defined as the best response across all time points (for example, a subject who has SD at first assessment, PR at second assessment, and PD on last assessment has a best overall response of PR). When SD is believed to be best response, it must also meet the protocol specified minimum time from baseline. If the minimum time is not met when SD is otherwise the best time point response, the subject's best response depends on the subsequent assessments. For example, a subject who has SD at first assessment, PD at second and does not meet minimum duration for SD, will have a best response of PD. The same subject lost to follow-up after the first SD assessment would be considered inevaluable.

Best response determination in trials where confirmation of CR or PR is required: CR or PR may be claimed only if the criteria for each are met at a subsequent time point as specified in the protocol (generally 4 weeks later). In this circumstance, the best overall response can be interpreted as in **Table 16**.

2.4.4 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 **Table 14** to **Table 16**.

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 14 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 15 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 16 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 = inevaluable. 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.

2.5 Frequency of Tumor Re-Evaluation

Frequency of tumor re-evaluation while on treatment should be protocol specific and adapted to the type and schedule of treatment. However, in the context of Phase 2 studies where the beneficial effect of therapy is not known, follow-up every 6–8 weeks (timed to coincide with the end of a cycle) is reasonable. The protocol should specify which organ sites are to be evaluated at baseline (usually those most likely to be involved with metastatic disease for the tumor type under study) and how often evaluations are repeated. Normally, all target and non-target sites are evaluated at each assessment. In selected circumstances certain non-target organs may be evaluated less frequently. For example, bone scans may need to be repeated only when complete response is identified in target disease or when progression in bone is suspected.

After the end of the treatment, the need for repetitive tumor evaluations depends on whether the trial has as a goal the response rate or the time to an event (progression/death). If "time to an event" (e.g. time to progression, disease-free survival, progression-free survival) is the main endpoint of the study, then routine scheduled re-evaluation of protocol specified sites of disease is warranted. In randomized comparative trials in particular, the scheduled assessments should be performed as identified on a calendar schedule (for example: every 6–8 weeks on treatment or every 3–4 months after treatment) and should not be affected by delays in therapy, drug holidays or any other events that might lead to imbalance in a treatment arm in the timing of disease assessment.

2.6 Confirmatory Measurement/Duration of Response

2.6.1 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. This will also permit appropriate interpretation of results in the context of historical data where response has traditionally required confirmation in such trials. However, in all other circumstances, i.e. in

randomized trials (Phase 2 or 3) or 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. However, elimination of the requirement for response confirmation may increase the importance of central review to protect against bias, in particular in studies which are not blinded.

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.

2.6.2 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.

2.6.3 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

2.7 PFS/TTP

2.7.1. Phase 2 trials

This guideline is focused primarily on the use of objective response endpoints for Phase 2 trials. In some circumstances, "response rate" may not be the optimal method to assess the potential anticancer activity of new agents/regimens. In such cases PFS/PPF at landmark time points, might be considered appropriate alternatives to provide an initial signal of biologic effect of new agents. It is clear, however, that in an uncontrolled trial, these measures are subject to criticism since an apparently promising observation may be related to biological factors such as subject selection and not the impact of the intervention. Thus, Phase 2 screening trials utilizing these endpoints are best designed with a randomized control. Exceptions may exist where the behavior patterns of certain cancers are so consistent (and usually consistently poor), that a non-randomized trial is justifiable. However, in these cases it will be essential to document with care the basis for estimating the expected PFS or proportion progression-free in the absence of a treatment effect.