Clinical Study Protocol

Study title:	A Randomized, Open-label, Multi-center, Phase II Study to Evaluate the Efficacy and Safety of IBI308 versus Paclitaxel or Irinotecan in Patients with Advanced/Metastatic Esophageal Squamous Cell Carcinoma After Failure of First-line Treatment (ORIENT-2)
Protocol ID:	CIBI308A201
Version Number and Date:	May 19, 2019/Version 2.1
Product name:	IBI308
Phase of study:	Phase II
Sponsor:	Innovent Biologics (Suzhou) Co., Ltd 168 Dongping Street, Suzhou Industrial Park, Jiangsu Province, China
Sponsor's Contact:	WANG Yan, Senior Medical Director + 86 021-31652896 hui.zhou@innoventbio.com

Sponsor Signature Page

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Project ID: CIBI308A201

Title	Name (Print)	Signature	date
Senior Medical Director	WANG Yan		May-19-2019
Senior Director Biostatistics	SUN Xing		2019.5.19

Synopsis

Protocol ID	CIBI308A201
Sponsor	Innovent Biologics (Suzhou) Co., Ltd
Investigational Product	IBI308
Active Ingredient	Recombinant fully human anti-programmed cell death receptor 1 (PD-1) monoclonal antibody
Study Title	A Randomized, Open-label, Multi-center, Phase II Study to Evaluate the Efficacy and Safety of IBI308 versus Paclitaxel or Irinotecan in Patients with Advanced/Metastatic Esophageal Squamous Cell Carcinoma After Failure of First-line Treatment (ORIENT-2)
Phase	II
Estimated Duration of Study	27 months estimated
Study Objectives	Primary objective: ● To evaluate the overall survival (OS) for IBI308 versus Paclitaxel or Irinotecan in patients with advanced/metastatic esophageal squamous cell carcinoma after failure of first-line treatment. Secondary objectives: ● To evaluate progression-free survival (PFS), objective response rate (ORR), disease control rate (DCR) and duration of response (DoR) for IBI308 versus Paclitaxel or Irinotecan in patients with advanced/metastatic esophageal squamous cell carcinoma after failure of first-line treatment; ● To evaluate the safety of IBI308 versus Paclitaxel or Irinotecan in patients with advanced/metastatic esophageal squamous cell carcinoma after failure of first-line treatment; ● To evaluate the quality of life (QoL) for IBI308 versus Paclitaxel or Irinotecan in patients with advanced/metastatic esophageal squamous cell carcinoma after failure of first-line treatment. Exploratory objectives:

	● To evaluate the relationship between PD-L1 expression / immune-related gene mRNA expression and efficacy in patients with advanced/metastatic esophageal squamous cell carcinoma. ● To evaluate the relationship between the dynamic expression of PD-L1 on the surface of circulating tumor cells (CTCs) / ctDNA results and efficacy in the IBI308 group. ● To explore the iPFS, iORR, iDCR and iDoR assessed per Immune-modified Response Evaluation Criteria in Solid Tumors (iRECIST) in the IBI308 group.
Study Design	This is a randomized, open-label, multi-center, phase II study designed to evaluate the efficacy and safety of IBI308 versus paclitaxel or irinotecan in patients with advanced/metastatic esophageal squamous cell carcinoma after failure of first-line treatment. It is planned to enroll about 180 subjects with advanced/metastatic esophageal squamous cell carcinoma after failure of first-line treatment, and the subjects will be randomized using central randomization stratified by Eastern Cooperative Oncology Group performance status (ECOG PS) score of 0 or 1. Subjects in this study will be randomized into an IBI308 group or single-agent chemotherapy group in a 1:1 ratio. The IBI308 group will be administered with IBI308 200 mg IV Q3W, until disease progression, death, intolerable toxicity, withdrawal of consent, or occurrence of other protocol-specified situations. For a subject who experienced disease progression initially, if the subject is clinically stable, the decision is left to the discretion of the investigator as to whether IBI308 treatment should be continued or not (see 5.1.2 for details). The treatment regimen for the chemotherapy group, determined by the investigator based on prior first-line regimen, is Paclitaxel 175 mg/m^2 IV Q3W or Irinotecan 180 mg/m^2 IV Q2W, until disease progression, death, intolerable toxicity, withdrawal of consent, or occurrence of other protocol-specified situations. In this study, Response Evaluation Criteria in Solid Tumors 1.1 (RECIST v1.1) is used for response assessment and iRECIST is adopted as the exploratory response assessment criteria. After discontinuation of study treatment, the subjects will be followed for safety and survival (every 60 days). The primary endpoint of this study is OS, defined as the time from randomization to the date of death, and subjects who did not die will be censored at the most recent known date of survival.
Inclusion Criteria	1. Histologically or cytologically confirmed locally advanced unresectable or metastatic esophageal squamous cell carcinoma (excluding mixed adenosquamous carcinoma and other pathological types).

	2. Imaging evidence (e.g. CT scan) or clinical evidence (e.g. cytological report of new ascites or pleural effusion) of disease progression during or after first-line chemotherapy; Subjects have to receive at least one dose of first-line treatment, permitting discontinuation or dose reduction of one drug or exchange of fluorouracil drugs used during first-line treatment, and patients discontinuing first-line treatment due to intolerable toxicity are allowed to be enrolled; Neoadjuvant or adjuvant therapy (chemotherapy or chemo-radiotherapy) should be regarded as first-line treatment if there is disease progression during treatment or within 6 months after treatment discontinuation. 3. At least one measurable lesion according to RECIST v1.1. 4. ECOG PS score of 0 or 1. 5. Subjects who have signed the written informed consent form and are able to follow the visit schedule and relevant procedures as specified in the study protocol. 6. Age ≥ 18 and ≤ 75 years. 7. Life expectancy ≥ 12 weeks. 8. Female subjects of childbearing potential or male subjects with sexual partners of childbearing potential should use effective contraception throughout and within 6 months after treatment (see Section 4.3). 9. Adequate organ and bone marrow functions, defined as follows: 1) Hematology: absolute neutrophil count (ANC) ≥ 1.5×10^9/L; Platelet (PLT) count ≥ 100×10^9/L; Hemoglobin (HGB) ≥ 9.0 g/dL. 2) Liver function: serum total bilirubin (TBIL) ≤ 1.5×upper limit of normal (ULN); Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ≤2.5×ULN; Serum albumin ≥ 28 g/L. 3) Renal function: Serum creatinine (Cr) ≤ 1.5 × ULN, or creatinine clearance (Ccr) ≥ 40 mL/min (calculated using the standard Cockcroft - Gault formula): $\text{Females: CrCl} = \frac{(140-\text{age}) \times \text{body weight (kg)} \times 0.85}{72 \times \text{serum creatinine (mg/dL)}}$ $\text{Males: CrCl} = \frac{(140-\text{age}) \times \text{body weight (kg)} \times 1.00}{72 \times \text{serum creatinine (mg/dL)}}$
Exclusion Criteria	1. Prior exposure to any anti-PD-1 or anti-PD-L1 antibody. 2. Concurrent participation in another interventional clinical study, except for observational (non-interventional) clinical studies or in the follow-up phase of an interventional study.

	3. Receipt of any investigational products within 4 weeks prior to the first dose of study treatment. 4. Receipt of the last dose of anti-tumor therapy (chemotherapy, targeted therapy, tumor immunotherapy, tumor embolization) within 3 weeks prior to the first dose of study treatment. 5. Radiotherapy within 4 weeks prior to the first dose of study treatment. 6. Receipt of immunosuppressive agents within 4 weeks prior to the first dose of study treatment, excluding topical glucocorticoids for intranasal, inhalation or other routes of administration, or physiological doses of systemic glucocorticoids (i.e., no more than 10 mg/day prednisone or equivalent doses of other glucocorticoids). 7. Receipt of a live attenuated vaccine within 4 weeks prior to the first dose of study treatment or planned receipt of a live attenuated vaccine during the study. 8. Subjects who have undergone major surgical procedures (craniotomy, thoracotomy or laparotomy) within 4 weeks prior to the first dose of study treatment or have unhealed wound, ulcers or bone fracture. 9. Presence of toxicities induced by previous anti-tumor therapy that have not recovered to Grade 0 or 1 as assessed per NCI CTCAE 4.03 (National Cancer Institute Common Terminology Criteria for Adverse Events version 4.03) prior to the first dose of study treatment, excluding alopecia, and non-clinically significant and asymptomatic laboratory abnormalities. 10. Known symptomatic metastases to central nervous system (CNS) and/or carcinomatous meningitis. Subjects previously treated for brain metastasis are eligible for the study provided the brain metastasis has remained stable for at least 4 weeks before first dose of study treatment; Neurological symptoms must be recovered to grade 0 or 1 as per NCI CTCAE version 4.03. 11. Active, known or suspected autoimmune diseases (refer to Appendix 6) or a history of such disease in the past 2 years (patients with vitiligo, psoriasis, alopecia or Grave's disease requiring no systemic treatment in the past 2 years, patients with hypothyroidism requiring only thyroid hormone replacement therapy and patients with type I diabetes requiring only insulin replacement therapy can be enrolled). 12. Known history of primary immunodeficiency. 13. Known active tuberculosis (TB).

	14. Known history of allotransplantation and allogeneic hematopoietic stem cell transplantation. 15. Known hypersensitivity to any component of the monoclonal antibody, paclitaxel or irinotecan formulation. 16. Uncontrolled concurrent diseases, including but not limited to: ● HIV infection (HIV antibody positive). ● Active or clinically uncontrolled severe infections. ● Symptomatic congestive heart failure (New York Heart Association Class II-IV) or symptomatic or poorly controlled arrhythmia. ● Uncontrolled arterial hypertension (systolic blood pressure ≥ 160 mmHg or diastolic blood pressure ≥ 100 mmHg) despite standard treatment. ● Any arterial thromboembolism events within 6 months prior to inclusion for treatment, including myocardial infarction, unstable angina, cerebrovascular accident or transient ischemic attacks. ● Significant malnutrition, if intravenous nutrient solution supplement is required; Except for malnutrition corrected for more than 4 weeks before first dose of study treatment. ● Tumor invasion into surrounding vital organs (e.g., aorta and trachea) or a risk for esophagotracheal fistula or esophagopleural fistula. ● Post esophageal or intratracheal stenting. ● History of deep vein thrombosis (DVT), pulmonary embolism, or any other serious thromboembolism within 3 months prior to enrollment (implanted venous access port or catheter-related thrombosis, or superficial venous thrombosis is not considered as "serious"thromboembolism). ● Uncontrolled metabolic disorders or other non-malignant organic or systemic diseases or reactions secondary to cancer, which can result in high medical risks and/or uncertainty in survival evaluations. ● Hepatic encephalopathy, hepatorenal syndrome, or Child-Pugh class B or even more severe cirrhosis. ● History of intestinal obstruction or the following diseases: inflammatory bowel disease or extensive bowel resection

	(partial colectomy or extensive resection of the small intestine, concurrent chronic diarrhea), Crohn's disease, ulcerative colitis, or chronic diarrhea. ● Other acute or chronic diseases, mental disorders or abnormal laboratory findings that may lead to the following results: increase risks associated with study participation in the study or use of the study drug, or interfere with the interpretation of study results, and render the patient ineligible for the study at the investigator's discretion. 17. Known acute or chronic active hepatitis B (HBsAg positive and HBV DNA ≥200 IU/mL or ≥ 10^3 copies/mL) or acute or chronic active hepatitis C (HCV antibody positive and positive for HCV RNA test). 18. History of gastrointestinal perforation and/or fistula within 6 months prior to study inclusion. 19. Presence of interstitial lung disease. 20. Clinically uncontrollable effusion of the third space, such as pleural effusion and ascites that can not be controlled by drainage or other methods before enrollment. 21. History of other primary malignancies, excluding: ● A malignancy with complete remission for at least 2 years before enrollment and requiring no other treatment during the study; ● Adequately treated non-melanoma skin cancer or lentigo maligna without evidence of relapse; ● Adequately treated carcinoma in situ without evidence of relapse. 22. Pregnant or breastfeeding women.
Study Drugs, Strength and Route of Administration	● IBI308 – Strength: 10 ml: 100 mg – Route of administration: 200 mg IV Q3W ● Paclitaxel – Strength: 16.7 ml: 100 mg or 5 ml: 30 mg – Route of administration: 175 mg/m^2 IV Q3W ● Irinotecan – Strength: 2 ml: 40 mg or 5 ml: 0.1g

	– Route of administration: 180 mg/m^2 IV Q2W
Evaluation Criteria	**Efficacy evaluation:** ● To evaluate OS, 6-month overall survival rate, PFS, ORR, DCR and DoR after treatment. **Safety Evaluation:** ● The incidences and severity of all adverse events (AE), treatment-emergent adverse events (TEAE), adverse events of special interest (AESI) and serious adverse events (SAE), as well as their relationship to the investigational product. ● Changes in vital signs, physical examination findings, and laboratory results before, during, and after study treatment. **Immunogenicity evaluation (IBI308 group only):** ● Perform testing for anti-drug antibody (ADA) and neutralizing antibody (NAb). **Biomarker evaluation:** ● Tumor tissue samples were collected for analysis of tumor biomarkers, including but not limited to the expression of PD-L1 and the expression of immune-related genes (including but not limited to the expression of IDO1, CXCL9, CXCL10, HLA-DRA, STAT1, IFNG messenger RNA). ● For subjects treated with IBI308, blood samples will be collected for analysis of circulating tumor cells (CTCs) (including but not limited to PD-L1 dynamic expression) and ctDNA analysis. **Quality of life (QoL) assessment:** ● To assess quality of life (QoL) and health status for the subjects treated with IBI308 and chemotherapy respectively as measured by the EQ 5D-5L, EORTC QLQ-C30, and EORTC QLQ-OES18.
Statistical Methods	**Estimation of sample size:** Since this study is a phase II clinical study with overall survival (OS) as the primary measure, assuming a two-sided α level of 0.2, power of 80% and a hazard ratio (HR) of 0.7 for the IBI308 group compared with the chemotherapy group, a number of 142 subjects with OS events is required. Further, presuming 21% of the patients are censored, an estimated number of 180 subjects will be enrolled, with about 90 subjects in the IBI308 and chemotherapy groups each, respectively (35 sites, with 0.7 subjects enrolled per month in every site, the expected duration of this study is 27 months).

	Considering a possible delay of OS benefit with the anti-tumor therapy and based on an estimated median OS of approximately 8.7 months for IBI308, it should be ensured that the subjects have been followed up for about 10 months (from randomization) by the time of OS analysis. **Hypothesis test:** H_0: HR≥1; H_1: HR<1; $\alpha = 0.2$ (two-sided) for analysis of the primary efficacy endpoint, stratified log-rank test for OS for the IBI308 group compared with the chemotherapy group. **Primary efficacy endpoints:** Overall survival (OS); Kaplan-Meier estimator will be used to estimate the median survival and its 95% CI, survival curves will be plotted, and stratified Log-Rank test will be utilized for comparison between groups. In addition, stratified Cox proportional-hazards model will be employed for estimating HRs and their 95% CIs. The 6-month and 1-year survival rates will be estimated using Kaplan-Meier method. Meanwhile, the comparison of OS between groups will be performed by the RMST method. **Secondary efficacy endpoints:** Survival data: analyses of PFS and DoR will be performed using the same method as OS analysis. For analyses of ORR and DCR, Fisher's exact test will be used for inter-group comparison. **Safety data:** The incidence and severity of adverse events were summarized by group, and abnormal changes in laboratory test indicators were described. **Immunogenicity data:** The positive rates of anti-drug antibody (ADA) and neutralizing antibody were summarized **Quality of life (QoL):** Variations of QoL scale scores as assessed per EQ 5D-5L, EORTC QLQ-C30 and EORTC QLQ-OES18 will be described by group and visit, so as to evaluate the QoL and health status of the subjects treated by IBI308 and chemotherapy, respectively. **Biomarkers:** The results and distribution of PD-L1 expression and immune-related gene expression were summarized descriptively, and the potential relationship between the above indicators and efficacy was investigated.

Table 1. Visit Schedule

Period	Screening Period	Treatment period				Safety follow-up[19]		Survival follow-up[20]
		Cycle 1	Cycle 2	Cycle 3	Cycle 4 and thereafter			
Visit	1	2	3	4	5 ~ N	First	Second	
Day	-28~-1	1	22 (±3 days)	43 (± 3 days)	Every 3 weeks (± 3 days)	Day 30 (± 7 days) after treatment discontinuation visit or the last dose	Day 90 (± 7 days) after the last dose	Every 60 days (± 7 days)
General Study Procedures								
Written ICF[1]	X							
Inclusion/exclusion criteria	X							
Demographics/past medical history/ past medications[2]	X							
Vital signs[3]	X	X	X	X	X	X	X	
Body weight/height[4]	X	X	X	X	X			
Physical examination	X		X	X	X	X	X	
ECOG PS score	X	X	X	X	X	X	X	
12-lead ECG[5]	X			X	X	X	X	
Hematology/blood biochemistry/urinalysis[6]	X		X	X	X	X	X	
Pregnancy test[7]	X					X		

Period	Screening Period	Treatment period				Safety follow-up[19]		Survival follow-up[20]
		Cycle 1	Cycle 2	Cycle 3	Cycle 4 and thereafter			
Visit	1	2	3	4	5 ~ N	First	Second	
Day	-28~-1	1	22 (±3 days)	43 (± 3 days)	Every 3 weeks (± 3 days)	Day 30 (± 7 days) after treatment discontinuation visit or the last dose	Day 90 (± 7 days) after the last dose	Every 60 days (± 7 days)
Thyroid function[8]	X		X	X	X	X		
Immunogenicity[9]		X	X		X		X	
HIV, HBV and HCV[10]	X							
AE assessment[11]	X	X	X	X	X	X	X	
Concomitant Medications	X	X	X	X	X	X	X	
Survival status		←	—	—	—	—	→	
Subsequent anti-tumor treatment						X	X	X
Efficacy Evaluation								
Radiologic evaluation of tumor[12]	X			X	X			
Randomization								
IWRS[13]		X						
Study Drug Infusion								
IBI308 group: IBI308[14]		X	X	X	X			
Chemotherapy group: Paclitaxel or irinotecan[15]		X	X	X	X			

Period	Screening Period	Treatment period				Safety follow-up[19]		Survival follow-up[20]
		Cycle 1	Cycle 2	Cycle 3	Cycle 4 and thereafter			
Visit	1	2	3	4	5 ~ N	First	Second	
Day	-28~-1	1	22 (±3 days)	43 (± 3 days)	Every 3 weeks (± 3 days)	Day 30 (± 7 days) after treatment discontinuation visit or the last dose	Day 90 (± 7 days) after the last dose	Every 60 days (± 7 days)
QoL Assessment[16]								
EQ 5D-5L/ EORTC QLQ-C30/ EORTC QLQ-OES18 questionnaires		X		X	X	X		
Biomarker Evaluation								
Archived or fresh tumor tissue samples[17]	X							
Blood samples[18]		X		X	X			

Remarks:

1. The signing of the ICF should precede any protocol-specified procedures.
2. Past medication includes treatments for initial diagnosis, including chemotherapy, radiotherapy and surgical treatment.
3. Vital signs include body temperature, pulse rate, respiratory rate, and blood pressure.
4. Height and weight measurements are only performed during the screening period.
5. 12-lead ECG is performed at the following time points: during screening period, prior to administration of study drug every 2 cycles (excluding Cycle 1) and at safety follow-up.
6. Hematology includes: red blood cell count (RBC), HGB, white blood cell count (WBC), PLT, WBC differential [lymphocyte count (LYM), ANC]. Blood biochemistry includes: liver function [TBIL, ALT, AST, gamma-glutamyltransferase (γ-GT), alkaline phosphatase (ALP), albumin (ALB), total protein (TP), lactate dehydrogenase (LDH)], renal function [blood urea

nitrogen (BUN), Cr], blood electrolytes (Na, K, Cl, Mg, Ca, P), lipase, amylase and fasting blood glucose (FBG). Urinalysis includes pH, urine albumin (UALB), urine protein (UPRO), urine red blood cell (URBC) and urine glucose (UGLU). Hematology, blood biochemistry and urinalysis are performed during the screening period, within 7 days before each dose and at safety follow-up. The test will be performed at various sites.

7. For women of child-bearing potential, urine or serum pregnancy test will be performed within 3 days prior to the first dose and at the first safety follow-up visit. If negative cannot be confirmed with the result of urine pregnancy test, serum pregnancy test is required and the result of serum pregnancy test should prevail. The test will be performed at various sites.
8. This test will be performed at screening, within 3 days prior to administration of study drug in each cycle since Cycle 2, and at the first safety follow-up visit. During the screening period, the test will cover thyroid stimulating hormone (TSH), triiodothyronine (T3), tetraiodothyronine (T4), free triiodothyronine (FT3) and free tetraiodothyronine (FT4). Only TSH will be examined since Cycle 2, and if any abnormalities, examination of other thyroid function parameters will be considered. The test will be performed at various sites. Thyroid function test will be performed for all subjects during the screening period. However, test results not older than 28 days prior to randomization at the site are acceptable, and thyroid function test is only limited to the IBI308 group since Cycle 2.
9. Immunogenicity test will be performed only for the IBI308 group, within 1 hour before IBI308 infusion in Cycle 1, Cycle 2, Cycle 4 and then every 4 cycles (Cycles 8, 12, 16 and so on), and at the 2nd safety follow-up visit. The test will be performed at the central laboratory.
10. Hepatitis B testing (HBsAg, HBsAb, HBcAb, HBeAg and HBeAb), and HCV antibody/HIV antibody test are performed during the screening period. If HBsAg test reports positive, HBV DNA test will be further performed. If HCV antibody test reports positive, HCV RNA test will be further performed. Test results not older than 28 days prior to randomization at the site are acceptable. For hepatitis B virus carriers, it is recommended to provide subjects randomized to chemotherapy with prophylactic antiviral therapy in reference to the guidelines and to monitor viral activity regularly during the study. The test will be performed at various sites.
11. AE assessment and evaluation of laboratory findings will be performed according to NCI CTCAE 4.03. The definitions, documentation, relationship judgment, severity judgment, reporting time-line and handling of AEs and SAEs are subject to description in Section 7 of the protocol.
12. Tumor assessment includes evaluation per RECIST v1.1 and evaluation per iRECIST. For the same subject, the imaging technique used should remain unchanged throughout this study. Baseline assessment will be performed within 28 days prior to enrollment, and the investigators may collect imaging results not older than 28 days prior to enrollment for assessment. Tumor imaging evaluation will be performed every 6 weeks (± 7 days) in the first 24 weeks following the first dose of study drug, and then every 9 weeks (± 7 days) after Week 24, until initiation of new anti-tumor treatment, disease progression, withdrawal of ICF, or death. For subjects treated by IBI308 who developed disease progression initially, radiographic confirmation needs to be performed intervals of 4~6 weeks. If the patient is clinically stable, the decision is left to the discretion of the investigator as to whether IBI308 treatment should be continued or not (see 5.1.2). For subjects who continue treatment beyond disease progression, radiologic evaluation should be continued. For patients who discontinued treatment for reasons other than radiographic disease progression, imaging evaluations should, wherever possible, be performed every 6 weeks (± 7 days) after discontinuation, until occurrence of any

of the following: initiation of new anti-tumor therapy, disease progression, withdrawal of ICF, and death. For subjects treated by IBI308 who have a disease progression as assessed per RECIST v1.1, radiologic evaluation should be continued as per iRECIST assessment requirements and the frequency of follow-up, wherever possible.

13. Eligible subjects will be randomized into the IBI308 or chemotherapy group in a 1:1 ratio prior to the first dose in the treatment period, stratified by ECOG PS score (0 or 1).
14. IBI308 200 mg, administered via intravenous infusion every 3 weeks (Q3W), until disease progression, death, intolerable toxicity, withdrawal of consent, or occurrence of other protocol-specified situations. Some subjects meeting specific conditions can continue treatment beyond disease progression (refer to Section 5.1.2 in the protocol). Cycle 1/Day 1 dosing must occur within 3 working days of randomization.
15. Paclitaxel 175 mg/m^2 IV Q3W or Irinotecan 180 mg/m^2 IV Q2W, until disease progression, death, intolerable toxicity, withdrawal of consent, or occurrence of other protocol-specified situations. Cycle 1/Day 1 dosing must occur within 3 working days of randomization.
16. QoL assessment: will be performed using EQ 5D-5L, EORTC QLQ-C30 and EORTC QLQ-OES18 questionnaires on the day of the first dose, and at each radiographic evaluation and the first safety follow-up visit.
17. Subjects are required to provide archived or fresh tumor tissue samples meeting the testing requirements at the time of screening for PD-L1 and immune-related gene mRNA assays.
18. Subjects need to provide 10 ml of whole blood specimen at the following time points: prior to the first dose, and before each efficacy evaluation prior to start of the next treatment. Only for the IBI308 group.
19. Two safety follow-ups will be performed. The first takes place at the treatment discontinuation visit or on Day 30 (± 7 days) after the last dose, and the second on Day 90 (± 7 days) after the last dose.
20. Survival follow-up: takes place every 60 days (± 7 days) after safety follow-up, and telephone follow-up is acceptable.

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Abbreviations and Definitions of Terms

Abbreviation	Full English
ADA	Anti-drug antibody
AE	Adverse event
AESI	Adverse events of special interest
ALB	Albumin
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
ANC	Absolute neutrophil count
AST	Aspartate aminotransferase
AUC	Drug exposure
BUN	Urea nitrogen
CCr	Creatinine clearance
CI	Confidence interval
C_{max}	Observed maximum concentration
Cr	Serum creatinine
CR	Complete response
CRO	Contract research organization
CSR	Clinical study report
CT	Computed tomography
CTC	Circulating tumor cells
CTCAE	Common Terminology Criteria for Adverse Events
ctDNA	Tumor circulating deoxyribonucleic acid
CTLA-4	Cytotoxic T lymphocyte antigen-4
DCR	Disease control rate
DLT	Dose-limiting toxicity
DoR	Duration of response
ECG	Electrocardiogram
ECOG PS	Eastern Cooperative Oncology Group Performance Status
eCRF	Electronic Case Report Form
EORTC QLQ-C30	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30
EORTC QLQ-OES18	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Esophageal Cancer 18
EQ 5D-5L	EuroQol Five Dimensions Questionnaire-5 Levels
FAS	Full analysis set
FBG	Fasting blood glucose
FFPE	Formalin-fixed paraffin-embedded
FT3	Free triiodothyronine
FT4	Free thyroxine
GCP	Good Clinical Practice
HBV	Hepatitis B virus
HCT	Hematocrit

HCV	Hepatitis C
HGB	Hemoglobin
HIV	Human immunodeficiency virus
ICF	Signed informed consent
ICH	International Council for Harmonisation
IgG	Immunoglobulin G
irAE	Immune-related adverse event
IRR	Infusion-related reactions
iRECIST	Immune-Related Response Evaluation Criteria in Solid Tumors
IV	Intravenous infusion
LDH	Lactic dehydrogenase
LYM	Lymphocyte count
MedDRA	Medical Dictionary for Regulatory Activities
mOS	Median overall survival
mPFS	Median progression free survival
MRI	Magnetic resonance imaging
MTD	Maximum tolerated dose
NAb	Neutralizing antibody
NCI	National Cancer Institute
NOAEL	No-observed-adverse-effect level
NOEL	No-observed-effect level
ORR	Objective response rate
OS	Overall survival
PD	Pharmacodynamic Properties
PD-1	Programmed death 1
PD-L1	Programmed death-ligand 1
PFS	Progression-free survival
PH	pH
PK/PD	Pharmacokinetics/pharmacodynamics
PLT	Platelet count
PR	PR
PVC	Polyvinyl chloride
Q2W	Every 2 weeks
Q3W	Every 3 weeks
RBC	Red blood cell count
RECIST	Response Evaluation Criteria in Solid Tumors
SAE	SAE
SAP	Statistical Analysis Plan
SD	Stable disease
SS	Safety Analysis Set
$t_{½}$	Half-life
T3	Triiodothyronine
T4	Thyroxine
TBIL	Total bilirubin

TEAE	Treatment-emergent adverse events
TP	Total protein
TSH	Thyroid-stimulating hormone
UWBC	White blood cells in urine
UGLU	Urine glucose
ULN	Upper limit of normal
UPRO	Urine protein
URBC	Urine red blood cell
WBC	White blood cell
γ-GT	Gamma-glutamyl transferase

1 Study Background

1.1 Disease Background

With the increase in human average life span and changes in lifestyle, malignant tumors have become the most important life-threatening disease that poses a serious threat to the health of Chinese people. Globally, esophageal cancer has the 8th highest incidence and the 6th highest mortality among malignancies, mostly in developing countries[1]. China has the greatest number of esophageal cancer cases in the world, with both incidence and mortality of esophageal cancer higher than the mean global levels. It is estimated that there were 4.29 million cases of new cancer in China, with 2.81 million cases of new cancer death in 2015[2]. Among all causes of cancer death, esophageal cancer has the 3rd and 4th highest incidence and mortality, with 0.478 million and 0.375 million cases of morbidity and mortality, respectively[2]. Though there are certain advances in the treatment of esophageal cancer, there is still a huge unmet medical need.

Esophageal cancer refers to malignancy of esophageal epithelial origin between hypopharynx and esophagogastric junction. In China, most esophageal cancer cases originate from upper and middle segments of esophagus, with the main pathology of squamous cell carcinoma, which accounts for approximately 90% in upper, middle and lower segments of esophagus, while adenocarcinoma accounts for less than 2%. There are great differences in primary sites and pathology of esophageal cancer between China and developed countries in Europe and America[3], indicating that clinical diagnosis and treatment of esophageal cancer should be explored based on actual situation in China.

A surgery is the main treatment method for early- and - middle-stage esophageal cancer. However, there may be local relapse and/or metastasis after surgery, with poor overall prognosis. A study of clinical data from 1,510 patients with esophageal cancer surgically treated in Shanxi Tumor Hospital reported cumulative survival rates of 78%, 38% and 30% at post-operative 1, 5 and 10 years, respectively, with a median survival time of 2.68 years. Prognosis is even worse for patients with locally advanced and advanced esophagus cancer. Mean survival time is less than 1 year for advanced patients[4].

Advanced esophageal cancer is rarely investigated in randomized controlled studies, and often investigated together with gastric cancer. First-line treatment is primarily platinum-based dual or triple chemotherapy[5-10]. In a randomized controlled phase

III clinical study (REAL-2) to evaluate the efficacy of capecitabine versus fluorouracil and oxaliplatin versus cisplatin in patients with advanced first-line gastric cancer and esophageal cancer, 1,002 patients were randomized at 1:1:1:1 ratio to 4 treatment groups of ECF (epirubicin + cisplatin + fluorouracil), ECX (epirubicin + cisplatin + capecitabine), EOF (epirubicin + oxaliplatin + fluorouracil) or EOX (epirubicin + oxaliplatin + capecitabine). Each treatment group included 30-40% esophageal cancer and approximately 10% squamous cell carcinoma. Median survival time was 9.9, 9.9, 9.3 and 11.2 months in ECF, ECX, EOF and EOX treatment groups, respectively, and one-year survival rate was 37.7%, 40.8%, 40.4% and 46.8%, respectively[5]. In a randomized controlled phase III study (REAL-3) investigating EOX regimen versus EOX + panitumumab, panitumumab did not increase survival time. A total of 275 subjects were enrolled in EOX treatment group, including 40% of subjects with esophageal cancer, and 99% of subjects with adenocarcinoma. Overall survival was 11.3 months in EOX treatment group[6]. In a phase II clinical study to evaluate the efficacy of docetaxel plus cisplatin in first-line esophageal squamous cell carcinoma, 39 subjects were enrolled, objective response rate was 33.33%, progression free time was 5 months and overall survival was 8.5 months[7]. In a single-arm phase II clinical study evaluating the efficacy of paclitaxel plus cisplatin and fluorouracil in advanced esophageal cancer, 61 subjects were enrolled, including 30 subjects with squamous cell carcinoma. ORR was 48% (48% for adenocarcinoma , 50% for squamous cell carcinoma) and OS was 10.8 months[8]. In a randomized controlled study to evaluate the efficacy cisplatin plus fluorouracil versus cisplatin plus fluorouracil and cetuximab in first-line esophageal squamous cell carcinoma, 30 subjects received cisplatin plus fluorouracil, resulting in objective response rate of 13%, disease control rate of 57%, PFS of 3.6 months and OS of 5.5 months[9]. In a single-arm study evaluating the efficacy of paclitaxel plus cisplatin in Chinese patients with first-line esophageal squamous cell carcinoma, 39 subjects were enrolled, objective response rate was 48.6%, and OS was 13 months[10].

There is no large-scale randomized controlled clinical study of second-line treatment for advanced esophageal cancer. Docetaxel[11, 12], paclitaxel[13] and irinotecan monotherapy[14-16] have demonstrated certain efficacy in several single-arm studies, and are commonly used as second-line treatment of esophageal cancer in clinical practice (recommended by NCCN guideline)[17]. In a single-arm clinical study to evaluate the efficacy of paclitaxel monotherapy in advanced esophageal cancer, 102 subjects were enrolled, PR was 13%, duration of response was 172 days, and mean

survival time was 274 days[13]. In a study evaluating the efficacy of irinotecan monotherapy in patients with advanced esophageal cancer failing cisplatin-based chemotherapy, 14 patients were enrolled. Among 13 subjects evaluable for efficacy, 2 subjects reached partial response, and 3 subjects remained stable disease. Median time to disease progression was 2 months, and overall survival was 5 months[14]. In a study evaluating the efficacy of irinotecan monotherapy in advanced gastric and esophageal cancer, 46 patients were enrolled, objective response rate was 14% and median survival time was 6.4 months[15]. In a study evaluating the efficacy of irinotecan monotherapy in patients with unresectable esophageal cancer, 13 subjects (10 subjects with squamous cell carcinoma and 3 subjects with adenocarcinoma) were enrolled, and 2 subjects reached partial response (1 with squamous cell carcinoma and 1 with adenocarcinoma). Median time to disease progression was 3.8 months, and median survival time was 6.1 months[16].

Several studies reported the PD-L1 expression in esophageal cancer and the relationship between PD-L1 expression and prognosis of esophageal cancer, but study conclusions were inconsistent. In a case analysis including 288 cases of esophageal squamous cell carcinoma, PD-L1 positive rate was 50.7%. The PD-L1 expression and prognosis varied with tumor staging and status of lymph node metastasis. In patients with stage IV disease and patients without lymph node metastasis, PD-L1 expression was negatively correlated with disease free survival and overall survival, while there was no significant correlation in stage III-IV patients[18]. In another case study including 162 cases of esophageal squamous cell carcinoma, PD-L1 positive rate was high in patients with stage IV disease, lymph node metastasis and local treatment failure. PD-L1 positive patients had poor response to treatment and poor prognosis[19]. In a report including 41 cases of esophageal cancer, PD-L1 positive was associated with poor prognosis, with stronger association in cases at later disease stage[20]. PD-L1 expression was variable in esophageal cancer. In a study comparing PD-L1 expression in tumor tissue before and after neoadjuvant therapy in 28 patients with esophageal cancer (19 patients for concurrent chemoradiotherapy, 9 patients for chemotherapy), PD-L1 expression in tumor tissue significantly increased after concurrent neoadjuvant chemoradiotherapy, but significantly decreased after neoadjuvant chemotherapy[21].

In a phase Ib clinical study (KEYNOTE-028) of Pembrolizumab in patients with advanced esophageal cancer (PD-L1 expression >1%) who had failed or were intolerable to at least one line of systemic treatment, ORR was 30% (95% CI, 13-53)[22]. In a phase II clinical study of Nivolumab in patients with advanced esophageal

cancer who had failed or were intolerable to at least one line of systemic treatment, ORR was 17.2% and mOS was 12.1 months[23]. Based on efficacy observed in early trials, phase III studies evaluating the efficacy of Nivolumab[24] and Pembrolizumab[25] versus chemotherapy in second-line esophageal cancer are currently ongoing.

1.2 Study Drug (IBI308)

1.2.1 Mechanism of Action of IBI308

Immune checkpoints are a class of immunosuppressive molecules. Their physiological function is to modulate intensity and extent of immune response, so as to avoid injury and damage of normal tissues. Tumor cells often utilize the property of immune checkpoints to escape attack from immune cells. At present, clinically verified immune checkpoints include CTLA-4 and PD-1/PD-L1. Due to good safety and extensive indications, immune checkpoint inhibitors targeting PD-1/PD-L1 are more promising in clinical practice.

PD-1 is mainly expressed on activated T cells and has two ligands: PD-L1 and PD-L2, of which PD-L1 is its main ligand and is expressed in activated T cells, antigen-presenting cells, and tumor cells[26]. PD-1/PD-L1 binding plays an important role in regulating T cell activation and maintaining peripheral immune tolerance. When there is no PD-1 expression in T cells, T cells interact with antigen presenting cells, resulting in activation, proliferation of T cells and secretion of active cytokines, which act on tumor cells, leading to tumor cell killing; The activated T cells begin to express PD-1. When they bind to antigen-presenting cells or ligand PD-L1 on tumor cells, the inhibitory signal transmitted by PD-1 inhibits the proliferation of T cells and the secretion of active cytokines, diminishing the T cell function. Most tumor cells utilize this mechanism to escape attack from immune cells; If the interaction between PD-1 and PD-L1 is blocked by medications, the activity of T cells can be restored and the ability to kill cancer cells can be improved[27].

Up to date, three PD-1/PD-L1 products have been approved for marketing by the US FDA, i.e., anti-PD-1 monoclonal antibody Nivolumab (trade name: OPDIVO) of BMS, anti-PD-1 monoclonal antibody Pembrolizumab (trade name: KEYTRUDA) of Merck, and anti-PD-L1 monoclonal antibody Atezolizumab (trade name: Tecentriq) of Genetech, under the indications for advanced melanoma, advanced NSCLC, advanced classical Hodgkin lymphoma, advanced renal cell carcinoma, advanced urothelial

carcinoma, and advanced head and neck tumors. In addition, many indications are currently under phase III clinical studies or NDA submissions. The marketing of the above drugs has established the important position of PD-1/PD-L1 immune checkpoint inhibitors in cancer immunotherapy. For the moment, there is no PD-1/PD-L1 immune checkpoint inhibitor marketed in China. Therefore, it is of great significance to actively develop such inhibitors to provide better treatment options for Chinese patients with advanced tumors.

Recombinant fully human anti-PD-1 monoclonal antibody injection (R&D code: IBI308) is a recombinant fully human IgG4 monoclonal antibody. The effect of blocking PD-1 pathway with IBI308 has been investigated in various preclinical in vitro tests, and the anti-tumor activity of the murine analogue of IBI308 has been demonstrated in several non-immunocompromised mouse tumor models (refer to the Investigator's Brochure for detailed study results). The results of preclinical studies suggested a promising future for the development of IBI308 for PD-1 blockade.

1.2.2 Results of IBI308 Clinical Study

In September 2016, a phase Ia dose-escalation trial of IBI308 was initiated. The phase Ia was planned to enroll approximately 12 to 24 subjects with advanced solid tumors who had failed standard of care, to evaluate IBI308 at four dose levels (1 mg/kg, 3 mg/kg, 200 mg, and 10 mg/kg), with the dose escalation decision based on the classic “3+3” design. After completion of the 1 mg/kg dose group, subjects were randomized to the 3 mg/kg and 200 mg dose groups at a 1:1 ratio for independent evaluation. There was a 28-day DLT observation period for the two dose groups each after initial dosing, and only subjects who completed the DLT observation period could enter the subsequent treatment period to receive IBI308 Q2W (1 mg/kg, 3 mg/kg and 10 mg/kg) or Q3W (200 mg), until disease progression, intolerable toxicity, withdrawal of consent, or occurrence of other conditions that require discontinuation of study treatment, whichever occurs first.

Preliminary pharmacokinetic results of IBI308 in subjects with various tumors (n=3) showed that maximum exposure after a single dose was achieved at the end of 1 mg/kg IBI308 infusion; after the peak exposure, the drug was rapidly distributed and slowly eliminated (t1/2 was approximately 17.3d), demonstrating typical 2-compartment PK characteristics of monoclonal antibody drugs, with elimination half life similar to physiological half life of IgG4.

Preliminary pharmacodynamic results showed that, at the dose of 1 mg/kg, IBI308 rapidly (24h) occupied peripheral PD-1 in saturation (95.8±2.3%), and maintained PD-1 occupation during the study when concentration continued to decrease (28d, C28d: 3.70± 0.15 μg/mL). It is expected that steady state will be achieved after continuous administration of 1 mg/kg Q2W for 84 days (6 doses). If there is no significant variation of drug elimination characteristics, trough concentration at steady state is expected to be approximately 13 μg/mL, which can persistently maintain occupation of peripheral PD-1 receptor.

As of February 8, 2017, enrollment of 3 patients each and protocol specified observation of dose limiting toxicities had been completed in 1 mg/kg, 3 mg/kg and 200 mg dose groups in phase Ia, with no occurrence of dose limiting toxicity.

1.3 Risk/Benefit Assessment

Based on the mechanism of action of this product and on the clinical safety information of products with the same mechanism, adverse events expected to possibly occur with this product during the clinical trial are mainly various immune-mediated inflammations caused by activation of the immune system, such as pneumonia, colitis, hepatitis, renal insufficiency and inflammation of the endocrine system. According to available clinical data of anti-PD-1 monoclonal antibody drugs, although the incidence of adverse reactions is high, the drugs were well tolerated, with only a small portion of subjects discontinuing treatment due to adverse reactions, most of which resolved after appropriate treatment. As the early symptoms of immune-related adverse reactions are variable, the investigator(s) should pay special attention to the early symptoms and signs of various immune-related reactions in the clinical study, make appropriate judgment in a timely fashion, and perform dose adjustment and appropriate effective treatment as described 5.4.2 of the protocol to reduce the risks of drug use for the patients. In addition, the investigator(s) should exclude patients with autoimmune diseases during the clinical trial to avoid worsening of pre-existing diseases as a result of immune system activation.

The phase Ia clinical pharmacology and safety data for IBI308 show that IBI308 has clear pharmacological activity and is well tolerated in patients with advanced tumors.

The above data preliminarily indicates that IBI308 has good safety and pharmacological activity, and drugs of the same class have significant anti-tumor activity in patients with advanced esophageal cancer, supporting clinical studies in Chinese patients with

advanced esophageal cancer.

2 Study Objectives

2.1 Primary Objective

- To evaluate the overall survival (OS) for IBI308 versus Paclitaxel or Irinotecan in patients with advanced/metastatic esophageal squamous cell carcinoma after failure of first-line treatment.

2.2 Secondary Objectives

- To evaluate progression-free survival (PFS), objective response rate (ORR), disease control rate (DCR) and duration of response (DoR) for IBI308 versus Paclitaxel or Irinotecan in patients with advanced/metastatic esophageal squamous cell carcinoma after failure of first-line treatment;
- To evaluate the safety of IBI308 versus Paclitaxel or Irinotecan in patients with advanced/metastatic esophageal squamous cell carcinoma after failure of first-line treatment;
- To evaluate the quality of life (QoL) for IBI308 versus Paclitaxel or Irinotecan in patients with advanced/metastatic esophageal squamous cell carcinoma after failure of first-line treatment.

2.3 Exploratory Objectives

- To evaluate the relationship between PD-L1 expression / immune-related gene mRNA expression and efficacy in patients with advanced/metastatic esophageal squamous cell carcinoma.
- To evaluate the relationship between the dynamic expression of PD-L1 on the surface of circulating tumor cells (CTCs) / ctDNA results and efficacy in the IBI308 group.
- To explore the iPFS, iORR, iDCR and iDoR assessed per Immune-modified Response Evaluation Criteria in Solid Tumors (iRECIST) in the IBI308 group.

3 Overall Study Design

3.1 Overall Design

This is a randomized, open-label, multi-center, phase II study designed to evaluate the efficacy and safety of IBI308 versus paclitaxel or irinotecan in patients with

advanced/metastatic esophageal squamous cell carcinoma after failure of first-line treatment. It is planned to enroll 180 subjects with advanced/metastatic esophageal squamous cell carcinoma after failure of first-line treatment, and the subjects will be randomized using central randomization stratified by Eastern Cooperative Oncology Group performance status (ECOG PS) score of 0 or 1.

Subjectswill be randomized into an IBI308 group or chemotherapy group in a 1:1 ratio. The IBI308 group will be administered with IBI308 200 mg IV Q3W, until disease progression, death, intolerable toxicity, withdrawal of consent, or occurrence of other protocol-specified situations. For a subject who experienced disease progression initially, if the subject is clinically stable, the decision is left to the discretion of the investigator as to whether IBI308 treatment should be continued or not (see 5.1.2 for details). The treatment regimen for the chemotherapy group, determined by the investigator based on prior first-line regimen, is Paclitaxel 175 mg/m^2 IV Q3W or Irinotecan 180 mg/m^2 IV Q2W, until disease progression, death, intolerable toxicity, withdrawal of consent, or occurrence of other protocol-specified situations. In this study, Response Evaluation Criteria in Solid Tumors 1.1 (RECIST v1.1) is used for response assessment and iRECIST is adopted as the exploratory response assessment criteria.

After discontinuation of study treatment, the subjects will be followed for safety and survival (every 60 days).

The primary endpoint of this study is OS, defined as the time from randomization to the date of death, and subjects who did not die will be censored at the most recent known date of survival.

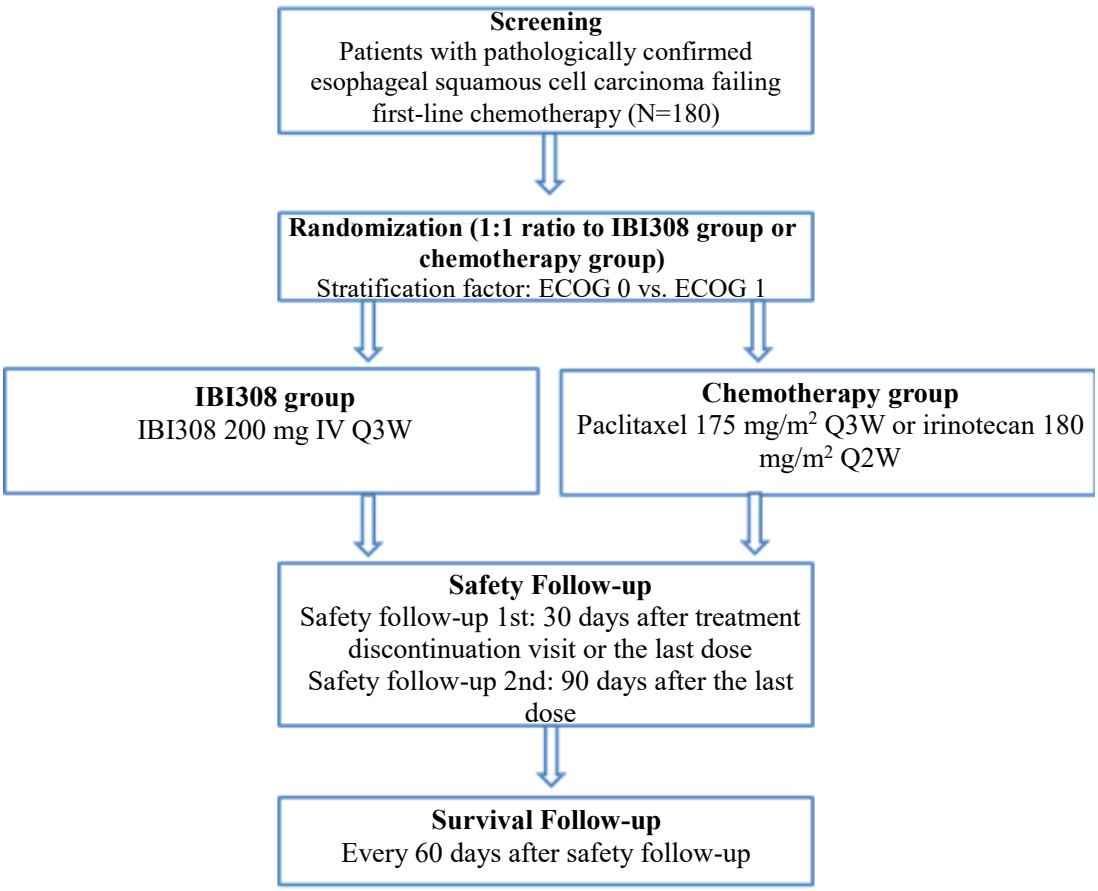

Figure 1. Schematic diagram of study design and dosing regimen of CIBI308A201

3.2 Design Rationale

3.2.1 Rationale for Selection of Open-label Study Design

As IBI308 has a different mechanism of action from paclitaxel and irinotecan, subjects may experience different AEs. IBI308 may induce immune related AEs, which may involve various tissues and organs. Adverse event profile of paclitaxel mainly includes myelosuppression and neurotoxicity, while adverse event profile of irinotecan mainly includes myelosuppression and diarrhea. Even for AEs involving the same tissue or organ, IBI308 and chemotherapy have different mechanisms to induce AEs, requiring different dose adjustment and rescue treatment. IBI308-induced AEs are mainly immune related, and require treatment with glucocorticoid in most cases. If this trial is blinded, treatment of AEs may be delayed or there may be injury of subjects. Additionally, different treatment adjustment rules (no dose reduction of IBI308, while doses of paclitaxel and irinotecan can be reduced) and different drug-drug interaction profile also increase complexity, making it difficult to use any blinding strategy. Therefore, this study selects an open-label study design.

3.2.2 Rationale for Selection of Treatment Regimen of 200 mg Every 3 Weeks

It is planned to administer 200 mg IBI308 Q3W in this study. Selection of this administration mode is mainly based on data of safety and exposure (concentration)-response (PD-1 receptor occupation) relationship from a currently ongoing phase I study (CIBI308A101), in conjunction with pre-clinical in vitro/ in vivo pharmacodynamic data and comparative data of similar drugs.

In vivo pharmacodynamic studies in mouse SCID-Winn model and MC38 mouse colon cancer model indicated that anti-tumor ability of IBI308 increased with dose, and tumor growth was significantly inhibited at 10 mg/kg IBI308 dose, which was equivalent to 0.8 mg/kg dose in human. In human, IBI308 1 mg/kg can rapidly (24h) occupy peripheral PD-1 in saturation, and maintain peripheral PD-1 occupation level during the study when concentration continues to decrease. Results of IBI308 tissue distribution in cynomolgus monkeys showed IBI308 exposure in lung, liver, colon, small intestine and lymph node was approximately 3.5-1/10 of serum exposure. If there is no significant variation of drug elimination characteristics in subjects, it is expected that steady state will be achieved after continuous administration of IBI308 200 mg Q3W for 84 days (4 doses), and mean steady state trough concentration is expected to persistently maintain occupation of peripheral and target organ PD-1 receptor. The above evidence supports selection of IBI308 200 mg Q3W as dosing regimen.

3.2.3 Rationale for Selection of Paclitaxel or Irinotecan as Control

There is no large-scale randomized controlled clinical study of second-line treatment for advanced esophageal cancer. Docetaxel[11, 12], paclitaxel[7, 13] and irinotecan monotherapy[14-16] have demonstrated certain level of efficacy in several single-arm studies, and are commonly used as second-line treatment for esophageal cancer in clinical practice (recommended by NCCN guideline)[17]. In a single-arm clinical study evaluating the efficacy of paclitaxel monotherapy in previously untreated advanced esophageal cancer patients, treatment regimen was 150-280 mg/m^2 D1 Q3W. A total of 52 subjects were enrolled, and ORR was 32%[7]. In a single-arm clinical study evaluating the efficacy of paclitaxel monotherapy in advanced esophageal cancer, treatment regimen was 80 mg/m^2 QW. A total of 102 subjects were enrolled, PR was 13%, duration of response was 172 days, and mean survival time was 274 days[13]. In a study evaluating the efficacy of irinotecan monotherapy in patients with advanced esophageal cancer failing cisplatin-based chemotherapy, treatment regimen was 100 mg/m^2 D1, 8, 15 in a 28-day cycle. A total of 14 patients were enrolled. In 13 subjects

evaluable for efficacy, 2 subjects reached partial response, and 3 subjects remained stable disease. Median time to disease progression was 2 months, and median overall survival was 5 months[14]. In a study evaluating the efficacy of irinotecan monotherapy in advanced gastric and esophageal cancer, treatment regimen was 125 mg/m^2 D1, 8, 15, 22 in a 42-day cycle. A total of 46 patients were enrolled, objective response rate was 14% and median survival time was 6.4 months[15]. In a study evaluating the efficacy of irinotecan monotherapy in patients with unresectable esophageal cancer, treatment regimen was 125 mg/m^2 D1, 8, 15, 22 in a 42-day cycle. A total of 13 subjects (10 subjects with squamous cell carcinoma and 3 subjects with adenocarcinoma) were enrolled, and 2 subjects reached partial response (1 with squamous cell carcinoma and 1 with adenocarcinoma). Median time to disease progression was 3.8 months, and median survival time was 6.1 months[16].

3.2.4 Rationale for Treatment after Disease Progression

Clinical data of marketed products indicate that a few patients receiving immunotherapy may still obtain clinical benefit in spite of preliminary evidence of disease progression (as per routine response criteria) before clinical objective response and/or stable disease[28]. At present, this phenomenon is hypothetically due to two reasons. First, aggravated inflammation within tumor may cause increased tumor volume, manifested as enlarged measurable lesion and new visible non-measurable lesion. Over time, malignant portion and inflammatory portion of mass may diminish, resulting in significant radiological response and improvement of clinical signs. Second, in some patients, anti-tumor immune response has a slow onset, with early tumor inhibition lower than tumor growth kinetics. Over time, anti-tumor activity will become predominant, manifested as radiological response and improvement of clinical signs. Therefore, for IBI308-treated subjects, if they are assessed as clinical benefit and tolerable to study drug, the subjects will be allowed to continue with the study treatment after preliminary assessment of disease progression by the investigator as per RECIST v1.1 (see Section 5.1.2).

4 Study Population

4.1 Inclusion Criteria

1. Histologically or cytologically confirmed locally advanced unresectable or metastatic esophageal squamous cell carcinoma (excluding mixed adenosquamous carcinoma and other pathological types).

2. Imaging evidence (e.g. CT scan) or clinical evidence (e.g. cytological report of new ascites or pleural effusion) of disease progression during or after first-line chemotherapy; Subjects have to receive at least one dose of first-line treatment, permitting discontinuation or dose reduction of one drug or exchange of fluorouracil drugs used during first-line treatment, and patients discontinuing first-line treatment due to intolerable toxicity are allowed to be enrolled; Neoadjuvant or adjuvant therapy (chemotherapy or chemo-radiotherapy) should be regarded as first-line treatment if there is disease progression during treatment or within 6 months after treatment discontinuation.
3. At least one measurable lesion according to RECIST v1.1.
4. ECOG PS score of 0 or 1.
5. Subjects who have signed the written informed consent form and are able to follow the visit schedule and relevant procedures as specified in the study protocol.
6. Age ≥ 18 and ≤ 75 years.
7. Life expectancy ≥ 12 weeks.
8. Female subjects of childbearing potential or male subjects with sexual partners of childbearing potential should use effective contraception throughout and within 6 months after treatment (see Section 4.3).
9. Adequate organ and bone marrow functions, defined as follows:

1) Hematology: Absolute neutrophil count (ANC) ≥ 1.5×10^9/L; Platelet (PLT) count ≥ 100×10^9/L; Hemoglobin (HGB) ≥ 9.0 g/dL.
2) Liver function: serum total bilirubin (TBIL) ≤ 1.5×upper limit of normal (ULN); Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ≤ 2.5×ULN; Serum albumin ≥ 28 g/L.
3) Renal function: Serum creatinine (Cr) ≤ 1.5 × ULN, or creatinine clearance (Ccr) ≥ 40 mL/min (calculated using the standard Cockcroft -Gault formula):

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

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

4.2 Exclusion Criteria

1. Prior exposure to any anti-PD-1 or anti-PD-L1 antibody.
2. Concurrent participation in another interventional clinical study, except for observational (non-interventional) clinical studies or in the follow-up phase of an interventional study.
3. Receipt of any investigational products within 4 weeks prior to the first dose of study treatment.
4. Receipt of the last dose of anti-tumor therapy (chemotherapy, targeted therapy, tumor immunotherapy, tumor embolization) within 3 weeks prior to the first dose of study treatment.
5. Radiotherapy within 4 weeks prior to the first dose of study treatment.
6. Receipt of immunosuppressive agents within 4 weeks prior to the first dose of study treatment, excluding topical glucocorticoids for intranasal, inhalation or other routes of administration, or physiological doses of systemic glucocorticoids (i.e., no more than 10 mg/day prednisone or equivalent doses of other glucocorticoids).
7. Receipt of a live attenuated vaccine within 4 weeks prior to the first dose of study treatment or planned receipt of a live attenuated vaccine during the study.
8. Subjects who have undergone major surgical procedures (craniotomy, thoracotomy or laparotomy) within 4 weeks prior to the first dose of study treatment or have unhealed wound, ulcers or bone fracture.
9. Presence of toxicities induced by previous anti-tumor therapy that have not recovered to Grade 0 or 1 as assessed per NCI CTCAE 4.03 (National Cancer Institute Common Terminology Criteria for Adverse Events version 4.03) prior to the first dose of study treatment, excluding alopecia, and non-clinically significant and asymptomatic laboratory abnormalities.
10. Known symptomatic metastases to central nervous system (CNS) and/or carcinomatous meningitis. Subjects previously treated for brain metastasis are eligible for the study provided the brain metastasis has remained stable for at least 4 weeks before first dose of study treatment; Neurological symptoms must be recovered to grade 0 or 1 as per NCI CTCAE version 4.03.

11. Active, known or suspected autoimmune diseases (refer to Appendix 6) or a history of such disease in the past 2 years (patients with vitiligo, psoriasis, alopecia or Grave's disease requiring no systemic treatment in the past 2 years, patients with hypothyroidism requiring only thyroid hormone replacement therapy and patients with type I diabetes requiring only insulin replacement therapy can be enrolled).
12. Known history of primary immunodeficiency.
13. Known active tuberculosis (TB).
14. Known history of allotransplantation and allogeneic hematopoietic stem cell transplantation.
15. Known hypersensitivity to any component of the monoclonal antibody, paclitaxel or irinotecan formulation.
16. Uncontrolled concurrent diseases, including but not limited to:
    - HIV infection (HIV antibody positive).
    - Active or clinically uncontrolled severe infections.
    - Symptomatic congestive heart failure (New York Heart Association Class II-IV) or symptomatic or poorly controlled arrhythmia.
    - Uncontrolled arterial hypertension (systolic blood pressure ≥ 160 mmHg or diastolic blood pressure ≥ 100 mmHg) despite standard treatment.
    - Any arterial thromboembolism events within 6 months prior to inclusion for treatment, including myocardial infarction, unstable angina, cerebrovascular accident or transient ischemic attacks.
    - Significant malnutrition, if intravenous nutrient solution supplement is required; Except for malnutrition corrected for more than 4 weeks before first dose of study treatment.
    - Tumor invasion into surrounding vital organs (e.g., aorta and trachea) or a risk for esophagotracheal fistula or esophagopleural fistula.
    - Post esophageal or intratracheal stenting.
    - History of deep vein thrombosis (DVT), pulmonary embolism, or any other serious thromboembolism within 3 months prior to enrollment (implanted

venous access port or catheter-related thrombosis, or superficial venous thrombosis is not considered as "serious"thromboembolism).

- Uncontrolled metabolic disorders or other non-malignant organic or systemic diseases or reactions secondary to cancer, which can result in high medical risks and/or uncertainty in survival evaluations.
- Hepatic encephalopathy, hepatorenal syndrome, or Child-Pugh class B or even more severe cirrhosis.
- History of intestinal obstruction or the following diseases: inflammatory bowel disease or extensive bowel resection (partial colectomy or extensive resection of the small intestine, concurrent chronic diarrhea), Crohn's disease, ulcerative colitis, or chronic diarrhea.
- Other acute or chronic diseases, mental disorders or abnormal laboratory findings that may lead to the following results: increase risks associated with study participation in the study or use of the study drug, or interfere with the interpretation of study results, and render the patient ineligible for the study at the investigator’s discretion.

17. Known acute or chronic active hepatitis B (HBsAg positive and HBV DNA ≥200 IU/mL or ≥ 10^3 copies/mL) or acute or chronic active hepatitis C (HCV antibody positive and positive for HCV RNA test).
18. History of gastrointestinal perforation and/or fistula within 6 months prior to study inclusion.
19. Presence of interstitial lung disease.
20. Clinically uncontrollable effusion of the third space, such as pleural effusion and ascites that cannot be controlled by drainage or other methods before enrollment.
21. History of other primary malignancies, excluding:
    - A malignancy with complete remission for at least 2 years before enrollment and requiring no other treatment during the study;
    - Adequately treated non-melanoma skin cancer or lentigo maligna without evidence of relapse;
    - Adequately treated carcinoma in situ without evidence of relapse.

22. Pregnant or breastfeeding women.

4.3 Restrictions throughout Study

Women of childbearing potential who are sexually active with male partners not surgically sterilized must begin to use 2 acceptable effective contraception methods (see Table 2) from screening phase, and must agree to continue with these contraception measures for 6 months after the last dose of the study drug; After this time point, they should discuss with a responsible physician about discontinuation of contraception measures. Periodic abstinence, safe period contraception and coitus interruptus are not acceptable contraception methods.

Women of childbearing potential are defined as women not surgically sterilized (i.e. bilateral tubal ligation, bilateral salpingectomy or total hysterectomy) or postmenopausal (defined as amenorrhea for 12 months without an alternative medical cause).

Women with amenorrhea for 12 months without an alternative medical cause are considered to have menopause. Requirements by age are as follows:

- If women ≥50 years have amenorrhea for 12 months or more after stopping treatment with exogenous hormones, and levels of luteinizing hormone and follicle stimulating hormone are within recognized postmenopausal range, they are considered as postmenopausal women.
- If women <50 years have amenorrhea for 12 months or more after stopping treatment with exogenous hormones, radiotherapy induced oophorotomy and the last menses occurred >1 year ago, chemotherapy induced amenorrhea and the time from the last menses was >1 year, or have undergone surgical sterilization (bilateral oophorotomy or hysterectomy), they are considered as postmenopausal women.

Table 2. Effective contraception methods (must use 2 methods)

Barrier methods	Intrauterine device (IUD) methods	Hormonal methods
Male condoms with spermicide	T-ring with copper	Implants
Cervical cup plus spermicide	Progesterone-containing T-ring [a]	Contraceptive injections
Diaphragm plus spermicide	Levonorgestrel-releasing intrauterine systems (e.g., Mirena®) [a]	Combined contraceptives Low-dose oral contraceptive pills Birth control patches

[a] This is also regarded as a hormonal method

4.4 Discontinuation of Treatment/Withdrawal of Subjects from Study

Subjects should discontinue/withdraw from the study if any of the following situations occurs:

1. The subject does not meet inclusion/exclusion criteria, and the investigator determines the subject is not suitable to continue participation in this study after discussion with the sponsor;
2. The subject deviates seriously from the study protocol, and the investigator determines the subject is not suitable to continue participation in this study after discussion with the sponsor.
3. The subject has been enrolled in another study of any type of drugs scientifically or medically not appropriate to be concurrent with this study.
4. The subject is lost to follow-up (the study site personnel should contact the subject to determine the reason for lost to follow-up and re-schedule visit as far as possible. The site should document the date of the subject to be contacted and the contact information used in the study file).
5. Investigator Decision

- The investigator considers the subject should discontinue treatment or study based on the subject's safety and benefit.
- If the subject needs another drug treatment for any reason, and the drug has been demonstrated to effectively treat the study indication, the subject should discontinue this study before use of the new drug.

- Disease progression or the investigator considers the subject is not suitable to continue with treatment.
- Occurrence of any life-threatening treatment-related events, regardless of severity.
- Study drug meets discontinuation criteria due to toxicity (see 5.4).

6. The subject or his/her representative (e.g. parents or legal guardian) requests withdrawal from this study or discontinuation of study drug (if the subject withdraws informed consent for treatment but not informed consent for follow-up, he or she may still enter into long-term follow-up).
7. The sponsor may terminate the study or discontinue subject's participation in this study for other medical, safety, regulatory or applicable laws, regulations and Good Clinical Practice (GCP) related reasons.

Reason and date for study discontinuation will be collected for all subjects. For subjects discontinuing treatment, relevant study procedures specified in schedule of study visits will also be performed as far as possible.

5 Study Drug and Other Treatments

5.1 Treatment Regimen

5.1.1 Treatment Regimen

Study drug in this study refers to IBI308, paclitaxel and irinotecan. Other drugs used in the study are non-study drugs. Treatment regimen is shown in the table below. For paclitaxel and irinotecan pretreatment, refer to Section 5.3.1 of the protocol.

Table 3. Dose and regimen

Cohort	Treatment Regimen	Dosage time
IBI308 group	IBI308 200 mg IV, Day 1, Q3W	Until disease progression, death, intolerable toxicity, withdrawal of consent, or occurrence of other protocol-specified situations; Eligible subjects can continue IBI308 treatment beyond initial disease progression (see Section 5.1.2).

Chemotherapy group[a]	Paclitaxel 175 mg/m^2 IV, Day 1, Q3W or Irinotecan 180 mg/m^2 IV, Day 1, Q2W At the investigator's discretion based on previous first-line treatment regimen	Until disease progression, death, intolerable toxicity, withdrawal of consent, or occurrence of other protocol-specified situations.

[a] This study site will determine actual drug dose the subject should receive by calculating the subject's body surface area on the day of scheduled administration in each cycle. The maximum body surface area used in the protocol is 2.0 m^2. For subjects whose body surface area is >2.0 m^2, the study site personnel will calculate based on the body surface area of 2.0 m^2. To facilitate administration, the protocol allows a deviation of ±5% for each calculated overall infusion dose.

5.1.2 Re-administration after Disease Progression

During IBI308 treatment, subjects initially assessed as disease progression (initial disease progression) per RECIST v1.1 have to meet all the following criteria to continue IBI308 treatment:

1. The investigator considers the continuation of study treatment may be expected to lead to clinical benefits and no rapid disease progression;
2. IBI308 was tolerated;
3. ECOG PS score is stable;
4. Any urgent intervention for serious complications (e.g. central nervous system metastasis) will not be delayed ;
5. The subject should be sufficiently informed and the investigator should explain all predictable risks or discomfort and other alternative treatment methods in details before continuation of IBI308 treatment.

If all the above criteria are met, the investigator has to discuss with the sponsor's medical manager to make the decision on continued treatment after disease progression, and the decision should be documented on study record.

The data of subjects continuing IBI308 treatment after initial disease progression have to be collected refering to Table 1. Treatment will be continued until death, intolerable toxicity, withdrawal of consent, no clinical benefit evaluated by the investigator, or initiation of new anti-tumor therapy (whichever occurs first).

If there is worsening of clinical symptoms, IBI308 treatment should be discontinued for subjects continuing IBI308 treatment after initial disease progression, and "worsening of clinical symptoms" should be documented.

5.2 Study Drug (IBI308)

5.2.1 Description

The study drug is recombinant fully human anti-programmed cell death receptor 1 monoclonal antibody injection, referred to as IBI308.

Its main active ingredient is recombinant fully human anti-programmed cell death receptor 1 monoclonal antibody, with the finished product supplied in strength of 10 mL: 100 mg. IBI308 is free of preservatives at a concentration of 10 mg/mL, and contains the following excipients: mannitol 140 mmol/L, histidine 25 mmol/L, sodium citrate dihydrate 20 mmol/L, sodium chloride 50 mmol/L, edetate disodium (disodium edetate) 0.02 mmol/L, and polysorbate 80 0.2 mg/mL, with a pH value of 6.0.

The product is a clear colorless liquid, free of foreign matters, floccules and precipitates.

Manufacturer: Innovent Biologics (Suzhou) Co., Ltd (hereinafter referred to as Innovent).

5.2.2 Labeling

IBI308 is supplied in the minimum packaging unit of boxes, with per box containing 2 pieces of IBI308 injection packaged in a vial. Printed on the packaging boxes of IBI308 are drug name, drug number, dosage form, strength, drug code, lot number, shelf life, storage conditions, usage and dosage, precautions and sponsor information. The same information is also printed on the labels for the vials and packaging boxes, except for dosage form and precautions information, which is not provided on the vial labels. The labels of all packaging boxes and vials are clearly indicated with "For clinical trial only".

5.2.3 Storage conditions

It is stored at 2 to 8℃, protect from light, shelf life of 24 months. If the injection has quality issue of opacity or precipitation, it should be sealed immediately, and the sponsor is informed immediately.

5.2.4 Preparation and infusion

IBI308 is prepared and infused according to procedures as follows:

1. Completely draw 2 vials of IBI308 injection into an intravenous infusion bag containing 100 mL of 0.9% (weight/volume) sodium chloride-sterile normal saline, and record the start time of preparation.

2. Gently invert the infusion bag for mixing to ensure the homogeneity of drug in the infusion bag, and avoid foaming from violently shaking.

3. Administer infusion intravenously via an IV pump installed with a 0.2-1.2 μm on-line filter (it is recommended that the infusion be completed within 30-60 minutes), and record the start time and end time of infusion.

Precautions: drug products from different batches should not be mixed for a single infusion; Before preparation, confirm IBI308 injection is clear, without quality issue of opacity or precipitation; Ensure the time from drawing of the first vial of IBI308 injection to the end of administration will not exceed 24 hours (prepared drug will be stored at 2-8℃ in a refrigerator); Avoid mixture with other drugs; Avoid intravenous bolus injection.

5.3 Study drug (paclitaxel and irinotecan)

Both paclitaxel and irinotecan are approved anti-tumor drugs, and will be centrally supplied by the sponsor after additional re-labeling. The study site has to store, prepare and administer drugs according to approved labels. The following information is provided for reference.

5.3.1 Pre-medication for chemotherapy

For details of pre-medication regimen for chemotherapy, please refer to requirements in package insert and local clinical practice. The table below lists recommended pre-medication for chemotherapy.

Table 4. Recommended pre-medication for chemotherapy

Paclitaxel	
Dexamethasone	20 mg divided into 2 doses, orally administered 12 h and 6 h before chemotherapy
Diphenhydramine	50 mg, intravenous injection 30-60 min before chemotherapy (or other similar drugs of equivalent dose)

Cimetidine or ranitidine	Cimetidine (300 mg) or ranitidine (50 mg), intravenous injection 30-60 min before chemotherapy
Irinotecan	
Antiemetics	Recommended prophylactic use, per routine practice at each study site
Atropine	If the subject develops cholinergic syndrome, consider prophylactic atropine in subsequent treatment cycles

5.4 Dose Adjustments

5.4.1 General Principles

- The subjects must have adequate hematologic, hepatic, and renal functions prior to Day 1 of each drug administration cycle, and all toxicities must have resolved to NCI CTCAE 4.03 grade 0-1 or baseline (excluding alopecia, fatigue).
- All dosage modifications should be documented, including the reason and the method(s) used.

5.4.2 Dose adjustment for IBI308

No dose reduction for IBI308 is allowed throughout the study. The dosage modification scheme for IBI308 (only for AEs judged as IBI308-related by the investigator) is presented in the table below.

Table 5. Dose adjustment scheme of IBI308

Adverse reaction	**Seriousness**	**Dose Modifications**
Pneumonia	Grade 2 pneumonitis	Interruption[a]
	Grade 3 or 4 pneumonitis	Permanent discontinuation
Diarrhea/enterocolitis	Grade 2 or 3 diarrhea or enterocolitis	Interruption[a]
	Grade 4 diarrhea or enterocolitis	Permanent discontinuation
Dermatitis	Grade 3 dermatitis	Interruption[a]
	Grade 4 dermatitis	Permanent discontinuation

Adverse reaction	**Seriousness**	**Dose Modifications**
Hepatitis	Grade 2 AST, ALT or TBIL elevation	Interruption[a]
	Grade 3 or 4 AST, ALT or TBIL elevation	Permanent discontinuation
Hypophysitis	Grade 2 hypophysitis	Interruption[b]
	Grade 3 or 4 hypophysitis	Permanent discontinuation
Adrenal insufficiency	Grade 2 adrenal insufficiency	Interruption[b]
	Grade 3 or 4 adrenal insufficiency	Permanent discontinuation
Hyperthyroidism	Grade 3 or 4 hyperthyroidism	Permanent discontinuation
Type 1 diabetes	Grade 3 hperglycaemia	Interruption[b]
	Grade 4 hperglycaemia	Permanent discontinuation
Renal insufficiency	Grade 2 or 3 elevated Cr	Interruption[a]
	Grade 4 elevated Cr	Permanent discontinuation
Neurotoxicity	Grade 2 neurotoxicity	Interruption[a]
	Grade 3 or 4 neurotoxicity	Permanent discontinuation
Infusion reactions	Grade 3/4 infusion reaction	Permanent discontinuation
Other AEs	First occurrence of other grade 3 AEs	Interruption[a]
	Second occurrence of the same grade 3 AEs	Permanent discontinuation
	Grade 3 AEs that did not return to grade 0 - 2 or the baseline level within 7 days or did not resolve to grade 0/1 or the baseline level within 14 days	Permanent discontinuation
	Grade 4 AEs	Permanent discontinuation[c]

a: The drug may be resumed after the symptoms resolve to grade 0 - 1 or the baseline level.

b: The drug may be resumed after hypophysitis, adrenal insufficiency, and/or type 1 diabetes mellitus is adequately controlled, only requiring physiological hormone replacement therapy (HRT).

c: For grade 4 laboratory abnormalities, discontinuation of treatment should be based on concomitant clinical symptoms/signs and the investigator's clinical judgment.

The maximum permitted duration of temporary discontinuation is 6 weeks. If the abnormalities do not return to a status allowing for resumption of IBI308 within 6 weeks, the subject will permanently discontinue IBI308 treatment and proceed to follow-up period. Except for the following two situations:

- Glucocorticoid is used for treatment of irAE and tapering of glucocorticoid causes temporary discontinuation of IBI308 for more than 6 weeks: In this case, the investigator should discuss with the sponsor's medical manager to determine whether IBI308 treatment can be resumed. Radiological examination assessing efficacy will be performed as scheduled, not influenced by temporary discontinuation.
- Treatment of AEs unlikely related or unrelated to IBI308 results in temporary discontinuation of IBI308 for more than 6 weeks: In this case, the investigator should discuss with the sponsor's medical manager to determine whether IBI308 treatment can be resumed. Radiological examination assessing efficacy will be performed as scheduled, not influenced by temporary discontinuation.

5.4.3 Dose adjustment of paclitaxel

Hematological toxicity

The next cycle of paclitaxel treatment can be started only if ANC is recovered to ≥1.5 x 10^9/Land PLT is recovered to ≥100 x 10^9/L. If severe neutropenia (ANC ≤0.5 x 10^9/L lasting for one week or more) or febrile neutropenia occurs during paclitaxel treatment, dose of paclitaxel should be reduced by 20% in subsequent treatment.

If there is platelet count <25 x 10^9/L or <50 x 10^9/L with bleeding or requiring transfusion in the previous treatment cycle, dose of paclitaxel should be reduced by 20% in subsequent treatment.

Once dose of chemotherapeutic drug is reduced due to febrile neutropenia or thrombocytopenia (platelet <25 x 10^9/L or <50 x 10^9/L with bleeding or requiring transfusion), it is not permitted to restore the original dose. If dose reduction is required again due to febrile neutropenia or thrombocytopenia, dose of paclitaxel should be further reduced by 20%. If the subject develops a condition requiring dose reduction for the third time, chemotherapy should be discontinued immediately.

The maximum permitted delay of chemotherapy is 3 weeks. If ANC is not ≥1.5 x 10^9/L or platelet is not ≥100 x 10^9/L on pre-specified Day 1 of chemotherapy after a 3-week delay, the subject should permanently discontinue chemotherapy; If the above values are met, the next cycle of chemotherapy can be continued.

The investigator should carefully monitor subjects for toxicities, particularly early and obvious signs of myelosuppression/infection/febrile neotropenia, so as to appropriately

treat these complications in time.

Dose adjustment is not necessary for anemia, but the study physician should provide treatment according to routine practice at each study site.

Neurotoxicity

In case of severe peripheral neuropathy (G3-4), temporarily discontinue till the subject is recovered to grade 1, and dose of paclitaxel should be reduced by 20% in subsequent treatment. Once dose is reduced due to neurotoxicity, it is not allowed to restore the original dose. If toxicity is not recovered to grade 1 after temporary discontinuation for 3 weeks, paclitaxel should be permanently discontinued.

Allergic reaction hypersensitivity

If allergic reaction is re-induced in subjects with previous mild to moderate hypersensitivity, prophylactic medication (see below) is recommended, with close monitoring of vital signs.

- Mild symptoms: complete paclitaxel infusion. Bedside observation, not required for treatment.
- Moderate symptoms: stop paclitaxel infusion, provide intravenous administration of diphenhydramine 25-50 mg and dexamethasone 10 mg. After resolution of symptoms, resume infusion of paclitaxel at low rate (20 mL/hr infusion for 15 min, followed by 40 mL/hr for 15 min; after that, if there is no allergic reaction/hypersensitivity, complete infusion at normal infusion rate). If the same symptoms recur, stop paclitaxel infusion and permanently discontinue subsequent cycles of paclitaxel infusion.
- Severe life-threatening symptoms: stop paclitaxel infusion, provide intravenous administration of diphenhydramine and dexamethasone (as above). If indicated, add epinephrine or bronchodilator. Permanently discontinue subsequent cycles of paclitaxel infusion.

Other toxicities

In case of other grades 3-4 toxicities not mentioned previously, temporarily discontinue infusion of chemotherapeutic drug till resolution of symptoms or recovery of toxicities to grade 1. Then resume infusion at 20% dose (not restored to the original dose thereafter). If toxicity is not recovered to grade 1 after temporary discontinuation for 3

weeks, chemotherapy should be permanently discontinued. For grades 1 and 2 toxicities, no dose adjustment is recommended.

5.4.4 Dose adjustment of irinotecan

The next cycle of irinotecan treatment can be started only if ANC is recovered to ≥1.5 x 10^9/L, PLT is recovered to ≥100 x 10^9/L, and treatment related diarrhea completely resolved. Treatment should be delayed by 1-2 weeks to allow recovery of related toxicities. If the patient is not recovered after delay of 2 weeks, permanent discontinuation of irinotecan chemotherapy should be considered.

If the subject develops toxicities listed in the table below, dose of irinotecan for the next cycle should be reduced by a decrement of 30 mg/m^2.

Table 6. Recommended dose adjustment of irinotecan monotherapy

Toxicity grade	**Dose for the next cycle**
Neutropenia	
− Grade 1-2 neutropenia	Maintain the original dose level
− Grade 3-4 neutropenia	Reduce by 1 dose level
Febrile neutropenia	Reduce by 1 dose level
Diarrhoea	
− Grade 1-2 diarrhoea	Maintain the original dose level
− Grade 3 diarrhea	Reduce by 1 dose level
− Grade 4 diarrhea	Reduce by 2 dose level
Other non-hematological toxicities	
− Other grade 1 non-hematological toxicities	Maintain the original dose level
− Other grade 2-4 non-hematological toxicities	Reduce by 1 dose level

5.5 Principles for Management of Toxicities Associated with Immune Checkpoint Inhibitors

IBI308 pharmacologically promotes the activation and proliferation of T cells to cause immune hyperfunction, thereby leading to autoimmune disorders of multiple systems. Immune-related adverse events were reported with clinical application of other immune checkpoint inhibitors (ipilimumab, nivolumab, pembrolizumab and atezolizumab),

including immune-related pneumonia, diarrhea/enterocolitis, renal insufficiency, rash, hepatitis, endocrine disorders, and peripheral or central neuritis. If the subject experiences any of the above AEs in this study, the subject's symptoms and signs should be monitored, related examinations performed, and causes identified. If no alternative causes (e.g., disease progression, concomitant medication and infection) are identified and treatment with glucocorticoids and/or other immunosuppressive agents is required (except for endocrine events such as hyperthyroidism/hypothyroidism, hypophysitis, type 1 diabetes and adrenal insufficiency, which may not be treated with immunosuppressive therapy but are still considered related to immune hyperfunction caused by IBI308), the above AEs should be considered related to immune hyperfunction caused by IBI308 and diagnosed as irAEs.

Guidelines on dose adjustment and toxicity management for potential major irAEs, potential other irAEs and infusion-related reactions are provided in Appendix 7.

5.6 Concomitant Treatment

5.6.1 Prohibited Medications

- Other chemotherapy, immunotherapy, targeted therapy and hormone therapy for treatment of tumor.
- Immunosuppressive agents and high-dose glucocorticoids (excluding those for AEs).
- Immunoglobulins.
- Live attenuated vaccine.

5.6.2 Permitted Medications

- Medications that comply with the protocol requirements in the investigator's judgment (e.g., concomitant medications for disease-related symptoms and treatment-related AEs).
- Long-term medications that are required for management of underlying diseases such as hypertension and diabetes.
- During study treatment, local surgery or radiotherapy (radiation field excluding lung) will be used for isolated lesions (excluding target lesions).
- Supportive treatment to relieve tumor related symptoms is permitted, such as bisphosphonates for bone metastasis.

- Glucocorticoids that are intended for topical use, such as topical skin application, eye application, nasal spray and inhalation.
- Carriers of hepatitis B virus are permitted to receive prophylactic anti-viral treatment. For specific dosage and administration, refer to applicable guidelines.

5.6.3 Drug-Drug Interactions

- IBI308: at present, there is no data on drug interaction with IBI308.
- Paclitaxel:
  - Cytochrome P450 isoenzymes CYP2C8 and CYP3A4 promote metabolism of paclitaxel. When paclitaxel is used concurrently with known substrates, inducers (e.g. rifampicin, carbamazepine, phenytoin, efavirenz and nevirapine) or inhibitors (e.g. erythromycin, fluoxetine and gemfibrozil) of cytochrome P450 isoenzymes CYP2C8 and CYP3A4, pharmacokinetics of paclitaxel will be changed, and caution is recommended.
  - Interaction between paclitaxel and substrates of CYP3A4 and protease inhibitors acting as substrates or inhibitors of CYP3A4 (ritonavir, saquinavir, indinavir and nelfinavir) has not been confirmed in a clinical study.
  - In vitro, many drugs (ketoconazole, verapamil, apauvin, quinidine, dexamethasone, cyclosporine, teniposide, etoposide and vincristine) can inhibit metabolism of paclitaxel into 6α-hydroxy paclitaxel, but concentrations used exceed normal in vivo therapeutic doses. Testosterone, 17α-ethinyloestradiol, retinoic acid and CYP2C8 specific inhibitor quercetin can also inhibit generation of 6α-hydroxy paclitaxel in vitro.
- Irinotecan:
  - Neuromuscular blocking agents: interaction between irinotecan hydrochloride and neuromuscular blocking agents cannot be excluded. Since irinotecan hydrochloride has cholinesterase inhibitor activity, drugs with cholinesterase inhibiting activity may prolong the neuromuscular blocking effects of suxamethonium chloride and the neuromuscular

blockade of non-depolarising drugs may be antagonised.

- Anticonvulsants: concomitant use of CYP3A induced anticonvulsants (e.g. carbamazepine, phenobarbital or phenytoin) may result in decreased exposure of SN-38. For patients requiring anticonvulsant treatment, consider initiate or switch to non-enzyme induced anticonvulsants at least one week prior to initial dose of irinotecan hydrochloride.
- Ketoconazole: concomitant ketoconazole treatment will significantly reduce clearance of irinotecan hydrochloride, resulting in increased exposure to its active metabolite SN-38. Ketoconazole should be stopped at least one week prior to initiation of irinotecan hydrochloride. Also, it should not be used concomitantly with irinotecan hydrochloride.
- **St. John's Wort** (Hypericum perforatum): the exposure to active metabolite SN-38 is reduced in patients concomitantly treated with Hypericum perforatum. Hypericum perforatum should be stopped at least one week prior to initial dose of irinotecan hydrochloride. Also, it should not be used concomitantly with irinotecan hydrochloride.
- Atazanavir: concomitant use of atazanavir, an inhibitor of CYP3A4 and UGT1A1, may increase exposure of SN-38. This should be considered when these drugs are used concomitantly.
- Dexamethasone: lymphocyte decreased has been reported in patients treated with irinotecan hydrochloride, which may be aggravated when dexamethasone is used as antiemetic. However, no serious opportunistic infection or any complication due to lymphopenia has been found. Increased blood glucose has been reported in patients using this product. This usually occurs in patients with a history of diabetes or impaired glucose tolerance before treatment with this product. Increased blood glucose in some patients may be due to dexamethasone.
- Prochlorperazine: in a clinical study of monotherapy using weekly regimen, incidence of akathisia was higher in patients receiving prochlorperazine on the same day of irinotecan hydrochloride treatment (8.5%, 4/47 patients), and lower when the two drugs were administered on different days (1.3%, 1/80 patient). However, the incidence of akathisia 8.5% was still within the reported range of akathisia when

prochlorperazine was used as pre-medication for other chemotherapies.

- During treatment with this product, concomitant use of laxatives may increase severity or incidence of diarrhea. However, there is no relevant study.
- Diuretics: as there is potential risk of dehydration secondary to vomiting and/or diarrhea, physicians should avoid use of diuretics during treatment with irinotecan hydrochloride as well as diarrhea or vomiting.

5.7 Treatment Compliance

Study treatment is administered at the study site, and treatment compliance is monitored using drug receipt & dispensing records, medical records and eCRFs.

5.8 Drug Recovery and Destruction

In this study, the used and partially used containers, bottles, infusion bags, and syringes of the study drug may be destroyed on site according to the applicable guidelines and operating procedures established by the study site and local authorities after confirmation by the clinical research associate (CRA).

All unused study drugs will be returned to the sponsor for central destruction after study completion/termination or beyond expiration date. The clinical research associate designated by the sponsor will be responsible for return of study drugs.

5.9 Documentation of Study Drug

The designated site personnel should keep a record of the receipt, dispensing, use, inventory, loss, recovery and destruction of the study drugs in time according to the requirements of relevant regulations and guidelines as well as the operating procedures of this trial.

5.10 Handling of Complaints

To ensure safety of study participants, monitor quality, and promote improvement of flow process and drug product, the sponsor will collect product complaints related to study drugs used in the clinical trial.

Complaints involving concomitant drugs will be reported directly to the manufacturers according to product label.

The investigator or the designee will be responsible to complete the following flow

process of product complaint according to relevant specifications in this study:

- Use study specific complaint form to document reported product complaint and relevant complete description.
- Fax the completed product complaint form to the sponsor or the designee within 24 hours.

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

6 Study Evaluations and Procedures

6.1 Subject Enrollment and Randomization Process

6.1.1 Subject Enrollment and Randomization

The investigator(s) will enroll subjects according to the following procedures:

1. Obtain the signed ICF from the subject prior to initiation of any study-related procedures.
2. The principal investigator (PI) or the appropriately trained designee formally should confirm the subject's eligibility according tothe inclusion/exclusion criteria.
3. IWRS system will be used for randomization at 1:1 ratio, stratified by ECOG PS score (0 or 1).

Re-screening may be performed for patients who do not meet the relevant criteria for this study (screening failure). If re-screening is considered, the investigator must contact the sponsor's medical manager. Each patient can be re-screened once. At re-screening, the patient must re-sign the ICF and will be reassigned with an identification number.

6.1.2 Handling Procedures for Wrongly Enrolled Subjects

Inclusion/exclusion criteria must be strictly followed. If an enrolled subject is found not meeting inclusion/exclusion criteria, the sponsor's medical manager and the investigator should discuss to determine whether the subject should continue in the study, and whether study drug should be used. If the investigator considers it medically appropriate for the subject to continue in the study, and agreed by the sponsor's medical manager, the subject can continue in the study and receive study drug. If the investigator

considers is medically appropriate for the subject to continue in the study, but not agreed by the sponsor's medical manager, the subject cannot continue in the study (whether receive study drug or not). The investigator may allow the accidentally enrolled subject to continue participation in the study only after receiving written approval from the sponsor.

6.2 Study Plan and Schedule

6.2.1 Screening Period

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

- Signing ICF
- Inclusion/exclusion criteria
- Demographics, past medical history and previous medication
- Vital signs, height and weight
- Physical Examination
- ECOG PS score
- 12-lead electrocardiogram
- Hematology/blood biochemistry/urinalysis (within 7 days prior to the first dosing)
- Pregnancy test (within 3 days prior to the first dose)
- Thyroid function (test results not older than 28 days prior to randomization at the site are acceptable)
- HIV antibody, hepatitis B panel (for HBsAg positive patients, further test HBV DNA) and HCV antibody (for HCV antibody positive patients, further test HCV RNA), test results not older than 28 days prior to randomization at the site are acceptable
- Adverse event assessment
- Concomitant medications
- Tumor imaging evaluation

- Archived or fresh tumor tissue sample

For details of tumor radiological assessment and safety assessment, refer to Sections 6.3 and 6.4.

6.2.2 Baseline (Prior to Dosing on Cycle 1/Day 1)

- IWRS randomization (first dose must occur within 3 working days of randomization)
- Vital signs
- Weight
- ECOG PS score
- Immunogenicity (IBI308 group only)
- Adverse event assessment
- Concomitant medications
- EQ 5D-5L questionnaires
- EORTC QLQ-C30 questionnaires
- EORTC QLQ-OES18 questionnaires
- Biomarker blood sample collection (IBI308 group only)

6.2.3 Treatment Visits

- Vital signs
- Weight
- Physical Examination
- ECOG PS score
- 12-lead electrocardiogram
- Hematology/blood biochemistry/urinalysis
- Thyroid function (IBI308 group only)
- Immunogenicity (IBI308 group only)
- Adverse event assessment

- Concomitant medications
- Tumor imaging evaluation
- Administration of study drug (for visits requiring tumor radiological assessment, the assessment will be completed before dosing)
- EQ 5D-5L questionnaires
- EORTC QLQ-C30 questionnaires
- EORTC QLQ-OES18 questionnaires
- Biomarker blood sample collection (IBI308 group only)
- Survival status

The flow chart of study treatment visits is provided in Table 1.

For details of tumor radiological assessment, safety assessment and immunogenicity blood sample collection, refer to Sections 6.3, 6.4 and 6.5.

6.2.4 Safety Follow-up

Two safety follow-ups will be performed. The first takes place at the treatment discontinuation visit or on Day 30 (± 7 days) after the last dose, and the second on Day 90 (± 7 days) after the last dose. Include:

- Vital signs
- Physical Examination
- ECOG PS score
- 12-lead electrocardiogram
- Hematology/blood biochemistry/urinalysis
- Thyroid function (only the 1st one, IBI308 group only)
- Pregnancy test (only the 1st one)
- Immunogenicity (only the 2nd one, IBI308 group only)
- Adverse event assessment
- Concomitant medications
- Subsequent anti-tumor treatment (if applicable)

- Survival status
- EQ 5D-5L questionnaires (only the 1st one)
- EORTC QLQ-C30 questionnaires (only the 1st one)
- EORTC QLQ-OES18 questionnaires (only the 1st one)

6.2.5 Survival Follow-up

After the 2nd safety follow-up, subjects will be contacted every 60 days (±7 days) (phone visit is acceptable). Information about survival, any subsequent systemic anti-tumor treatment and disease progression will be obtained as far as possible. Long-term follow-up will be continued till subject's death or the end of study.

6.3 Efficacy Evaluation

The method used for baseline tumor burden assessment must be consistent with the method used for each subsequent follow-up assessment. Other involved sites will be examined as suggested by each subject’s symptoms and signs. Baseline assessment should be performed within 28 days prior to the first dose of study drug. The investigators may collect imaging results within 28 days prior to enrollment for assessment.

Tumor imaging evaluation will be performed every 6 weeks (± 7 days) in the first 24 weeks following the first dose of study drug, and then every 9 weeks (± 7 days) after Week 24, until initiation of new anti-tumor treatment, disease progression, withdrawal of ICF, or death. For patients with initially documented radiological progression in IBI308 treatment group, radiological confirmation is required at an interval of 4-6 weeks. Some subjects meeting specific conditions can continue treatment beyond disease progression (refer to Section 5.1.2 in the protocol). For subjects who continue treatment beyond disease progression, radiologic evaluation should be continued. For patients who discontinued treatment for reasons other than radiographic disease progression, imaging evaluations should, wherever possible, be performed every 6 weeks (± 7 days) after discontinuation, until occurrence of any of the following: initiation of new anti-tumor therapy, disease progression, withdrawal of ICF, and death.

If the investigator cannot determine whether there is the disease progression or not, particularly uncertain about non-target lesions and new lesions, the subject can continue treatment. Disease status will be re-assessed in case of clinical signs or at the next scheduled assessment time point. If repeated scan confirms disease progression, the

date of progression should be the date of initial discovery.

The primary analysis in this study is based on tumor assessment of the study site using RECIST v1.1. See Attachment 3 for assessment methods. For subjects treated by IBI308 who have a disease progression as assessed per RECIST v1.1, radiologic evaluation should be continued as per iRECIST (Attachment 4) assessment requirements and the frequency of follow-up, wherever possible.

6.4 Safety Assessment

6.4.1 Routine Laboratory Safety Evaluations

Table 7. Routine laboratory safety evaluations

Hematology	RBC, HGB, WBC, PLT, LYM, ANC
Blood Biochemistry	TBIL, ALT, AST, γ-GT ALP, ALB, TP, LDH, BUN, Cr, Na, K, Cl, Mg, Ca, P, Lipase, Amylase and FBG
Urine Routine	PH, UWBC, UPRO, URBC 和 UGLU

6.4.2 Physical Examination and ECOG PS Score

Complete physical examination includes: general condition, respiratory, cardiovascular, abdominal, skin, head and neck (including ears, eyes, nose and throat), lymph nodes, thyroid, musculoskeletal (including spine and limbs), genital/anal and neurological assessments.

Refer to Table 1 visit schedule for the specific time of physical examination. Refer to Appendix 2 for ECOG PS scoring system.

6.4.3 12-lead Electrocardiogram

Resting 12-lead ECG will be analyzed at a local laboratory according to Table 1 visit schedule.

A 12-lead ECG is performed for each subject after a rest of minimum 5 minutes in recumbent position. All 12-lead ECGs should be recorded with the subject in a recumbent position. Further ECG will be performed as clinically indicated, e.g., when there is an occurrence of cardiac-related AE. The investigator completes ECG assessment on the day of the examination and write down the results of assessment on the electrocardiogram. The same assessment method(s) should be used throughout the

study.

The investigator should assess all ECGs according to the category of clinically significant abnormality/not clinically significant abnormality. If the abnormality is clinically significant, the investigator should record this result as an AE in the eCRF.

6.4.4 Vital Signs

Vital signs examination will be performed as described in Table 1 study visit schedule. Vital signs include body temperature, pulse rate, respiratory rate, and blood pressure.

Additional monitoring of vital signs may be performed at the discretion of the investigator based on standard clinical practice or as clinically indicated.

In the event of an AE/SAE, additional vital sign values may be collected from the eCRF (if appropriate). The date(s) and time of collection and measurement will be recorded in the appropriate section of the eCRF.

Pulse and Blood Pressure

Blood pressure (BP) and pulse rate are measured with the subject a supine position after a rest of at least 5 minutes. Two ore more readings should be obtained with measurement performed at intervals of two minutes, and the mean of the measurements is calculated. If the first two systolic blood pressure readings differ by more than 5 mmHg, another measurement should be performed to calculate the mean value. The date(s) and time of collection and measurement will be recorded in the appropriate section of the eCRF.

Measurement of pulse and blood pressure measurements needs to be performed prior to administration of the study drug.

Body Temperatureand Respiratory Rate

Blood temperature and respiratory rate should be collected prior to infusion on the scheduled dosing day(s).

6.4.5 Body Weight and Height

Body height is measured only during the screening period.

Body weight measurement needs to be performed at screening and prior to each scheduled dosing throughout this study.

6.4.6 Pregnancy Test

For women of childbearing potential (see 4.3 for definition), a pregnancy test using urine or serum human chorionic gonadotropin (hCG) samples should be performed within 3 days prior to the first dose of study drug. If urine hCG test reports positive or negative cannot be confirmed, a pregnancy test using serum β-hCG samples should be performed, and the result of serum pregnancy test should prevail. If the pregnancy test is positive, the subject is not eligible for enrollment/must be discontinued from the study. In the event of suspected pregnancy during the study, a test should be repeated for confirmation.

6.4.7 Other Safety Tests

- Hepatitis B: hepatitis B panel (HBsAg, HBsAb, HBcAb, HBeAg, HBeAb), if HBsAg positive, further test HBV DNA.
- HIV antibody, HCV antibody (if HCV antibody positive, further test HCV RNA).
- Thyroid function (except screening period, other time points for IBI308 group only): TSH, T3, T4, FT3 and FT4.

6.5 Immunogenicity

Immunogenicity test will be performed only for the IBI308 group, within 1 hour before IBI308 infusion in Cycle 1, Cycle 2, Cycle 4 and then every 4 cycles (Cycles 8, 12, 16 and so on), and at the 2nd safety follow-up visit. The test will be performed at the central laboratory.

Testing on anti-drug antibody titer will be performed for each subject, and ADA-positive serum specimens will be further tested for neutralizing antibodies (NAbs).

Four (4) mL of whole blood will be collected into a coagulation-promoting vacuum tube, then separated serum, split and frozen for ADA and NAb analysis.

For details of sampling method, sample preservation, shipping and analysis, refer to the Laboratory Manual provided by the sponsor designated central laboratory.

6.6 Quality of Life Assessments

QoL assessment will be performed using EQ 5D-5L, EORTC QLQ-C30 and EORTC QLQ-OES18 questionnaires on the day of the first dose, and at each radiographic evaluation and the first safety follow-up visit. For details of assessment questionnaires

and requirements, refer to Quality of Life Assessment Manual provided by the sponsor.

6.7 Biomarker Analysis

As permitted by the Ethics Committee, all subjects meeting inclusion criteria have to provide diagnosed tumor tissue at baseline. Acceptable tumor tissues include 10 unstained 4-5 micron slides prepared from archived tumor tissue or freshly collected in screening period, which will be used for tumor tissue PD-L1 testing and mRNA expression analysis of immune related genes (including but not limited to mRNA expression of IDO1, CXCL9, CXCL10, HLA-DRA, STAT1, IFNG).

Subjects in IBI308 group have to provide 10 ml of whole blood samples at the following time points: screening period, at each efficacy evaluation before initiation of the next treatment in treatment period, for analysis of circulating tumor cell (CTC) (including but not limited to dynamic change of PD-L1) and ctDNA sequencing.

For details of sampling method, sample preservation, shipping and analysis, refer to the Laboratory Manual provided by the sponsor designated central laboratory.

6.8 Storage and Destruction of Biological Samples

Samples will be anonymized and pooled. In addition, they will be disposed of or destroyed appropriately. Additional analyses may be performed for the anonymized, pooled samples to further assess and validate the analytical methods. Any results obtained from these analyses may be reported separately from the CSR.

Sample reproducibility analysis (if performed) will be performed in parallel with the bioanalysis of the test samples. The assessment results will be separately reported in a bioanalysis report rather than in the clinical study report.

7 Safety Report and AE Management

7.1 Definition of Adverse Events

An adverse event (AE) is defined as any adverse medical event that occurs from the clinical trial subject's signing of the informed consent form to 90 days after the last dose of study drug regardless of causality with the study drug. AEs include but are not limited to the following situations:

- Worsening of preexisting medical conditions/diseases (including worsening of symptoms, signs and laboratory abnormalities);

- Any new adverse medical conditions (including symptoms, signs and newly diagnosed diseases);
- Clinically significant abnormal laboratory test values or results.

7.2 Definition of Serious Adverse Events

A Serious Adverse Event (SAE) refers to an AE that meets at least one of the following criteria:

- Results in death, excluding deaths due to disease progression from the studied indication.
- Life-threatening (a "life-threatening" AE in the definition refers to an AE whose occurrence will have the subject under the risk of death, excluding AEs that may cause death if aggravated).
- Requires inpatient hospitalization or prolongation of existing hospitalization, with the exception of the following:
  - ✓ Rehabilitation facility
  - ✓ Nursing home
  - ✓ Conventional emergency room admission and treatment
  - ✓ Day surgery (e.g. outpatient/same-day/ambulatory surgery)
  - ✓ Hospitalization or prolonged hospitalization itself unrelated to AE deterioration is not an SAE, such as hospitalization due to the original disease without the occurrence of new adverse events or aggravation of the original disease (e.g.: for examination of laboratory test abnormalities that have persisted from before the trial to the present); hospitalization for administrative reasons (e.g.: routine yearly physical examination); hospitalization stipulated by the trial protocol during the clinical trial (e.g.: operations as required by the trial protocol); elective hospitalization unrelated to the deterioration of adverse events (e.g.: elective surgery); pre-defined treatment or surgery should be recorded in the entire trial protocol and/or the subject's personal baseline information; hospitalization only for the use of blood products.
- Leading to persistent or significant disability/incapacity.

- Leading to congenital anomalies/birth defects.
- Other significant medical events: defined as events that jeopardize the subject, or require medical intervention to prevent any of the above situations.

7.3 Criteria for AEs Severity Judgment

The investigator(s) will assess the severity of AEs according to the five-grade judgment criteria as established in NCI CTCAE v4.03.

AEs that are not included in NCI CTCAE v4.03 will be graded according to the following CTCAE principles:

- Grade 1 mild; No symptom or slight sign; Only clinical or diagnostic observation; Medical intervention not indicated.
- Grade 2 moderate; Minimal, local or non-invasive intervention indicated; Limiting age-appropriate instrumental activities of daily living (ADL, e.g., preparing meals, shopping for groceries, using the telephone, managing money, etc.).
- Grade 3 severe or clinically significant, but not immediately life-threatening; Hospitalization or prolonged hospitalization; With disability; Limiting daily activities (e.g. bathing, dressing, eating, toileting and drug use), but not bed-ridden.
- Grade 4 life-threatening consequences; Urgent intervention indicated.
- Grade 5 death related to AEs

7.4 Judgment on Correlation between AEs and Study Drug

The relationship of the study drug with the AEs or the role it plays in the occurrence of AE can be judged using the following classification and criteria:

Table 8. Judgment on correlation between AEs and study drug

Correlation	Criteria
Definitely related	● There exists a reasonable temporal consequence in use of the study drug with occurrence of the AEs; ● The AEs can be more reasonably explained by the investigational drug than other causes (e.g., the subject's preexisting disease, environmental or toxic factors or other treatments the subject received, etc.);

Correlation	Criteria
	● The AEs disappear or are mitigated after treatment discontinuation or dose reduction; ● It falls into the known AEs types of the suspected drug or similar drugs; ● The adverse event appears again after resumption of the drug;
Possibly related	● There exists a reasonable temporal consequence in use of the study drug with occurrence of the AEs; ● The AEs can be reasonably explained by the investigational drug as well as by other causes (e.g., the subject's preexisting disease, environmental or toxic factors or other treatments the subject received, etc.); ● The AEs disappear or are mitigated after treatment discontinuation or dose reduction (if applicable).
Unlikely related	● The AEs can be more reasonably explained by other reasons (e.g., the subject's preexisting disease, environmental or toxic factors or other treatments the subject received, etc.) than the investigational drug; ● It is unknown whether the AEs disappear or are mitigated after treatment discontinuation or dose reduction (if applicable); ● It is unknown whether the AEs appear again or not after resumption of the drug.
Definitely unrelated	● There does not exist a reasonable temporal consequence in use of the drug with occurrence of the AEs, or ● There are other obvious explanations for the AEs (e.g., the subject's preexisting disease, environmental or toxic factors or other treatments the subject received, etc.).
Unable to judge	● The above information is unknown; the investigator considers it impossible to judge based on available information and is unable to obtain further follow-up information.

7.5 Recording of AEs

The investigator(s) should record AEs or SAEs using medical terminology/concepts. Use of colloquialisms and abbreviations should be avoided. All AEs (including SAEs) should be recorded on the adverse event form of the eCRF.

7.5.1 Collection of AEs and Time Period

The investigator is aware of AEs by asking the subjects non-inductive questions.

All AEs (including SAEs), whether observed by the investigator or spontaneously reported by the subjects, should be collected from the signing of the ICF through 90 days after the last dose.

Beyond 90 days after the last dose, the investigator should report SAEs that are

considered related to the study drug or procedures.

7.5.2 Follow-up of AEs

All AEs should be followed up until they resolve to baseline or grade 0 - 1 or the investigator consider further follow-up unnecessary for good justification (e.g, the AEs cannot resolve or has improved). If the AEs cannot resolve, the reasonable explanation(s) should be recorded on the eCRF. The outcomes of AEs or SAEs in the subjects and their dates should be documented on the eCRF and medical records, irrespective of their relationship with the study drug.

7.5.3 AEs Records

The investigator should keep a complete record of any adverse event, including diagnosis (if no diagnosis, record the symptoms and signs including abnormal laboratory findings), start and end dates and time (if applicable), CTCAE severity grade and change (Grade 3 events and above), whether it is an SAE, whether it is an AESI, actions taken for the study drug, treatment administered due to the AE and the outcome of the event, and the relationship of AE with the study drug.

For an SAE, the investigator should also provide the following details: the date on which the AE is judged to meet the criteria for an SAE, the date the investigator became aware of the SAE, rationale for determining the AE as an SAE, the date of hospitalization, the date of discharge, the possible cause(s) of death, the date of death, whether an autopsy was performed, the assessment of causality with the study procedures, assessment of causality with other drugs, and other possible explanations for the SAE. The investigator should also provide the rationale for correlation judgment and a description of the SAE. SAE description should also include subject number, age, gender, height and body weight; Indication of study treatment, disease stage and relevant systemic condition; Clinical disease course including onset, development and outcome of SAE; Laboratory results associated with SAE (test time, unit and normal range must be provided); Past history, concurrent disease associated with SAE, as well as onset time and duration; Medication history, concomitant drug associated with SAE, as well as treatment start, duration, dosage and administration; Details of start, duration, dosage and administration of study drug treatment.

The items of AEs records are described as follows:

Diagnosis, symptoms and signs

If a diagnosis has been made, the diagnosis should be recorded in the eCRF rather than the individual signs and symptoms (e.g., record liver failure other than jaundice, elevated transaminases, and asterixis). If symptoms and signs cannot be determined to be a result of the diagnosis at the time of reporting, they should be recorded as a separate AE/SAE. If the symptoms and signs are determined to be a result of the diagnosis, only the diagnosis is reported separately, with the symptoms and signs included in the diagnosis. For an AE, the records of signs and symptoms need to be deleted; for an SAE, the updated follow-up report needs to be sent.

AEs secondary to other events

For adverse events secondary to other events (e.g. caused by other events or clinical sequelae), their primary events should be documented in general, unless such a secondary event is of high severity or an SAE. However, a secondary event of great clinical significance should be recorded as a separate AE in the eCRF provided it occurred at different time from the primary event. If the correlation between the events is unclear, the events should be recorded separately in the eCRF.

Persistent or recurred AE

A persistent AE refers to an AE that persists and does not resolve between two evaluations for the subject.

A recurred AE refers to an AE that resolved between two evaluations but occurred later again. The occurrence of such events should be recorded separately on the eCRF.

Abnormal laboratory findings

Clinically significant abnormal laboratory findings should be reported as AEs. It is the responsibility of the investigator to review all abnormal laboratory findings and make medical judgment on each abnormal laboratory finding as to whether they should be reported as an AE.

Death

All deaths that occurred throughout the trial, including the 90-day follow-up period that begins from the last dose, should be recorded on the death report form on the eCRF and reported to the sponsor in a timely manner, irrespective of relationship with the study drug.

When recording death, if cause of death is determined, it will be recorded as AE with

outcome of death, and the event will be reported as SAE; If cause of death is unclear at the time of report, “unexplained death” should be recorded on AE page of eCRF. “Unexplained death” will be reported as SAE, followed by further investigation to determine the cause of death.

If the death is clearly due to tumor progression, it will not be recorded and reported as AE/SAE, but the investigator should keep a record of the death on the death report form on the eCRF and inform the sponsor timely.

Preexisting medical conditions

The preexisting symptoms/signs a subject has already presented in the screening period of the trial should be recorded and reported as AE only when there is worsening in severity, frequency and nature (excluding worsening of the medical condition studied) after entry into the trial. Changes from the previous state should be reflected in the record, e.g., “increased frequency of headache”.

Hospitalization, prolonged hospitalization, or surgery

All AEs resulting in hospitalization or prolonged hospitalization should be recorded and reported as SAE, except the following:

- Scheduled hospitalization or prolonged hospitalization as requirement of the protocol (e.g. for administration, efficacy assessment, etc.)
- Hospitalization for medical condition pre-existing before participation in the study without any change. For example, elective surgery/treatment scheduled before participation in the study.

However, the required elective surgery and treatment due to condition deterioration of the existing disease during the study shall be considered as AE.

Disease progression

Progressive disease (PD) is defined as worsening of a subject’s condition due to the primary tumor the investigational drug is targeted on. Appearance of new lesions relative to the primary tumor or progression of the original lesions is considered as PD. PD is not reported as an AE. Death due to signs and symptoms of disease progression, events that were life-threatening, required inpatient hospitalization or prolongation of existing hospitalization, resulted in persistent or significant disability/incapacity, or were a congenital anomaly/birth defect, and other important medical events warrant

expedited reporting as SAE.

Overdose

Overdose is defined as use beyond the protocol-specified dose. Overdose will be recorded in eCRF.

7.6 Expedited reporting of SAEs and pregnancies

Reporting of SAEs:

The time limit of SAE reporting is from signing of the ICF to 90 days (including Day 90) after the last dose. In case of an SAE during this period of time, the investigator must immediately fill out, sign and date "CFDA Serious Adverse Event Report Form", and submit the completed form to the sponsor, National Medical Products Administration and the Ethics Committee no later than 24 hours after awareness, regardless of an initial report or a follow-up report. Detailed contact information on SAE reporting is provided in the Table below.

If any serious adverse event occurred beyond the above - mentioned time limit is considered as related to the study drug, it should also be reported to the sponsor.

The investigator must submit the completed SAE report form to the sponsor as soon as possible and within 24 hours after awareness of an SAE. For deaths or life-threatening serious adverse events, the investigator should immediately follow up missing information and provide a complete SAE report.

Meanwhile, the investigator should report to the drug regulatory authorities, health administrative department and the Ethics Committee according to regulatory requirements.

Table 9. Contact information for SAE reporting

Unit	Contact	Fax/Phone/Address
Hospital name	Ethics Committee	Fax/Phone of each hospital
Innovent Biologics (Suzhou) Co., Ltd.	Clinical Research Department PV	Fax: 021-31652800 Email: drugsafety@innoventbio.com
Division of Drug Research Supervision, Department of Drug and Cosmetics		Address: Building 2, No.26 Xuanwumen West Street, Xicheng

Registration, CFDA		District, Beijing. P.R. China Postcode: 100053 Tel.: 010-88330732 Fax: 010-88363228
The Bureau of Health Administration, the National Health Commission		Address: No. A38 Lishi Road, Xicheng District, Beijing, P.R. China Tel.: 010-68792001 Fax: 010-68792734
Provincial, autonomous region and municipal drug regulatory authorities	Refer to reporting requirements of provincial, autonomous region and municipal drug regulatory authorities	

Pregnant women

Considering embryotoxicity risks are reported for similar drugs, all clinical trial participants of childbearing potential must take effective contraceptive measures.

If any female subject becomes pregnant during the clinical trial, the subject should be withdrawn from the study, and the investigator should report the pregnancy to the sponsor within 24 hours after awareness, and fill out the Innovent Clinical Trial Pregnancy Report/Follow-up Form.

If any partner of a male subject becomes pregnant during the clinical trial, the subject may continue the clinical trial, and the investigator should report the pregnancy to the sponsor within 24 hours after awareness, and fill out the Innovent Clinical Trial Pregnancy Report/Follow-up Form.

The investigator shall follow up the outcome of the pregnant subject until 8 weeks after childbirth, and shall report the outcome to the Sponsor.

If the outcome of pregnancy is stillbirth, spontaneous abortion, fetal malformation (any congenital anomaly/birth defect), or induced abortion for medical reasons, it should be considered as SAE and reported according to the procedures and time limit for SAE reporting.

If a subject experienced a concurrent SAE during pregnancy, CFDA Serious Adverse Event Report Form should also be completed for reporting according to the SAE reporting procedures.

7.7 Liver function abnormality events

If there is abnormal AST and/or ALT with abnormally elevated total bilirubin meeting the following criteria, without alternative cause of liver injury, this should be considered as drug induced liver injury. Such condition should always be regarded as important medical events.

Table 10. Liver impairment that should be reported as SAE

Baseline	Normal (AST/ALT and total bilirubin)	Abnormal (AST/ALT and total bilirubin)
Treatment period	ALT or AST ≥3x ULN With total bilirubin ≥2×ULN And alkaline phosphatase ≤2×ULN And no hemolysis	AST or ALT ≥8×ULN With total bilirubin increase ≥1×ULN or value ≥3×ULN

Subjects should return to the study site for evaluation as soon as possible (preferably within 48 hours) after discovery of abnormal result. This evaluation should include laboratory tests, detailed medical history and physical assessment, and the possibility of hepatic neoplasia (primary or secondary) should be considered.

In addition to repeating AST and ALT, laboratory tests should also include albumin, creatine kinase, total bilirubin, direct and indirect bilirubin, gamma-glutamyl transferase, prothrombin time/international normalized ratio and alkaline phosphatase. Detailed medical history collection should include: alcohol history, acetaminophen, soft drugs, various supplements, traditional Chinese medicine, history of chemical drug exposure, family history, occupational exposure, history of sexual behavior, travel history, history of contact with jaundice patient, surgery, blood transfusion, liver disease or allergic disease history, cardiac disease history and immune disease history. Further tests may also include tests of acute hepatitis A, B, C and E, liver imaging (e.g. biliary tract), autoantibody and cardiac ultrasound. If repeated test still meets laboratory criteria in Table 10, without alternative cause of liver function test abnormality, possibility of potential drug induced liver injury should be considered, with no need for results of all liver function etiological tests. Such cases of potential drug induced liver injury should be reported as SAE, and Attachment 5 "Monitoring of liver function abnormality and follow-up report form "will be submitted to the sponsor.

7.8 Management of drug related toxicities

The sponsor will perform periodic safety review at trial level during the trial. Details concerning frequency of review and type of reviewed data will be documented in a separate trial-level safety review plan.

7.8.1 Immune-related adverse events

Given that IBI308 pharmacologically acts to cause activation and proliferation of T cells, immune-related adverse events (irAEs) may be observed during this study. The definition of irAE is provided in Section 5.5 of the protocol. Subjects should be monitored for signs and symptoms of irAEs.

For details of IBI308 dose adjustment and principles of AE management, refer to Sections 5.4.2 and 5.5 of the protocol. Guidelines for the handling of irAEs are provided in Appendix 7 (Tables 1 - 2).

7.8.2 Adverse events of special interest

An adverse event of special interest (AESI) refers to an AE that needs to be closely monitored to better understand the safety profile of the investigational drug, and therefore AESI can be non-serious events.

AESI includes:

- ≥Grade 3 infusion related reactions
- ≥Grade 2 diarrhea, colitis, uveitis, interstitial pneumonia
- ≥ Grade 3 suspected irAEs

8 Statistical Considerations

8.1 Statistical Analysis Plan

A detailed statistical analysis plan (SAP) will be written after enrollment of the first subject and finalized before database lock. The SAP will provide a full presentation of all statistical analyses and their results.

8.2 Hypothesis Test

This study is a superiority design comparing test drug and reference drug using superiority hypothesis test:

H_0: HR≥1; H_a: HR< 1

For primary efficacy endpoint, α=0.2 (two-sided). Stratified log-rank test will be used for the comparison of OS between IBI308 group and chemotherapy group.

8.3 Statistical Analysis Population

The analysis population includes safety analysis set (SS), full analysis set (FAS), and per-protocol set (PPS):

1) SS: the population of subjects who received at least one dose of the study drug.

2) FAS: the population of randomized subjects.

3) PPS: a subset of the FAS, defined as the population of subjects with good compliance who constituted no gross protocol violations, without major protocol violations and used no concomitant medications prohibited by the protocol.

8.4 Statistical Analysis Methods

8.4.1 General Methods Forstatistical Analysis

Measurement data are presented by mean, standard deviation, median, maximum and minimum; Count data are described by frequency and percentage.

All statistical analyses will be completed using SAS 9.2 (or a higher version).

Except primary efficacy endpoint, nominal test significance level for other inter-group comparisons: α=0.05 (two-sided). If P value $\leq$0.05, inter-group difference is considered statistically significant.

8.4.2 Analysis of Primary Endpoint

Overall survival (OS): the time from randomization to the death of the subject, when the subject is still alive at the end of the study, with the known "date the subject was last alive" as the censoring date.

For OS analysis, Kaplan-Meier will be used to estimate median OS (mOS) and its 95% CI. Survival curve will be plotted. Comparison between groups will be performed by the stratified log-rank test. Stratified Cox proportional-hazards model will be employed for estimating HR. Stratification factors of randomization will be included in the model. Meanwhile, the comparison of OS between groups will be performed by the RMST method.

The 6-month and 1-year overall survival rates will be estimated using Kaplan-Meier method.

8.4.3 Analysis of secondary endpoints

All efficacy evaluations will be based on RECIST v1.1:

- Progression free survival (PFS)

PFS: the time from randomization to the first occurrence of disease progression (radiographic), or the time from randomization to death if a patient died of any cause before disease progression. For subjects without disease progression or death, the censoring date is the last date of imaging evaluation. Subjects without imaging evaluation after baseline will be censored at the date of randomization.

For PFS analysis, median PFS (mPFS) and its 95% CI will be estimated by the Kaplan-Meier. Survival curve will be plotted. Comparison between groups will be performed by the stratified log-rank test.

- Objective response rate (ORR)

$ORR = \frac{Number\ of CR\ +\ PR\ subjects}{Total\ number\ of\ subjects} * 100\%$, its 95% CI, inter-group difference and its 95% CI will be calculated by using the binomial distribution. Fisher exact probability will be used for inter-group comparison.

- Disease control rate (DCR)

$DCR = \frac{Number\ of CR+PR+SD\ subjects}{Total\ number\ of\ subjects} * 100\%$, its 95% CI, inter-group difference and its 95% CI will be calculated by using the binomial distribution. Fisher exact probability will be used for inter-group comparison.

- Duration of response (DoR)

For subjects achieving response (CR or PR), duration of response is the time from date of first response to time of disease progression or death. Subjects without disease progression or death will be censored at the date of last imaging evaluation.

Median DoR (mDoR) and its 95% CI will be estimated by Kaplan-Meier. Survival curve will be plotted. Comparison between groups will be performed by the stratified log-rank test.

8.4.4 Quality of Life Scale Analyses

Variations of QoL scale scores as assessed per EQ 5D-5L, EORTC QLQ-C30 and EORTC QLQ-OES18 will be described by group and visit, so as to evaluate the QoL

and health status of the subjects treated by IBI308 and chemotherapy, respectively.

8.4.5 Biomarker Analysis

- Tumor tissue samples will be collected for the analysis of tumor biomarkers, including but not limited to the expression of PD-L1 and the expression of immune-related genes (including but not limited to the expression of IDO1, CXCL9, CXCL10, HLA-DRA, STAT1, IFNG messenger RNA). The relationship between these markers and efficacy will be analyzed
- For subjects in IBI308 group, blood samples will be collected for the analysis of circulating tumor cells (CTCs) (including but not limited to PD-L1 dynamic expression) and ctDNA analysis.

8.4.6 Safety Analysis

The safety analysis will be performed using the SS population. Safety indicators include AEs, laboratory tests, vital signs, ECGs and immunogenicity.

Drug exposure

The exposure and duration (cycles) of the study drug in the subjects during the study period will be summarized.

Adverse events

All adverse events will be coded using MedDRA.

Incidence (frequency) of AEs, TEAEs, ADRs, irAEs, AESIs, SAEs and AEs leading to study discontinuation will be summarized separately; Severity distribution of TEAEs, ADRs, irAEs and AESIs will be summarized by MedDRA SOC and PT per NCI CTCAE v4.03.

Subjects who discontinued treatment due to AE, subjects who experienced SAEs and subjects who died will be tabulated (at least including the start date, end date and severity of AE, relationship with drug, actions taken, and outcome).

Laboratory tests

For hematology and blood biochemistry, the measured values and values of change before and after treatment will be described using mean ± SD, maximum, minimum and median, and cross classification table will be employed for describing normal and abnormal changes before and after treatment.

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

The percentage of subjects with abnormal changes evaluated as "abnormal and clinically significant" will be described. The investigator judges whether the abnormality is clinically significant or not.

A list of subjects with abnormal changes (clinically significant or not clinically significant) after treatment will be provided.

ECG examination

The changes of ECG indicators from baseline will be descriptively described. The normal and abnormal changes before and after treatment will be described by the cross-classification table, and a data list will be provided

Vital signs, physical examination and other safety-related examinations

The results of vital signs examination and changes from baseline will be summarized descriptively.

Subjects with abnormal changes from baseline in physical examination will be summarized by tabulation.

8.4.7 Immunogenicity Measures

Positive rates of ADA and neutralizing antibody will be calculated, and antibody level of positive subjects will be tabulated.

8.4.8 Compliance Analysis

The following will be summarized: the percentage and number of subjects with a violation of the intended dosing regimen

Percentage of subjects who have used the study drug at 80% - 120% of the dose specified in the protocol

Percentage of subjects having completed the study, and percentage of subjects having completed different treatment cycles.

8.4.9 Baseline Characteristics of Subjects

Descriptive statistics of subject demographics (gender, age); Information on diagnosis and treatment of tumor (pathological diagnosis, clinical stage, previous treatment);

Baseline tumor testing (number, site and total long diameter of target lesions and non-target lesions); Other baseline information: height, body weight (body mass index, body surface area), vital signs, laboratory tests, previous/ongoing/new concomitant medications.

8.4.10 Interim Analysis

This study is a phase II clinical study. Due to limited sample and potential delayed overall survival benefit of anti-tumor immunity, no interim analysis is planned in this study.

8.4.11 Subgroup Analysis

Efficacy analysis in PD-L1 positive subjects;

Subgroup analyses based on randomization stratification factors (e.g. PS score);

Subgroup analyses based on subjects' baseline characteristics, different chemotherapeutic drugs (paclitaxel or irinotecan), previous treatment (drug, best response), and other factors of potential clinical significance.

8.4.12 Multiple Comparison and Multiplicity Adjustment

Formal statistical test will be performed only for primary efficacy endpoint in this study. Multiple comparison is not applicable.

8.4.13 Data Listing of Valid Subjects

In addition to subject data listing, tumor evaluation (date of evaluation, lesion condition, evaluation result) and efficacy parameters of CR and PR subjects will be listed separately.

PFS and OS data of all subjects by the end of study (date of disease progression, date of death, PFS, OS)

8.4.14 Exploratory Analysis

Relationship between PD-L1 expression level and efficacy;

Clinical benefit evaluation based on iRECIST in IBI308 group, including iPFS, iORR, iDCR and iDoR (see Section 8.4.3 for analysis methods);

Relationship between biomarker levels and efficacy parameters.

8.5 Sample Size Determination

Since this study is a phase II clinical study with overall survival (OS) as the primary endpoint, assuming a two-sided α level of 0.2, power of 80% and a hazard ratio (HR) of 0.7 for the IBI308 group compared with the chemotherapy group, a number of 142 subjects with OS events is required. Further, presuming 21% of the patients are censored, an estimated number of about 180 subjects should be enrolled, with about 90 subjects in the IBI308 and chemotherapy groups each, respectively (35 study sites, with 0.7 subjects enrolled per month, the expected duration of this study is 27 months). Considering a possible delay of OS benefit with the anti-tumor therapy and based on an estimated median OS of approximately 8.7 months for IBI308, it should be ensured that the subjects have been followed up for about 10 months (from randomization) by the time of OS analysis.

8.6 Measures for Bias Control

8.6.1 Randomization and Blinding

In this study, the subjects will be randomized by an interactive web response system (IWRS), and the randomization stratification factor is ECOG PS score (0 or 1). The investigator or qualified designee will enter the interactive web response system with their own passwords, assign each subject a unique randomization number, and obtain the subject's corresponding study drug group from the IWRS: IBI308 group or chemotherapy group. If randomized into IBI308 group, the subject will receive IBI308 treatment. If the subject is randomized into chemotherapy group, the investigator should determine if paclitaxel or irinotecan will be used based on the subject's previous anti-tumor therapy. The independent statistician responsible for randomization will use block randomization method to generate a randomization table (subject randomization number) at 1:1 (IBI308:chemotherapy) ratio. Subject randomization numbers will be submitted to the randomization system as an electronic document.

This study is an open-label study without blinding of study drug.

8.6.2 Evaluation of Blinding Maintenance

Drugs will not be blinded in this study.

8.6.3 Unblinding and Emergency Unblinding

N/A.

9 Quality Assurance and Quality Control

Pursuant to GCP guidelines, the sponsor has the responsibility to implement and maintain the quality assurance and quality control systems for this study according to corresponding standard operating procedures (SOPs) to ensure that the implementation of the clinical trial, data authenticity, and the collection, recording and reporting of data comply with the protocol, GCP and corresponding regulatory requirements.

9.1 Clinical Monitoring

The sponsor or the sponsor-authorized CRO will conduct clinical monitoring of the study. The clinical research associate (CRA) should conduct monitoring according to the standard operating procedures of the sponsor or CRO, and have the same rights and responsibilities as the sponsor's monitor. The monitor (CRA) should hold regular communications with the investigator, the authorized study personnel and the sponsor.

Prior to the initiation of the study, the CRA will assess the competence of each study site and report problems regarding facilities, technical equipment, and/or medical personnel to the sponsor. During the study, the CRA will be responsible for monitoring whether the investigator has obtained the signed written ICFs from all subjects and whether the data records are correct and complete. Meanwhile, the CRA will also check the data entries in the eCRF against the source data and inform the investigator of any errors or omissions. The CRA will also control the site’s compliance with the protocol and study procedures, arrange for supplies of the study medications, and ensure that the drugs are stored under the specified conditions.

Monitoring visits will be conducted in accordance with applicable laws and regulations. Each site will receive regular monitoring visits from the start of subject enrollment. After each visit to the investigator, the CRA should submit a written report to the sponsor.

9.2 Data Management/Coding

An electronic data capture (EDC) system will be used for this study and study data will be entered into the eCRF by the investigator or the authorized study personnel. Prior to site initiation or data entry, appropriate training will be provided to the investigator and the authorized study personnel, and appropriate security measures will be taken for computers and other equipment used in the study.

Data entry into the eCRF should be completed during or as soon as possible after a visit

and updated promptly to ensure that it reflects the latest status of the subjects participating in the study. To avoid differences in the assessment of the results by different assessors, it is recommended that the baseline and all subsequent efficacy and safety assessments be completed by the same person. The investigator must review the data to ensure the accuracy and correctness of all data entered into the eCRF. If some assessments are not performed or some information is unavailable, inapplicable, or unknown during the study, the investigator should record it in the eCRF. The investigator should electronically sign the verified data.

The CRA will review the eCRFs and assess their completeness and consistency. In addition, the CRA will check the eCRFs against the source documents to ensure the consistency of key data. The entry, correction and modification of all data will be in the charge of the investigator or his/her designee. The data in the eCRF will be submitted to the data server, and any changes to the data will be recorded in the audit trail, i.e. the reason for the change, the name of the operator, the time and date of the change will all be recorded. The roles and authorities of the site staff responsible for data entry will be determined in advance. In case of any data query, the CRA or the data manager will send a query in the EDC system and the site staff is responsible for answering the query. The EDC system will document the audit trails of the queries, including the investigator’s name, time and date.

Unless otherwise specified, the eCRF will be used only as a form for collecting data rather than as source materials. Source documents refer to all records that are used by the investigator or hospital and related to the subjects and can prove the subjects’ existence and their eligibility per the inclusion and exclusion criteria as well as participation in this study, including laboratory records, ECG results, pharmacy dispensing records, subject folder, etc.

The investigator is responsible for maintaining all source documents and providing them to the CRA for monitoring at each visit. In addition, the investigator must submit a complete eCRF for each enrolled subject, regardless of the duration of their study participation. The protocol number and subject number on all supporting documents (e.g., laboratory records or hospital records) submitted together with the eCRF should be carefully verified, and all personal privacy information (including the subject's name) in these documents should be deleted or made illegible to protect the subject's privacy. The investigator uses electronic signature to testify that he or she has reviewed the record, and guarantees the accuracy of the data recorded. The electronic signature will

be completed through the investigator's user ID and password, and the data and time of signature will be generated by the system automatically. The investigator shall not share his/her user ID and password with other personnel. Any changes to the data in the eCRF, if necessarily required, should be made according to the work procedures as defined in the EDC system. All changes and the reasons for such changes will be documented on the audit trails.

Adverse events and accompanying diseases/medical history will be coded. The dictionary used for coding will be described in the Clinical Study Report (CSR).

9.3 Quality Assurance Audit

During the process of the study, the sponsor or its authorized representative may perform quality assurance audits of the study site, the study database and related study documents. Moreover, the appropriate regulatory authorities may conduct inspections of the study site, the study database and related study documents at their discretion. The investigator should notify the sponsor immediately upon receipt of an inspection notification from the regulatory authority.

The sponsor's quality assurance department will audit the clinical trial institution. Audits include the supply of drugs, trial documents required, documentation of the informed consent process, and consistency of case report forms with source documents. The content and scope of the audits may also be increased as appropriate. After reasonable notice, the investigator should allow the auditors entrusted by the sponsor to conduct trial-related audits and regulatory authorities to conduct inspections. The main purpose of the audit or inspection is to confirm that the rights or health of the subjects participating in the trial are protected, the informed consent is signed and the trial is carried out correctly, all data related to the evaluation of the study drug are handled and reported in accordance with the pre-planned arrangements, the protocol, facilities, ethical standard operating procedures, GCP and applicable regulatory requirements. The investigator should allow them to directly access all trial documents, source records and source data.

10 Ethics

10.1 Ethics Committee

The sponsor or the sponsor's authorized representative will prepare relevant documents to be submitted to the study site's Ethics Committee (EC), including study protocol,

informed consent form, investigator's brochure, subject recruitment materials or advertising and other legally required documents which should be submitted to the corresponding EC for review and approval. Written approval of the site EC must be obtained and provided to the sponsor prior to initiation of the study. The EC's approval letter must clearly indicate the study protocol title, number, version number and other documents' version number (e.g., ICF) and approval date. The investigator should inform the sponsor of the EC's written opinion on delay, suspension or re-approval.

The site must observe the requirements of the site's EC, which may include submission of protocol modifications, modifications to the ICF and modifications to subject recruitment materials to the EC for review and approval, local safety reporting requirements, periodical reporting and updates according to the EC provisions, and submission of final report. All the above documents and EC approval letters must be provided to the sponsor or its designee.

10.2 Ethics of the Study

The study process and acquisition of informed consent should follow the Declaration of Helsinki, relevant GCP requirements and Chinese laws and regulations on drugs and data protection.

The GCP provides a scientific global quality standard in line with ethical requirements for the design, implementation, recording and reporting of clinical studies involving the participation of human subjects. This study will be conducted in accordance with the GCP and relevant national regulations, and follow relevant ethical principles in the Declaration of Helsinki so as to protect the rights, safety and health of subjects.

The investigator should follow the trial protocol's stipulated process, and may not change it without the sponsor's permission. Any protocol deviation will be reported to the EC, the sponsor or regulatory agencies.

10.3 Subject Information and Informed Consent

Prior to initiation of any study procedures, the possible risks and benefits of this study will be explained to subjects who may participate in the study using the informed consent form (ICF), which should be written in plain language. The ICF statement should clarify that signing the ICF is voluntary, explain the possible risks and benefits associated with participation in this study, and that the subjects are free to withdraw from the study at any time. The investigator may enroll a subject only after the investigator has fully explained the details of the study, the subject's questions have

been answered satisfactorily, the subject has been given adequate time to think over, and written consent has been obtained from the subject or his/her legal representative. All signed ICFs must be kept in the investigator file or subject folder.

The investigator is responsible for explaining the contents of the informed consent to the subjects and obtaining the signed and dated ICFs from the subjects or their legal representatives prior to initiation of the study. The investigator should provide each subject with a copy of the signed ICF. The investigator should record the informed consent process in the original trial documents.

10.4 Protection of Subject Data

The ICF will contain (or in some cases, together with the use of separate documents) information on data protection and privacy protection.

Additional preventive measures should be taken to ensure the confidentiality of the documents and prevent the identification of subjects. However, under special circumstances, the genetic data and personal identification code of a certain subject may be accessed by some personnel. For example, in the event of a medical emergency, the sponsor, its representative physician or the investigator will be aware of the subject's identification code and have access to the genetic data of the subject. In addition, relevant regulatory authorities require access to relevant documents.

11 Study Management

11.1 Data Processing and Record Preservation

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

Study documents should be reasonably preserved for future access or data tracing. Security and environmental risks should be taken into account for document preservation.

Without the sponsor's and the investigator's written approval, no study documents may be destroyed. Only after the sponsor is notified and its written consent is obtained can the investigator/study site hand over the study documents to other parties following the document preservation requirements or transfer them to other locations meeting the requirements for preservation.

11.2 Access to Source Data/Documents

The investigator agrees that the sponsor, CRO and relevant authorized regulatory authorities may directly access all study-related documents, including the subjects' medical records.

11.3 Protocol Modification

In the course of the study, any possible appropriate modifications made to the protocol shall be communicated and approved by the sponsor and the investigator. The sponsor should ensure timely submission of protocol modifications to the administrative authorities.

All modifications to the protocol should be preserved as protocol addenda. Any modification to the protocol should be submitted to the Ethics Committee, and approved or filed according to the Ethics Committee's provisions. If necessary, the modification should also be submitted to the regulatory authorities for review and approval, and can be implemented only after approval by the EC and regulatory authorities (if needed) (except for changes to the protocol in order to eliminate direct harms to the trial subjects).

11.4 Investigator's Responsibilities

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

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

11.5 Publication Policy

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

All information related to this trial (not merely limited to the following documents: protocol, investigator's brochure) must be kept strictly confidential. The investigator must aware that the scientific or medical information derived from the trial may be of commercial value for the sponsor. The investigator should keep information and data related to this trial confidential. If information related to this trial or conclusion obtained

from the trial is to be published to the public, it is required to negotiate with the sponsor in advance and obtain the sponsor's written consent. In order to protect its own rights and interests, the sponsor may require the investigator not to publish any trial-related information until the investigational product is approved for marketing.

The sponsor has the right to publish or publicate information or data related to this trial, or submit the information or data to the drug administrative authorities. If the sponsor needs to include the investigator's name in the published, publicated or advertised content, consent from the investigator should be obtained.

11.6 Finance and Insurance

The sponsor will purchase insurance for subjects participating in the study according to local regulations and the minimum requirements. Relevant insurance clauses will be preserved in the study folder.

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13 Appendix

Appendix 1: Investigator Signature Page

Protocol Title: A Randomized, Open-label, Multi-center, Phase II Study to Evaluate the Efficacy and Safety of IBI308 versus Paclitaxel or Irinotecan in Patients with Advanced/Metastatic Esophageal Squamous Cell Carcinoma After Failure of First-line Treatment(ORIENT-2)

Protocol Number: CIBI308A201

This protocol is a trade secret of Innovent Biologics (Suzhou) Co., Ltd. I have read and fully understand this protocol and will conduct this study in accordance with its requirements and Good Clinical Practice, and in accordance with applicable laws, regulations and the Declaration of Helsinki. At the same time, I promise not to give any confidential information about this study to any third party without written consent from Innovent Biologics (Suzhou) Co., Ltd.

Guidance for the Investigator: Please sign and date this signature page, print the Investigator's name, title, and name of site conducting the study and return to Innovent Biologics (Suzhou) Co., Ltd. after signing.

I have read all the contents of this study protocol and guarantee to conduct this study as required:

Investigator's Signature: _ Date: _

Print Name: _____

Investigator Title: _____

Site Name/Address: _____

Appendix 2: ECOG PS Scoring Criteria

Score	Activity level
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all 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	Dead

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

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

1. Measurability of Tumor at Baseline

1.1 Definitions

At 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 1** 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 2** 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 3**.

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 1** to **Table 3**.

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

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

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

Target Lesions	Non-Target Lesions	New Lesions	Overall Response
CR	CR	No	CR
CR	Non-Cr/Non-PD	No	PR
CR	Not evaluated	No	PR
PR	Non-PD or not all evaluated	No	PR
SD	Non-PD or not all evaluated	No	SD
Not all evaluated	Non-PD	No	NE
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD
CR = complete response	PR = partial response	SD = stable disease	PD = progressive disease NE = inevaluable

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

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

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

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

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

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

Overall response first time point	Overall response subsequent time point	Best overall response
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.

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

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

3. IRECTIST Efficacy Assessment

Overall response will also be assessed using iRECIST. Immunotherapeutics may result in infiltration of immune cells leading to transient increase in the size in malignant lesions, or undetectable lesions becoming detectable. The criteria are identical to those of RECIST 1.1 in many respects but have been adapted to account for instances where an increase in tumor burden, or the appearance of new lesions, does not reflect true tumor progression.

Key differences are described below. All responses defined using iRECIST criteria are designated with a prefix. iRECIST time-point and best overall responses will be recorded separately.

3.1 Confirmed Progression

Unlike RECIST 1.1, iRECIST requires the confirmation of progression and uses the terms iUPD (unconfirmed progression) and iCPD (confirmed progression). Confirmatory scans should be performed at least 4 weeks, but no longer than 8 weeks after iUPD.

iCPD is confirmed if further increase in tumour burden, compared to the last assessment, is seen as evidenced by one or more of the following:

- Continued increase in tumour burden (from iUPD) where RECIST 1.1 definitions of progression had been met (from nadir) in target, non-target disease or new lesions
  - Progression in target disease worsens with an increase of at least 5 mm in the absolute value of the sum
  - Continued unequivocal progression in non-target disease with an increase in tumour burden
  - Increase in size of previously identified new lesion (s) (an increase of at least 5 mm in the absolute value of the sum of those considered to be target new lesions) or additional new lesions.
- RECIST 1.1 criteria are met in lesions types (target or non-target or new lesions) where progression was not previously identified, including the appearance of additional new lesions.

If iUPD is not confirmed at the next assessment, then the appropriate response will be assigned (iUPD if the criteria are still met, but no worsening, or iSD, iPR or iCR if those criteria are met compared to baseline). As can be seen in table 2, the prior documentation of iUPD does not preclude assigning iCR, iPR, or iSD in subsequent time-point assessments or as best overall response (BOR) providing that iCPD is not documented at the next assessment after iUPD.

3.2 New lesions

New lesions should be assessed and measured as they appear using RECIST 1.1 criteria (maximum of 5 lesions, no more than 2 per site, at least 10 mm in long axis (or 15 mm in short axis for nodal lesions), and recorded as New Lesions-Target (NLT) and New Lesion-Non-Target (NLNT) to allow clear differentiation from baseline target and non-target lesions.

New lesions may either meet the criteria of NLT or NLNT to drive iUPD (or iCPD). However, the measurements of target lesions should NOT be included in the sum of measures of original target lesions identified at baseline. Rather, these measurements will be collected on a separate table in the case record form.

PD is confirmed in the New Lesion category if the next imaging assessment, conducted at least 4 weeks (but not more than 8 weeks) after iUPD confirms further progression from iUPD with either an increase of at least 5 mm in the absolute value of the sum of NLT OR an increase (but not necessarily unequivocal increase) in the size of NLNT lesions OR the appearance of additional new lesions

All patients will have their iBOR from the start of study treatment until the end of treatment classified as outlined Table 3.

4. Time to Response and Stable Disease (RECIST 1.1 and iRECIST)

Time to response will be calculated from the time when the criteria for CR/PR or iCR/iPR are met (whichever occurs first) until relapse or disease progression, while minimum measurements (including baseline) during the study will also be recorded as reference.

Time to stable disease will be calculated from the start of treatment until disease progression, and the minimum measurement during the study (including baseline) will also be recorded as the reference.

Table 1. RECIST 1.1 and iRECIST

	RECIST 1.1	IRECIST

Definition of measurable and non-measurable lesions; number and location of target lesions	Measurable lesions ⩾ 10 mm in long diameter (15 mm for nodal lesions); up to 5 lesions (2 per organ); non-target lesions (⩾ 10 mm short axis for nodal lesions)	No change; however, new lesions will be recorded separately on the case report form according to RECIST 1.1 criteria (will not be included in the sum of target lesion measurements at baseline)
CR, PR, or SD	PD cannot be documented until CR, PR, or SD	IUPD (one or more) but no iCPD before iCR, iPR or iSD
Confirmed CR, PR	Required for non-randomized trials only	Same as RECIST 1.1
Confirm SD	Not necessary	Same as RECIST 1.1
New lesions	Will be assessed as PD but no measurements required	IUPD will be assessed, and iCPD will be recorded when the following conditions are met at the next assessment ● Appearance of other new lesions or ● Increase in size of new lesions (increase in sum of new target lesion measurements by ⩾ 5 mm or increase in any new non-target lesion) ICPD can also be confirmed by new lesions that have never been previously recorded
Independent Blind Review and Central Image Acquisition	Recommended in some cases	Image collection is recommended for all studies (but not for independent review)
Confirmed PD	Non-essential (unless ambiguous)	Required
Consider patient clinical status	Not considered in assessment	Continued use after iUPD should take into account whether the patient is clinically stable (see definitions)

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

Table 2: iRECIST Response Record by Assessment Point

This efficacy evaluation				
Target Lesions *	Non-target lesions *	New lesions *	Efficacy Assessment Results	
			No prior	Previous iUPD*, *

			iUPD*	
ICR	ICR	No	ICR	ICR
ICR	Non-iCR/Non-iUPD	No	IPR	IPR
IPR	Non-iCR/Non-iUPD	No	IPR	IPR
ISD	Non-iCR/Non-iUPD	No	ISD	ISD
IUPD unchanged or reduced from last assessment	IUPD unchanged or reduced from last assessment	YES	NA	ICPD was confirmed if new lesions had been previously identified and increased in size (increase in SOM of new target lesions by ⩾ 5 mm or increase in new non-target lesions). If new lesions remain unchanged (volume or number) from last assessment, they remain iUPD
ISD, iPR, iCR	IUPD	No	IUPD	An increase in the size of non-target lesions (unequivocal PD per RECIST 1.1 is not required) confirms iCPD, otherwise they remain iUPD
IUPD	Non-iCR/Non-iUPD; iCR	No	IUPD	ICPD shall be confirmed if: ● Increase in SOM of ⩾ 5 mm in target lesions, other cases remain iUPD
IUPD	IUPD	No	IUPD	ICPD shall be confirmed if: ● Previously noted increase in target lesion SOM of ⩾ 5 mm in iUPD and/or ● Increase in non-target lesions for iUPD (previous assessment - unequivocal PD was not required)
IUPD	IUPD	YES	IUPD	ICPD shall be confirmed if: ● Previously noted increase in target lesion SOM of ⩾ 5 mm in iUPD and/or ● Increase in non-target lesions for iUPD (where unequivocal PD is not required) and/or ● Increase in volume or number of previously identified new lesions
Non-iUPD/PD	Non-iUPD/PD	YES	IUPD	ICPD shall be confirmed if: ● Increase in volume or number of previously identified new lesions

* Refer to RECIST 1.1 principles. In the absence of pseudoprogression, CR, PR, and SD are defined consistently by RECIST 1.1 and iRECIST. * for any type of lesion. * Found at the last assessment prior to this assessment.

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

Table 3. Best overall response according to iRECIST criteria

Best overall response					
1st Assessment	2nd Assessment	3rd Assessment	4th Assessment	5th Assessment	Optimal overall immune response
ICR	ICR, iPR, iUPD, NE	ICR, iPR, iUPD, NE	IUPD	ICPD	ICR
IUPD	IPR, iSD, NE	ICR	ICR, iUPD, NE	ICR, iPR, iSD, iUPD, iCPD, NE	ICR
IUPD	IPR	IPR, iSD, iUPD, NE	IPR, iSD, iUPD, NE, iCPD	IPR, iSD, iUPD, NE, iCPD	IPR
IUPD	ISD, NE	IPR	IPR, iSD, iUPD, NE	IPR, iSD, iUPD, iCPD, NE	IPR
IUPD	ISD	ISD, iUPD, NE	ISD, iUPD, iCPD, NE	ISD, iUPD, iCPD, NE	ISD
IUPD	ICPD	Any	Any	Any	ICPD
IUPD	IUPD (without iCPD)	ICPD	Any	Any	ICPD
IUPD	NE	NE	NE	NE	IUPD
● For example only - more cases may exist but follow the same principles ● This table assumes a randomized study design and does not require confirmation of CR or PR ● For patients with only non-target lesions at baseline, the evaluation at each time point was only recorded as iCR or non-CR/non-PD, but was not reflected in the table for ease of presentation					

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

Appendix 5: Liver Function Abnormality Monitoring and Follow-up Report Form

Please report to Innovent PV:

Fax: 021-31652800 Email: drugsafety@innoventbio.com

Contact information of reporter (Please be sure to provide in case of timely receipt):

Reporter Email: Reporter Contact Number:

Signature of reporter: Date of Report:

Information on follow-up reports of liver function abnormalities:

Trial No.: Subject Number:

1. Symptoms of liver function abnormalities such as (check if present):

Appetite loss □, greasiness □, dyspepsia □, nausea □, vomiting □, abdominal distension □, abdominal pain □, diarrhea □, constipation □, clay stools □, fatigue □, weakness □, somnolence □, weight loss □, fluttering tremor □, altered mental status □, bleeding tendency □, fever □, other □

2. Signs of liver function abnormalities such as (tick if present):

Liver disease □, spider nevus □, liver palms □, ascites □, abdominal wall subcutaneous varicose veins □, jaundice □, body fluid yellowing □, hepatomegaly □, splenomegaly □, liver tenderness □, hepatic encephalopathy □, dyspnea □, lung rales □, peripheral edema □, cervical varicose veins □, abnormal heart sounds □, others □

3. Medical history (check if available):

Viral hepatitis (HBV-A □; HBV-B □; HBV-C □; HBV-D □; HBV-E □), alcoholic hepatitis □, fatty liver □, liver cancer □, liver metastasis □, liver cirrhosis □, liver transplantation □, blood transfusion □, liver enzyme elevation before the study medication □, autoimmune disease □, biliary disease □, cardiovascular disease □, hypotension □, diabetes □, surgery □, bone metastasis or bone injury □, HIV infection □, E-B virus infection □, drug toxicity □, obesity □, others □

4. Family history of liver disease (check if available) □

5. Concomitant medications and diet (check if yes):

Chemotherapy □, Chinese herbal medicine □, OTC □, dietary supplement □, drinking □, drug abuse □, history of exposure to chemicals □, anti-infective drugs □, paracetamol □, NSAIDS □, metronidazole □, others □

6. All relevant laboratory test results (including baseline period, treatment period and post-treatment period. If the test was performed, please check and provide the test results, unit and normal value):

Hematology test □,

Acid cell count □,

AST □, ALT □, ALP □, GGT □,

Total bilirubin □/Direct bilirubin □,

Serum total protein □/albumin □/globulin □,

Total Cholesterol □/Cholesteryl Ester □,

Coagulation function □, such as:

Others □, such as:

7. Serological tests (check and provide test results if performed):

Epstein-Barr virus (EBV) □,

Cytomegalovirus (CMV) □,

Herpes simplex virus (HSV) □,

Toxoplasmosis □,

Hepatitis (A □, B □, C □, D □, E □),

HIV □,

Antinuclear antibody □,

Other antibodies □, such as:

Others □, such as:

8. Ancillary tests or procedures (check and provide results if performed):

Liver ultrasound □,

Abdominal CT □,

Liver biopsy □,

Liver transplant (planned or completed) □,

Others □, such as:

Appendix 6: List of Autoimmune Diseases Present Before Inclusion

Subjects were asked in detail whether they had acquired or congenital immunodeficiency or autoimmune diseases, such subjects had to be excluded from this study. The likelihood of autoimmune disease is very low unless the subject has a previous history of allergic disease and childhood joint pain. In addition, transient autoimmune manifestations due to acute infectious disease (e.g., Lyme arthritis) may be included if cured with antibiotics. In case of uncertain autoimmune diseases requiring exclusion, please contact the medical manager of the sponsor.

Diseases associated with autoimmunity, including but not limited to:

Acute sporadic encephalomyelitis	Autoimmune myocarditis	Reiter's syndrome
IgA nephropathy	Neuromyotonia	Type I diabetes mellitus
Addison's disease	Autoimmune oophoritis	Rheumatoid arthritis
Inflammatory bowel disease	Myoclonic syndrome	Autonomic Dysfunction
Alopecia universalis	Autoimmune orchitis	Sarcoidosis
Interstitial cystitis	Optic neuritis	Eczema
Ankylosing spondylitis	Autoimmune	Scleroderma
Myasthenia gravis syndrome	thrombocytopenic purpura	Sjogren's syndrome
Antiphospholipid antibody	Ord's thyroiditis	Bullous skin lysis
syndrome	Behcet's disease	Catalepsy syndrome
Lupus erythematosus	Pemphigus	Pemphigoid in pregnancy
Aplastic anemia	Bullous pemphigoid	Takayasu arteritis
Lyme disease - chronic	Pernicious anemia	Giant cell arteritis
Asthma	Bran allergy	Ulcerative colitis
Meniere's syndrome	Polyarteritis	Pulmonary haemorrhage-
Autoimmune hemolytic	Chronic fatigue syndrome	nephritis syndrome
Anaemia	Polyarthritis	Vitiligo
Corneal ulcer	Chronic Inflammation	Graves' disease
Autoimmune hepatitis	Demyelination	Vogt-Kovanagi-Harada
Localized autoimmune	Polyneuropathy	disease
hypophysitis	Autoimmune syndrome	Guillain-Barre syndrome
Multiple sclerosis	Bell-Strauss syndrome	Vulvar pain
Autoimmune hypoparathyroidism	Primary biliary cirrhosis	Hashimoto's disease
Myasthenia gravis	Crohn's disease	Wegener's granulomatosis
	Psoriatic dermatomyositis	Kawasaki disease

Appendix 7: IBI308 Dose Modification and Toxicity Management Guidelines

Table 1. Dose Modification and Toxicity Management Guidelines for Potential Primary irAEs

	AE Grade/Administration Adjustments		**Toxicity Management**
General Principles	AEs are graded according to NCI CTCAE v4.03. Refer to this guideline if the event is an irAE		It is recommended to manage irAEs according to the guideline in this table. - Subjects shall be fully evaluated to rule out any alternative causes (e.g. PD, concomitant medication, infection, etc.) - The event is an irAE if there are no clear alternative causes and treatment with corticosteroids is required - Consider symptomatic and local treatment for low grade events (grade 1 or 2, unless otherwise stated) - Consider systemic glucocorticoid therapy for persistent low grade events (grades 1–2) or severe events (grade ≥ 3) - If the event re-occurs or worsens during tapering of glucocorticoids, the glucocorticoid dose shall be increased until symptoms resolve or
	Grade 1	No dose adjustments required	
	Grade 2	Interrupt • If worsens, treat as a grade 3/4 event • If reduces to grades 0–1 or baseline, continue the treatment at the next scheduled date	
	Grade 3	Interrupt or permanently discontinue	

	AE Grade/Administration Adjustments		**Toxicity Management**
	Grade 4	Permanently discontinue	improve, then taper with a lower rate – Once persistent clinical improvement is observed, subjects receiving glucocorticoids IV can start tapering the dose or switch to an equivalent dose of glucocorticoid PO at an earlier time (a lower bioavailability of oral administration should be considered) – For events that unresponsive to glucocorticoid treatment, consider a stronger immunosuppressants, e.g. TNF blockers (e.g. infliximab) or mycophenolate mofetil, after discussing with the physicians – For grade 3/4 local inflammation of lesions (such as local pain, irritation, and rash), IBI308 may be continued as determined by the investigator

	AE Grade/Administration Adjustments		**Toxicity Management**
Pneumonitis	Any grade		– Monitor signs and symptoms of pneumonitis or interstitial lung disease (e.g. new shortness of breath, cough, chest pain or exacerbation of existing symptoms and signs), evaluate subjects by imaging, pulmonary function, and other examinations – Initial examination may include clinical evaluation, arterial oxygen saturation, laboratory tests, and high-resolution CT scans
	Grade 1	No dose adjustments required However, consider interrupting the treatment based on clinical needs and during diagnostic tests for other causes	For grade 1 events: – Monitor signs and symptoms and arterial oxygen saturation for 2–4 days – Perform other laboratory tests if clinically indicated – Consider consulting a respirologist and infectious diseases specialist

	AE Grade/Administration Adjustments		**Toxicity Management**
	Grade 2	Interrupt • If worsens, treat as a grade 3/4 event • If reduces to grades 0–1 or baseline, continue the treatment at the next scheduled date	For grade 2 events: – Monitor signs and symptoms daily, consider hospitalization – Discuss with sponsor's medical manager, consider systemic glucocorticoid treatment – Repeat imaging if clinically indicated – If no improvement is seen within 3–5 days, consider other tests and increasing the glucocorticoid dose – If no improvement is seen within 3–5 days, consider a stronger immunosuppressant (e.g. infliximab) – Once improved, taper glucocorticoids within 4 weeks, and consider prophylactic antibiotic – Consider consulting a respirologist and infectious diseases specialist

	AE Grade/Administration Adjustments		**Toxicity Management**
	Grade 3 or grade 4	Permanently discontinue	For grade 3–4 events: - Discuss with sponsor's medical manager - Consider consulting a respirologist and infectious diseases specialist - Hospitalization - Supportive care (oxygen) - Begin systemic glucocorticoid treatment based on experience - If no improvement is seen within 3–5 days, consider other tests and stronger immunosuppressants (e.g. infliximab) - Once improved, taper glucocorticoids within 4 weeks, and consider prophylactic antibiotic

	AE Grade/Administration Adjustments		**Toxicity Management**
Diarrhea or Enterocolitis	Any grade		- Monitor possible signs and symptoms related to diarrhea/enterocolitis (abdominal pain, enterospasm, changes in bowel habits, melena, mucous stool, bloody stool, or muscle guarding) - Subjects shall be fully evaluated to rule out any alternative causes (e.g. PD, infection, etc.) - If alternative causes cannot be determined, consider glucocorticoid treatment for low grade events to prevent from escalating to high grade - Use analgesics with caution (may mask the symptoms of perforation and peritonitis)
	Grade 1	No dose adjustments required	For grade 1 events: - Closely monitor symptom exacerbation - Consider symptomatic treatment, including fluid replacement, electrolyte replacement, diet modifications, and loperamide administration

	AE Grade/Administration Adjustments		**Toxicity Management**
	Grade 2 or Grade 3	Interrupt • If worsens, treat as a grade 3/4 event • If reduces to grades 0–1 or baseline, continue the treatment at the next scheduled date	For grade 2–3 events: – Consider symptomatic treatment, including fluid replacement, electrolyte replacement, diet modifications, and loperamide and/or budesonide administration – If the event persists for > 3–5 days or worsens, consider systemic corticosteroid treatment – If no improvement is seen within 3–5 days, consider other tests and increasing the glucocorticoid dose – If no improvement is seen or exacerbation occurs within 3–5 days, consider other tests and stronger immunosuppressants (e.g. infliximab) – If not reduces to grade 0–1 within 3–4 days, discuss with sponsor's medical manager – Once improved, taper glucocorticoids within 4 weeks, and consider prophylactic antibiotic

	AE Grade/Administration Adjustments		**Toxicity Management**
	Grade 4	Permanently discontinue	For grade 4 events: - Monitor frequency and volume of bowel movement, maintain hydration - If applicable, perform emergency GI consultation and lower GI endoscopy and imaging to confirm the presence of intestinal perforation - Begin systemic glucocorticoid treatment based on experience - If no improvement is seen within 3–5 days, consider increasing the glucocorticoid dose - If no improvement is seen within 3–5 days, consider other immunosuppressants (e.g. infliximab, but not in subjects with perforations or sepsis) - Once improved, taper glucocorticoids within 4 weeks, and consider prophylactic antibiotic

	AE Grade/Administration Adjustments		**Toxicity Management**
Hepatitis (ALT, AST, or TBIL increased)	Any grade		– Monitor hepatitis-related signs and symptoms (e.g. jaundice, tea-colored urine, nausea, emesis, loss of appetite, hepatalgia, hemorrhagic tendency, etc.) – Monitor and evaluate hepatic function – Evaluate alternative causes (e.g. viral hepatitis, PD, concomitant medication) – The dose adjustments and toxicity management in this table is applicable only to subjects with normal ALT, AST, and TB at baseline; for subjects with ALT, AST, or TB > ULN at baseline, interrupt the drug if ALT, AST, or TB elevation of ≥ 50% for < 7 days and discontinue permanently if ALT, AST, or TB elevation of ≥ 50% for ≥ 7 days. Toxicities should be managed based on the investigator's clinical judgment.
	Grade 1	No dose adjustments required	For grade 1 events: – Continue monitoring hepatic function according to protocol

	AE Grade/Administration Adjustments		**Toxicity Management**
	Grade 2	Interrupt • If worsens, treat as a grade 3/4 event • If reduces to grades 0–1 or baseline, continue the treatment at the next scheduled date	For grade 2 events: – If not reduces to grade 0–1 within 3–4 days, discuss with sponsor's medical manager – For ALT, AST, or TBIL elevations, retest hepatic function within 3–4 days and increase monitoring frequency – If the event persists for > 3–5 days or worsens, consider systemic corticosteroid treatment – If no improvement is seen within 3–5 days, consider other tests and increasing the glucocorticoid dose – If no improvement is seen within 3–5 days, consider stronger immunosuppressants (e.g. mycophenolate mofetil) – Once improved, taper steroids within 4 weeks, and consider prophylactic antibiotic

	AE Grade/Administration Adjustments		Toxicity Management
	Grade 3 or grade 4	Permanently discontinue	For grade 3–4 events: - Discuss with sponsor's medical manager - Begin systemic glucocorticoid treatment based on experience - If no improvement is seen within 3–5 days, consider stronger immunosuppressants (e.g. mycophenolate mofetil) - If no improvement is seen within 3–5 days, consider other immunosuppressants based on local guidelines - If applicable, consult a gastroenterologist, perform abdominal examination and imaging - Once improved, taper glucocorticoids within 4 weeks, and consider prophylactic antibiotic
Dermatitis	Any grade		- Monitor signs and symptoms or dermatitis, e.g. rash, exudation, hypopigmentation, photaesthesia, and pruritus - If there is formation of bullae, contact the sponsor's medical manager - Consult a dermatologist - Perform skin biopsy when necessary

	AE Grade/Administration Adjustments		**Toxicity Management**
	Grade 1	No dose adjustments required	For grade 1 events: – Consider symptomatic treatment, including oral antipruritic agents (e.g. diphenhydramine or hydroxyzine) and local treatment (e.g. urea cream or topical glucocorticoids)
	Grade 2	No dose adjustments required • For a refractory (> 1–2 weeks) grade 2 event, interrupt until reduces to grades 0–1 or baseline, continue the treatment at the next scheduled date	For grade 2 events: – Consider symptomatic treatment including oral antipruritic agents and local treatment – Consider a medium-potency topical glucocorticoid – If no improvement is seen with 3–5 days, discuss with sponsor's medical manager and consider systemic glucocorticoid treatment – Consult a dermatologist – Consider skin biopsy if persists for > 1–2 weeks or relapses – Once improved, taper glucocorticoids within 4 weeks, and consider prophylactic antibiotic

<table>
<tr><th></th><th colspan="2">AE Grade/Administration Adjustments</th><th>Toxicity Management</th></tr>
<tr><td rowspan="2"></td><td>Grade 3</td><td>Interrupt
• If worsens, treat as a grade 4 event
• Permanently discontinue if a grade 3 rash does not reduce to grades 0–1 or baseline within 30 days</td><td rowspan="2">For grade 3–4 events:
– Discuss with sponsor's medical manager
– Consider hospitalization
– Monitor affected area (rule of nine)
– Consult a dermatologist
– If clinically feasible, consider skin biopsy (preferably more than once)
– Begin systemic glucocorticoid treatment based on experience
– If no improvement is seen within 3–5 days, consider other tests and increasing the glucocorticoid dose
– Once improved, taper glucocorticoids within 4 weeks, and consider prophylactic antibiotic</td></tr>
<tr><td>Grade 4</td><td>Permanently discontinue</td></tr>
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Hypopituitarism	All grades		– Monitor signs and symptoms of endocrine disorders, including weakness, fatigue, drowsiness, nausea, emesis, chills, changes in bowel habits, behavioral changes, mental state changes, hypotension, hypoglycemia, dizziness, headache, impaired vision, low libido in males, irregular menstruation in females, etc. – Subjects shall be fully evaluated to rule out any alternative causes (e.g. PD, brain metastasis, infection, etc.) – Monitor and evaluate pituitary function: TSH, FT3, FT4, adrenocorticotropic hormone, cortisol, luteinizing hormone, follicle stimulating hormone, growth hormone, prolactin, Na^+, blood glucose, estradiol, testosterone, and other laboratory parameters related to endocrine disorders. Perform functional tests when necessary (including adrenocorticotropic hormone (ACTH) stimulation test and insulin-induced hypoglycemia test) – Consider pituitary MRI – Consider consulting an endocrinologist – Consider testing for autoantibodies

	AE Grade/Administration Adjustments		**Toxicity Management**
	Grade 1	No dose adjustments required	For grade 1 events: – Monitor pituitary function – Subjects shall be fully evaluated to rule out any alternative causes – Consider consulting an endocrinologist if clinically indicated
	Grade 2	Interrupt • If worsens to grades 3–4, permanently discontinue • If reduces to grades 0–1 or baseline, continue the treatment at the next scheduled date	For grade 2–4 events: – Discuss with sponsor's medical manager – Consult an endocrinologist – Hospitalization when necessary – Evaluate endocrine function, consider pituitary MRI if clinically indicated – Begin hormone replacement therapy when necessary (cortisone

	AE Grade/Administration Adjustments		**Toxicity Management**
	Grade 3 or grade 4	Permanently discontinue	replacement therapy shall begin one week prior to levothyroxine treatment) – Begin immunosuppressive therapy based on experience, consider systemic glucocorticoid treatment – Once improved, taper glucocorticoids within 4 weeks (the dose of cortisone used for hormone replacement may be adjusted accordingly, but subjects whose endocrine function do not recover require long-term treatment); consider prophylactic antibiotic during taper to prevent infections

	AE Grade/Administration Adjustments		**Toxicity Management**
Adrenocortical Insufficiency	Any grade		– Monitor signs and symptoms of endocrine disorders, including fatigue, pigmentation, loss of appetite, hypotension, and weakness – Subjects shall be fully evaluated to rule out any alternative causes – Monitor and evaluate adrenal function: cortisol, adrenocorticotropic hormone, blood sodium, blood potassium, blood glucose, and other endocrine laboratory parameters suspected to be related to adrenal function. The ACTH stimulation test shall be performed when necessary – Immunosuppressive therapy when necessary – Hormone replacement therapy (cortisone) when necessary – Consider consulting an endocrinologist – Consider testing for autoantibodies
	Grade 1	No dose adjustments required	For grade 1 events: – Monitor adrenal function – Consider consulting an endocrinologist if clinically indicated

	AE Grade/Administration Adjustments		**Toxicity Management**
	Grade 2	Interrupt • If worsens to grades 3–4, permanently discontinue • If reduces to grades 0–1 or baseline, continue the treatment at the next scheduled date	For grade 2 events: – Discuss with sponsor's medical manager – Evaluate adrenal function, begin hormone replacement therapy when necessary
	Grade 3 or		

	AE Grade/Administration Adjustments		**Toxicity Management**
	grade 4	Permanently discontinue	For grade 3–4 events: – Discuss with sponsor's medical manager – Consult an endocrinologist – Consider systemic corticosteroid treatment – Begin corticosteroids with mineralocorticoid activity immediately for adrenal crisis, severe dehydration, hypotension, or shock – Once improved, taper glucocorticoids within 4 weeks (the dose of cortisone used for hormone replacement may be adjusted accordingly, but subjects whose endocrine function do not recover require long-term treatment); consider prophylactic antibiotic during taper to prevent infections

	AE Grade/Administration Adjustments		**Toxicity Management**
Hyperthyroidism/Hypothyroidism	Any grade		- Monitor signs and symptoms of thyroid dysfunction, e.g. hyperthyroidism (palpitations, sweating, increased appetite and bowel movement, and weight loss) and hypothyroidism (general weakness, fatigue, cold, memory loss, and constipation) - Subjects shall be fully evaluated to rule out any alternative causes - Monitor and evaluate thyroid function - Consider consulting an endocrinologist - Consider testing for thyroid autoantibodies (antithyroglobulin antibodies, anti-thyroid peroxidase antibodies, and thyroid-stimulating hormone receptor antibodies)
	Grade 1 or grade 2	No dose adjustments required	For grade 1–2 events: - Monitor thyroid function and thyroid autoantibodies regularly - L-thyroxine replacement therapy or anti-thyroid medications when necessary

	AE Grade/Administration Adjustments		**Toxicity Management**
	Grade 3 or grade 4	Hyperthyroidism • Permanently discontinue Hypothyroidism • No dose adjustments • required	For grade 3–4 events: – Discuss with sponsor's medical manager – Monitor thyroid function and thyroid autoantibodies – Consult an endocrinologist *Hyperthyroidism* – Anti-thyroid medications – Consider β-blockers for tachycardia *Hypothyroidism* – L-thyroxine replacement therapy
Type I Diabetes	Any grade		– Monitor signs and symptoms closely, e.g. polyuria, polydipsia, polyphagia, fatigue, weakness, and weight loss – Subjects shall be fully evaluated to rule out any alternative causes – Monitor and assess pancreas islet function: blood glucose, insulin, c-peptide, β-cell autoantibodies, blood ketones, and other endocrine laboratory parameters related to type I diabetes

	AE Grade/Administration Adjustments		**Toxicity Management**
	Grade 1 or grade 2	No dose adjustments required	For grade 1–2 events: – Monitor and assess pancreas islet function – Start insulin therapy when necessary
	Grade 3	Interrupt – Resume treatment after blood glucose is under control	For grade 3–4 events: – Consult with sponsor's medical manager – Monitor and assess pancreas islet function – Consider consulting an endocrinologist – Blood glucose control with insulin, adjust insulin dose accordingly – If ketoacidosis occurs, subjects shall be hospitalized to receive insulin, fluid replacement, and alkali therapy
	Grade 4	Permanently discontinue	

	AE Grade/Administration Adjustments		**Toxicity Management**
Renal Insufficiency (Creatinine Elevated)	Any grade		– Monitor signs and symptoms closely (e.g. oliguria, dark urine, anemia, fatigue, and weight loss) – Subjects shall be fully evaluated to rule out any alternative causes – Monitor and evaluate renal function – Consider consulting a nephrologist – Consider kidney biopsy when necessary to distinguish between inflammatory and non-inflammatory causes
	Grade 1	No dose adjustments required	For grade 1 events: – Monitor creatinine levels Q1W – If creatinine level returns to baseline level, resume routine creatinine monitoring according to the study protocol

	AE Grade/Administration Adjustments		**Toxicity Management**
	Grade 2 or grade 3	Interrupt • If reduces to grades 0–1 or baseline, continue the treatment at the next scheduled date • If persists for > 7 days or worsens, treat as a grade 4 event	For grade 2–3 events: – Discuss with sponsor's medical manager – Monitor creatinine levels every 2–3 days – Begin systemic glucocorticoid treatment based on experience – If reduces to grade 1, taper glucocorticoid for at least 1 month**,** consider prophylactic antibiotic to prevent infections – Consider kidney punch biopsy – Consult a nephrologist
	Grade 4	Permanently discontinue	For grade 4 events: – Discuss with sponsor's medical manager – Monitor creatinine levels once daily – Begin systemic glucocorticoid treatment based on experience – If reduces to grade 1, taper glucocorticoid for at least 1 month**,** consider prophylactic antibiotic to prevent infections – Consult a nephrologist – Consider kidney punch biopsy

	AE Grade/Administration Adjustments		**Toxicity Management**
Immune-related neurotoxicities (except for myasthenia gravis and Guillain-Barré syndrome)	Any grade		– Monitor the subject's systemic symptoms (headache, nausea, dizziness, behavioral changes, or weakness) – Subjects shall be fully evaluated to rule out any alternative causes (e.g. PD, infection, metabolic syndrome, medications, etc.) – Consider appropriate diagnostic tests (e.g. electromyography and nerve conduction study) – If applicable, begin symptomatic treatment and consult a neurologist
	Grade 1	No dose adjustments required	– Closely monitor signs and symptoms
	Grade 2	Interrupt • If reduces to grades 0–1 or baseline, continue the treatment at the next scheduled date • If worsens, treat as a grade 3 event	For grade 2–4 events: – Discuss with sponsor's medical manager – Consider consulting a nephrologist – Hospitalization when necessary – Manage neuropathy and neuropathic pain with appropriate
	Grade 3	Permanently discontinue	

	AE Grade/Administration Adjustments		**Toxicity Management**
	Grade 4		medications (e.g. gabapentin, duloxetine, etc) – Consider systemic corticosteroid treatment – If no improvement is seen within 3–5 days, consider other tests and immunosuppressants (e.g. intravenous immunoglobulin G, IVIgG) – Once stabilized, taper glucocorticoids within ≥ 4 weeks

Immune-related peripheral neuropathy, e.g. Guillain-Barré syndrome and myasthenia gravis	Any grade		- Monitor signs and symptoms closely (myasthenia gravis: eye or limb soreness and discomfort, blurred vision, fatigue, which worsens as the day goes on; Guillain-Barrésyndrome: sudden and severe nerve pain, paralysis of the limbs, and prickling or burning sensation in the limbs) - Timely diagnosis of immune-related peripheral neuropathy is very important, as subjects may suffer from unpredictable acute compensation, which may lead to severe disease or death.Pay special attention to signs and symptoms that may indicate serious consequences, e.g. significant dysphagia, rapidly progressive weakness, respiratory insufficiency, or autonomic dysfunction - Neuroelectrophysiological tests shall be performed to rule out any alternative causes (e.g. PD, infection, metabolic syndrome, medications, etc.) It is worth noting that cancer itself and cancer treatment can affect neural function. The diagnosis of immune-related peripheral neuropathies is thus difficult. Neurological consultation shall be actively carried out. - Plasmapheresis or IVIgG should be considered for subjects with

	AE Grade/Administration Adjustments		**Toxicity Management**
			Guillain-Barrésyndrome (glucocorticoids are generally ineffective)
	Grade 1	No dose adjustments required	For grade 1 events: - Discuss with a physician - Monitor signs and symptoms - Consider consulting a nephrologist
	Grade 2	Interrupt • If reduces to grades 0–1 or baseline, continue the treatment at the next scheduled date • If worsens, treat as a grade 3–4 event	For grade 2–4 events: - Discuss with sponsor's medical manager - Monitor signs and symptoms - Consider consulting a nephrologist - Hospitalization when necessary - Manage neuropathy and neuropathic pain with appropriate

	AE Grade/Administration Adjustments		Toxicity Management
	Grade 3 or grade 4	Permanently discontinue	medications (e.g. gabapentin, duloxetine, etc.) *Myasthenia Gravis* – Glucocorticoids may be used to treat myasthenia gravis (shall be used under the supervision of a neurologist since corticosteroids, especially high-dose, may result in initial exacerbation of symptoms) – Subjects intolerant to glucocorticoids may be treated with plasmapheresis or IVIgG – For myasthenia gravis-like neurotoxicities, consider acetylcholinesterase inhibitors in addition to glucocorticoids *Guillain-Barre Syndrome* – Plasmapheresis or IVIgG should be considered for subjects with Guillain-Barrésyndrome (glucocorticoids are generally ineffective)

Table 2. Dose Modification and Toxicity Management Guidelines for Potential Other irAEs

	CTD Grade/Administration Adjustments	Toxicity Management

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

Table 3. Dose Modification and Toxicity Management Guidelines for Infusion Reactions

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