CLINICAL STUDY PROTOCOL

Study Title:	A Randomized, Double-Blind, Multi-Center Phase III Clinical Trial Evaluating the Efficacy and Safety of IBI308 or Placebo in Combination with Oxaliplatin and Capecitabine (XELOX), for First-Line Treatment of Unresectable, Locally Advanced, Recurrent, or Metastatic Gastric or Gastroesophageal Junction Adenocarcinoma (ORIENT-16)
Protocol No.:	CIBI308E301
Version and Date:	Jun 11, 2021 Version 3.2
Product Name:	Sintilimab (Recombinant Fully Human Anti-PD-1 Monoclonal Antibody, R&D Code: IBI308)
Study Phase:	Phase III
Sponsor:	Innovent Biologics (Suzhou) Co., Ltd. No. 168 Dongping Street, Suzhou Industrial Park, Jiangsu, China
Sponsor Contact:	[redacted]

Sponsor's Signature Page

Protocol Title: A Randomized, Double-Blind, Multi-Center Phase III Clinical Trial Evaluating the Efficacy and Safety of IBI308 or Placebo in Combination with Oxaliplatin and Capecitabine (XELOX), for First-Line Treatment of Unresectable, Locally Advanced, Recurrent, or Metastatic Gastric or Gastroesophageal Junction Adenocarcinoma (ORIENT-16)

Project No.: CIBI308E301

Title	Name (Regular Script)	Signature	Date
Executive Director of Medical Science	[redacted]		
Executive Director of Biostatistics	[redacted]		

Protocol Synopsis

Protocol no.	CIBI308E301
Sponsor	Innovent Biologics (Suzhou) Co., Ltd.
Investigational drug	Sintilimab (R&D code: IBI308)
Active ingredient	Recombinant fully human anti-PD-1 monoclonal antibody
Study title	A Randomized, Double-Blind, Multi-Center Phase III Clinical Trial Evaluating the Efficacy and Safety of IBI308 or Placebo in Combination with Oxaliplatin and Capecitabine (XELOX), for First-Line Treatment of Unresectable, Locally Advanced, Recurrent, or Metastatic Gastric or Gastroesophageal Junction Adenocarcinoma (ORIENT-16)
Phase	Phase III
Study objectives	Primary objectives: • To compare the overall survival (OS) of IBI308 vs. placebo in combination with chemotherapy, for first-line treatment of unresectable, locally advanced, recurrent, or metastatic gastric or gastroesophageal junction adenocarcinoma (G/GEJ AC); • To compare the OS of IBI308 vs. placebo in combination with chemotherapy, for first-line treatment in PD-L1-positive subjects with unresectable, locally advanced, recurrent, or metastatic G/GEJ AC. Secondary objectives: • To compare the progress-free survival (PFS), objective response rate (ORR), disease control rate (DCR), and duration of response (DoR) between the two groups; • To compare the safety between the two groups. Exploratory objectives: • To compare changes in quality of life between the two groups; • To evaluate the pharmacokinetic (PK) characteristics of IBI308 in combination with chemotherapy in patients with unresectable, locally advanced, recurrent, or metastatic G/GEJ AC; • To evaluate the correlation between biomarkers in tumor tissue and efficacy, including PD-L1 expression level;

Study design	This is a randomized, double-blind, multi-center phase III clinical trial evaluating the efficacy and safety of IBI308 vs. placebo in combination with oxaliplatin and capecitabine (XELOX), for first-line treatment in patients with unresectable, locally advanced, recurrent, or metastatic G/GEJ AC. Subjects will be treated with IBI308 (weight < 60 kg: 3 mg/kg IV Q3W; weight ≥ 60 kg: 200 mg IV Q3W) or placebo, in combination with XELOX regimen (oxaliplatin 130 mg/m^2 IV Q3W, capecitabine 1000 mg/m^2 Bid PO × 14d Q3W), for up to 6 chemotherapy cycles (1 cycle = 3 weeks). Then subjects will receive maintenance therapy of IBI308 or placebo in combination with capecitabine (1000 mg/m^2 Bid PO × 14d Q3W) until progressive disease (PD), intolerable toxicity, initiation of new anti-tumor therapy, withdrawal of consent, loss to follow-up or death, or any other reason for treatment discontinuation (whichever comes first) judged by the investigator. Treatment of IBI308 or placebo, in combination with capecitabine, will last for up to 24 months (starting from the first dose). If a drug is discontinued for any reason during the treatment, other drugs will be permitted to be continued. Subjects with unresectable, locally advanced, recurrent, or metastatic G/GEJ AC will be randomized to IBI308 group or placebo group in a 1:1 ratio. A total of 650 subjects will be enrolled, of which 325 subjects will be in the IBI308 group and 325 subjects will be in the placebo group. The randomization stratification factors include the Eastern Cooperative Oncology Group Performance Status (ECOG PS) score (0 or 1), hepatic metastasis (positive or negative), and PD-L1 expression (CPS < 10 or ≥ 10). (CPS refers to combined positive score, which is the sum of PD-L1 expression in tumor cells and tumor-infiltrating lymphocytes). The primary endpoint of the study is the OS in the intention-to-treat (ITT) population or in the PD-L1 positive subjects (CPS ≥ 5). OS is defined as the time from randomization to death for any cause. Subjects who are still alive at the time of analysis are censored at the last date of survival. In this study, clinical tumor imaging evaluation will be performed according to RECIST v1.1. During the study, tumor imaging evaluation will be performed Q6W (± 7 days) initially, then once Q12W (± 7 days) after 48 weeks based on RECIST v1.1 until PD, initiation of new anti-tumor therapy, withdrawal of ICF, loss to follow-up, death, or end of the study (whichever occurs first). An interim analysis will be performed during the study and the results and report will be submitted to the iDMC. The iDMC will determine the treatment efficacy based on estimated effective boundaries and provide advices to the sponsor on whether the study can be continued. The iDMC charter will be finalized and approved by the iDMC and sponsor prior to the interim analysis. The responsibilities of iDMC members and related procedures will be defined in the iDMC charter. After the study treatment is discontinued and completed, safety follow-up and overall survival follow-up will be performed Q60D.

Inclusion criteria	1. Histopathologically confirmed unresectable, locally advanced, recurrent, or metastatic G/GEJ AC (including signet ring cell carcinoma, mucinous adenocarcinoma, and hepatoid adenocarcinoma). 2. Ages ≥ 18 years old 3. ECOG PS score of 0 or 1. 4. Time from the completion of previous (neo) adjuvant chemotherapy/adjuvant radiotherapy to disease recurrence > 6 months. 5. Time from the completion of palliative therapy for local lesions (non-target lesions) to randomization > 2 weeks. 6. Having at least one measurable or evaluable lesion according to RECIST v1.1. 7. Can provide archived (within 6 months prior to screening and signing of ICF) or fresh tissues for PD-L1 expression analysis with obtainable results. 8. Sufficient organ and bone marrow functions, as defined below: 1) Routine blood test: absolute neutrophil count (ANC) ≥ 1.5×10^9/L, platelets (PLTs) ≥ 100×10^9/L, and hemoglobin (HGB) ≥ 9.0 g/dL. G-CSF, GM-CSF, Meg-CSF, TPO, EPO, red blood cell (RBC) transfusion, and platelet transfusion should not be performed within 7 days prior to the test. 2) Hepatic function: total bilirubin (TBIL) ≤ 1.5 × normal upper limit (ULN), alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ≤ 2.5 × ULN in patients without liver metastasis. Patients with liver metastasis: TBIL ≤ 1.5 × ULN; ALT and AST ≤ 5 × ULN. 3) Renal function: glomerular filtration rate (GFR) ≥ 60 mL/min (calculated using the CKD-EPI formula detailed in Appendix 4). 4) Adequate coagulation function, defined as international normalized ratio (INR) ≤ 1.5 or prothrombin time (PT) ≤ 1.5 × ULN; if the patient is receiving anticoagulant therapy, as long as the PT is within the proposed range for anticoagulants; 5) Urinalysis: urine protein < 2+; if urine protein ≥ 2+, 24-h urine protein should be < 1.0 g. 9. Estimated survival ≥ 12 weeks. 10. Patients (female patients of childbearing age or male patients whose partners are of childbearing age) must take effective contraceptive measures during the entire course of the treatment and 6 months after the treatment (see Section 4.3). 11. Patients who have signed ICFs, and are able to comply with the follow-up visits and relevant procedures required in the protocol.
Exclusion criteria	1. Known sign of active hemorrhage in lesions. 2. Cardia or pylorus obstruction affecting eating and gastric emptying, or causing difficulty in swallowing tablets.

	3. Diagnosed with HER2-positive G/GEJ AC. 4. Previous systemic therapy of advanced or metastatic G/GEJ AC. 5. An accumulated cisplatin dose ≥ 300 mg/m^2 in previous neo (adjuvant) treatment. 6. Peripheral neurotoxicity has not resolved to grade 1 after previous treatment. 7. Known dihydropyrimidine dehydrogenase (DPD) enzyme deficiency (or prior grade 3 or higher mucosal toxicities in fluorouracil treatment). 8. Known allergic reactions (prior grade 3 or higher allergic reactions) to ingredients of any monoclonal antibody or chemotherapeutic agents (capecitabine and/or oxaliplatin). 9. Prior exposure to any anti-PD-1 or anti-PD-L1, anti-PD-L2, anti-CD137, anti-CTLA-4 antibody, or any other antibody or drug that specifically targets T-cell costimulation or immune checkpoint pathways. 10. Enrolled in another interventional clinical study, unless only involved in an observational study (non-interventional) or in the follow-up phase of an interventional study. 11. Received systemic treatment with Chinese herbal medicines for cancer indications or immunomodulators (including thymosins, interferons, and interleukins) within 2 weeks prior to the first dose of study drug 12. Received immunosuppressive drugs within 4 weeks prior to the first dose of study drug, excluding local glucocorticoids administered by nasal, inhaled, or other topical routes, or systemic glucocorticoids of physiological doses (no more than 10 mg/day of prednisone or equivalents), or glucocorticoids to prevent allergies to contrast media. 13. Received a live attenuated vaccine within 4 weeks prior to the first dose of study drug, or planned to receive this vaccine during the study period. Note: Seasonal inactivated influenza virus vaccines within 4 weeks prior to the first dose of study drug are permitted, but live attenuated influenza vaccines are not; 14. Received major surgery (craniotomy, thoracotomy, or laparotomy) within 4 weeks prior to the first dose of study drug, or will receive major surgery during the course of the trial; received exploratory laparoscopy within 2 weeks before the first dose of study drug. 15. Anti-tumor therapy-related toxicity (excluding alopecia, events that are not clinically significant, or asymptomatic laboratory abnormalities) that has not yet resolved to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) v5.0 grade 0 or 1 prior to the first dose of study drug. 16. Known symptomatic central nervous system (CNS) metastasis and/or carcinomatous meningitis. Patients with brain metastases received prior treatment are eligible if the diseases are stable (no imaging evidence of progression for at least 4 weeks prior to the first dose of study drug, and no evidence of new brain

	metastasis or enlargement of the primary brain metastatic lesion upon repeated imaging), and corticosteroids are not required for at least 14 days prior to the first dose of study drug. This exception excludes carcinomatous meningitis, regardless of whether the disease is clinically stable. 17. Ascites that can be detected in physical examination, ascites that has been treated with prior procedures, or currently requires treatment. Asymptomatic patients with small amount of ascitic fluid demonstrated by imaging are eligible. 18. Moderate-sized bilateral pleural effusion or large-sized unilateral pleural effusion, or pleural effusion that has caused respiratory dysfunction requiring drainage. 19. Patients with bone metastasis at risk of paraplegia. 20. Known or suspected autoimmune diseases or a history of these diseases within the past 2 years (subjects with vitiligo, psoriasis, alopecia, or Grave's disease who do not require systemic treatment within 2 years, or those with hypothyrodism only requiring thyroid hormone replacement, or those with type I diabetes mellitus only requiring insulin replacement treatment can be enrolled). 21. Known history of primary immunodeficiency diseases. 22. Known to have active pulmonary tuberculosis. 23. Known history of allotransplantation or allogeneic hematopoietic stem cell transplantation. 24. Known history of human immunodeficiency virus (testing positive for HIV). 25. Active or poorly clinically controlled serious infections. 26. Symptomatic congestive cardiac failure (NYHA Classes II–IV) or symptomatic or poorly controlled arrhythmia. 27. Uncontrolled hypertension (systolic blood pressure ≥ 160 mmHg or diastolic blood pressure ≥ 100 mmHg) despite standard treatment. 28. Any arterial thromboembolic event occurs within 6 months prior to enrollment, including myocardial infarction, unstable angina, cerebrovascular accident, or transient cerebral ischemic attack. 29. Significant malnutrition (gain loss by 5% within 1 month, gain loss by > 15% within 3 months, or food intake decrease by 1/2 or above within 1 week before signing of ICF), excluding those with 4 weeks and above of malnutrition correction before the first dose of study drug. 30. History of deep venous thrombosis, pulmonary embolism, or other severe thromboembolic events within 3 months prior to enrollment (implantable port or catheter-related thrombosis, or superficial venous thrombosis are not considered "serious" thromboembolisms). 31. Uncontrolled metabolic disorders, non-malignant organ or systemic diseases, or cancer-related secondary diseases that may lead to higher medical risks and/or survival evaluation uncertainties.

	32. Hepatic encephalopathy, hepatorenal syndrome, or cirrhosis with Child-Pugh grade B or C. 33. Tumor-related bowel obstruction (within 3 months before signing of ICF) or history of the following diseases: inflammatory bowel disease or extensive bowel resection (partial colectomy or extensive small bowel resection accompanied with chronic diarrhea), Crohn's disease, and ulcerative colitis. 34. Known acute or chronic active hepatitis B (positive HBsAg and HBV DNA viral load ≥ 200 IU/mL or ≥ 10^3 copies/mL), or acute or chronic active hepatitis C (positive anti-HCV antibody and positive HCV RNA). 35. Known infections with active syphilis requiring treatment. 36. History of GI perforation and/or fistula within 6 months prior to the enrollment, excluding resection of primary gastric cancer lesion due to perforation in gastric cancer cases. 37. Interstitial lung disease requiring corticosteroids. 38. History of other primary malignant tumors, excluding: • Malignant tumors that have achieved complete response (CR) for at least 2 years prior to enrollment and will require no treatment during the study; • Adequately treated nonmelanoma skin cancer or lentigo maligna with no signs of disease recurrence; • Adequately treated carcinoma in situ with no signs of recurrence. 39. Pregnant or breastfeeding female patients. 40. Acute or chronic diseases, psychiatric disorders, or laboratory abnormalities that may lead to the following consequences: increased study drug-related risks, or interference with interpreting study results, and considered ineligible for participating in the study by the investigator.
Study drug, strength, and administration	• IBI308 - Strength: 100 mg: 10 mL - Route of administration: weight < 60 kg: 3 mg/kg IV Q3W weight ≥ 60 kg: 200 mg IV Q3W • Capecitabine - Strength: 500 mg/tablet - Route of administration: 1000 mg/m^2 Bid PO × 14d Q3W • Oxaliplatin - Strength: 50 mg/vial - Route of administration: 130 mg/m^2 IV Q3W

Evaluation criteria	**Efficacy evaluation:** • Primary endpoint: OS in ITT population; OS in PD-L1-positive subjects in ITT population. • Secondary endpoints: PFS, ORR, DCR, and DoR. **Safety evaluation:** • The incidence, severity level, and association with the investigational drug of all adverse events (AEs), treatment-emergent adverse events (TEAEs), treatment-related adverse events (TRAEs) and serious adverse events (SAEs), and immune-related adverse events (irAEs). • Changes in vital signs, physical examination, and laboratory tests results before, during, and after the study treatment will be evaluated. **Immunogenicity evaluation (for IBI308 group only):** • Positive rates of anti-drug antibodies (ADAs) and neutralizing antibodies (NAbs). **Biomarker evaluation (performed at central laboratory):** • To evaluate the correlation between biomarkers in tumor tissue and efficacy, including PD-L1 expression level; **Quality of life evaluation:** • Quality of life and health status will be compared between IBI308 and placebo in combination with chemotherapy, according to EQ 5D-5L, EORTC QLQ-C30, and EORTC QLQ-STO22.
Statistical methods	This study is a phase III clinical study. The primary efficacy endpoints are OS in PD-L1-positive population and OS in ITT population. The test will be performed in a fixed order. The test of OS in ITT population will be performed only when the PD-L1-positive population reaches statistically significant, so as to strictly control the overall type I error of hypothesis test on the two populations for OS efficacy endpoints. For OS in the PD-L1-positive population, assuming the hazard ratio (HR) of IBI308 to placebo, in combination with chemotherapy, is 0.7 (median OS is 15.7 and 11 months, respectively), 287 OS events are required to be at a level of 0.05 (two sided) with 85% power. For OS in the ITT population, assuming that the HR of IBI308 to placebo, in combination with chemotherapy, is 0.75 (median OS is 14.7 and 11 months, respectively), 515 OS events are required to be at a level of 0.05 (two sided) with 90% power. The above calculations are based upon a 0.5% censoring rate of each month. The study will take 18 months to enroll 650 subjects, with 325 in each group. 515 OS events are estimated to be observed within 46 months. Based on the above assumptions, the PD-L1-positive population accounted for 56.2% (i.e., 365) of the ITT population with 287 OS events observed at the final analysis in the PD-L1-positive population. The enrollment rate and dropout rate observed as well as OS distribution when blinded

	will be used to predict and determine the cut-off time points for interim OS analysis and final OS analysis. **Hypothesis test:** This is a superiority trial. The primary efficacy endpoints are the OS in the ITT population and in the PD-L1-positive population. The superiority hypothesis test in each population is: Null hypothesis H0: HR ≥ 1 Alternative hypothesis Ha: HR < 1 **Interim analysis:** In this study, hypothesis tests will be performed in a fixed order. The superiority test will be performed on the OS of PD-L1 positive population first, and the OS test will be performed on the ITT population after the OS of PD-L1 positive population reaches statistically significance. This study plans to conduct an interim analysis of OS in both the PD-L1-positive population and the ITT population when the number of OS events is at least 70% (i.e., 361 in the ITT population and 201 in the PD-L1-positive population), and the test level will follow the Lan-Demets approach to approximate the O'Brien-Fleming boundary. At the interim analysis, with a nominal test of 0.0148, the minimum detectable difference (MDD) in OS was HR = 0.709 in the PD-L1-positive population and HR = 0.774 in the ITT population. At the final analysis, the nominal test level was 0.0455 with MDD for OS of HR = 0.790 for the PD-L1 positive population and HR = 0.838 for the ITT population. The exact alpha value of the OS analysis will be adjusted according to the Lan-DeMets approximation of the O'Brien-Fleming boundary based on the number of OS events that occur in real time to ensure an overall OS detection level of $\alpha = 0.05$. At the same time, this study plans to conduct an interim analysis of safety data at 200 PFS events to monitor the overall safety of clinical trial subjects. **Primary efficacy endpoints:** A stratified log-rank test will be used to compare the OS between groups. The HR and corresponding 95% CI will be estimated with a stratified Cox proportional hazards model. In the model, several important covariates will be considered, such as randomization stratification factors for randomization, to estimate the HR and 95% CI. The median OS and corresponding 95% CI will be estimated via Kaplan-Meier method, and the survival curves will be plotted. **Secondary efficacy endpoints:** The ORR, DCR, and the corresponding 95% CIs will be estimated for both groups. The difference between groups and 95% CI will be computed. The DoR and PFS will be analyzed by the same methods for OS analysis. **Safety data:** The incidence and severity level of AEs are summarized for each group. Abnormal changes in laboratory tests, ECG, vital signs, physical examination indexes are described.

	Immunogenicity analysis: Immunogenicity data will be presented with descriptive statistics. The numbers and percentages of subjects with ADAs and NAbs will be summarized. **Quality of life indicators:** Quality of life and health status will be compared between IBI308 and placebo, in combination with chemotherapy, according to EQ 5D-5L, EORTC QLQ-C30, and EORTC QLQ-STO22. Changes in quality-of-life scores will be presented according to follow-up for each group. **Biomarker:** Expression level and distribution of PD-L1 is subject to descriptive statistics and explored for its association with efficacy. **PK data:** The PK analysis will include but is not limited to descriptive summary statistics of IBI308 trough concentrations in cycles 1/3/11.

Table 1. Schedule of visits

Stage	Screening period	Combination treatment period						Maintenance treatment period	End-of-treatment visit Safety follow-up			Survival follow-up[25]
		Cycle 1	Cycle 2	Cycle 3	Cycle 4	Cycle 5	Cycle 6	Cycle 7 and beyond	End-of-treatment visit[22]	Safety follow-up		
Visit	1	2	3	4	5	6	7	8–N				
Day	−28 to −1	1	22 (± 3 days)	43 (± 3 days)	64 (± 3 days)	85 (± 3 days)	106 (± 3 days)	Every 3 weeks (± 3 days)	Within 7 days after the end of treatment	30 days (±7 days) after the last dose[23]	90 days (±7 days) after the last dose[24]	Every 60 days (± 15 days)
Standard study procedures												
Written ICF[1]	X											
Inclusion/Exclusion criteria	X											
Demographics/Past medical history/ Previous medication[2]	X											
Vital signs[3]	X	X	X	X	X	X	X	X	X	X		
Weight/Height[4]	X	X	X	X	X	X	X	X	X	X		
Physical examination	X		X	X	X	X	X	X	X	X		
ECOG PS score	X	X	X	X	X	X	X	X	X	X		
12-lead ECG[5]	X		X	X	X	X	X	X	X	X		
History of helicobacter pylori (HP) infection[6]	X											
Laboratory test												
Pregnancy test[7]	X								X			
HIV, HBV, syphilis, and HCV[8]	X											

Stage	Screening period	Combination treatment period						Maintenance treatment period	End-of-treatment visit Safety follow-up			Survival follow-up[25]
		Cycle 1	Cycle 2	Cycle 3	Cycle 4	Cycle 5	Cycle 6	Cycle 7 and beyond	End-of-treatment visit[22]	Safety follow-up		
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8–N**				
Day	**−28 to −1**	**1**	**22 (± 3 days)**	**43 (± 3 days)**	**64 (± 3 days)**	**85 (± 3 days)**	**106 (± 3 days)**	**Every 3 weeks (± 3 days)**	**Within 7 days after the end of treatment**	**30 days (±7 days) after the last dose[23]**	**90 days (±7 days) after the last dose[24]**	**Every 60 days (± 15 days)**
Thyroid function[9]	X		X	X	X	X	X	X	X			
Routine blood test/ blood chemistry/ urinalysis[10]	X		X	X	X	X	X	X	X	X		
Coagulation function[11]	X								X			
Safety evaluation												
AE evaluation[12]	X	X	X	X	X	X	X	X	X	X	X	
Concomitant medications	X	X	X	X	X	X	X	X	X	X		
Survival condition		←										→
Subsequent anti-tumor therapy											X	X
Quality of life evaluation[13]												
EQ 5D-5L/ EQ QLQ-C30/ EORTC QLQ-STO22		X		X		X		X	X	X		
Efficacy evaluation												
Tumor imaging evaluation[14]	X			X		X		X	X			
Randomization												
IWRS[15]		X										

Stage	Screening period	Combination treatment period						Maintenance treatment period	End-of-treatment visit Safety follow-up			Survival follow-up[25]
		Cycle 1	Cycle 2	Cycle 3	Cycle 4	Cycle 5	Cycle 6	Cycle 7 and beyond	End-of-treatment visit[22]	Safety follow-up		
Visit	1	2	3	4	5	6	7	8–N				
Day	−28 to −1	1	22 (± 3 days)	43 (± 3 days)	64 (± 3 days)	85 (± 3 days)	106 (± 3 days)	Every 3 weeks (± 3 days)	Within 7 days after the end of treatment	30 days (±7 days) after the last dose[23]	90 days (±7 days) after the last dose[24]	Every 60 days (± 15 days)
Study drug infusion												
IBI308[16]		X	X	X	X	X	X	X				
Placebo[17]		X	X	X	X	X	X	X				
Oxaliplatin[18]		X	X	X	X	X	X					
Capecitabine[18]		X	X	X	X	X	X	X				
Biomarker study												
Archived or fresh tumor tissue sample[19]	X											
PK and immunogenicity												
PK[20]		X	X		X			X				
Immunogenicity[21]		X	X		X			X		X		

Notes:

1. The ICF should be signed by subjects prior to any procedures outlined in the protocol.
2. Medical history includes all active diseases and diseases diagnosed within the past 10 years (note: All autoimmune diseases should be documented, regardless of the date of onset), surgery history, and drug allergy history. Personal history, such as smoking, drinking, needs to be recorded. Detailed information regarding G/GEJ AC (including IHC and/or FISH-tested HER2 expressions in pathological tissues) should be documented separately by EDC and not listed as part of the medical history. Previous medication includes drugs requiring elution in any protocol and those administered within 30 days before the first dose of investigational drug.
3. Vital signs include: body temperature, pulse, respiratory rate, and blood pressure.

4. Height is measured during screening or before the first dose and not required subsequently.
5. 12-lead ECG is scheduled during screening (within 7 days before the first dose), prior to administration of study drug in each cycle since cycle 2, during end-of-treatment visit, and during the first safety follow-up. Tests will be conducted at each study site.
6. Information on HP infection at the confirmed diagnosis of gastric cancer (including test methods if any) is collected during screening, and the specific HP infection method is documented. If no test result is available, the collection will not be required.
7. Women of childbearing age should undergo urine or blood pregnancy test within 3 days prior to the first dose and during the end-of-treatment visit. If the urine pregnancy test is not conclusive, then blood pregnancy test should be performed. The conclusion should be based on the blood pregnancy test. Tests will be conducted at each study site.
8. Hepatitis B panel (HBsAg, HBsAb, HBcAb, HBeAg, and HBeAb), anti-HCV antibodies, treponema pallidum antibodies, HIV antibodies will be tested during screening. HBV DNA should be further tested for HBsAg and/or HBcAb positive subjects. If the result shows HCV antibody positive, then HCV RNA test should be further conducted. The results obtained within 28 days prior to randomization are accepted. Prophylactic antiviral treatment is suggested to be performed according to the treatment guidelines for HBV carriers. HBV activity should be monitored during study treatment, end-of-treatment visits, and safety follow-up. Tests will be conducted at each study site.
9. The tests will be conducted during screening, within 3 days prior to the administration of the study drug from cycle 2, and during end-of-study visits. Tests include thyroid stimulating hormone (TSH), free triiodothyronine (FT3), and free tetraiodothyronine (FT4). Tests will be conducted at each study site. The results obtained within 28 days prior to randomization are accepted during screening.
10. Routine blood tests include: red blood cell (RBC), Hemoglobin (HGB), white blood cell (WBC), Platelet (PLT), white blood cell (WBC) differentials [lymphocyte (LYM) and absolute neutrophil count (ANC)]. Blood chemistry includes hepatic function [TBIL, ALT, AST, γ-glutamyltransferase (γ-GT), alkaline phosphatase (ALP), albumin (ALB), total protein (TP), and lactate dehydrogenase (LDH)], renal function [blood urea (UREA) and Cr], electrolytes (Na, K, Cl, Mg, Ca, and P), amylase, creatine kinase (CK), creatine kinase isoenzyme (CK-MB), and fasting blood glucose (FBG). Routine urinalysis includes pH (PH), urine white blood cell (UWBC), urine protein (UPRO), urine red blood cell (URBC), and urine glucose (UGLU). Routine blood test, blood chemistry, and urinalysis will be performed within 7 days before the first dose, within 3 days prior to each dose starting from cycle 2, at the end-of-study visit, and during the first safety follow-up. Tests will be conducted at each study site.
11. Coagulation function tests: PT and INR. The test is conducted during screening, within 7 days prior to the first dose, at the end-of-study visit. Tests will be conducted at each study site.
12. AE and laboratory safety evaluations are performed according to NCI CTCAE v5.0. Refer to Section 8 for definitions, recording, determination of causal relationship, severity level, reporting deadlines, and processing of AEs and SAEs.
13. Quality of life evaluation will be performed on the day of the first dose, during each imaging examination, and during the first safety follow-up using EQ 5D-5L, EORTC QLQ-C30, and EORTC QLQ-STO22 questionnaires.

14. Tumor evaluations are performed based on RECIST v1.1. The same imaging method should be used for a given subject during the study. Baseline evaluation is conducted within 28 days prior to enrollment. The investigator can evaluate imaging results obtained within 28 days prior to enrollment and document the tumor TNM classification based on AJCC (Edition 8). After the first dose of study drug, tumor imaging evaluation will be performed Q6W (± 7 days) initially, then Q12W (± 7 days) after 48 weeks until initiation of new anti-tumor treatment, PD, withdrawal of informed consent form (ICF), or death. If there is an interval of more than 4 weeks between last imaging evaluation and end-of-treatment visit, imaging evaluation at this visit as well as Q6/12W (± 7 days) thereafter should be performed for subjects, who are required to discontinue the treatment for reasons other than PD, until one of the followings occurs: initiation of new anti-tumor therapy, PD, withdrawal of ICF, or death.
15. Prior to the first dose, eligible subjects are randomized to IBI308 or placebo, in combination with chemotherapy, in a 1:1 ratio. Stratification factors include ECOG PS score (0 or 1), hepatic metastasis (positive or negative), and PD-L1 expression (CPS < 10 or ≥ 10).
16. IBI308: weight < 60 kg: 3 mg/kd IV Q3W; weight ≥ 60 kg: 200 mg IV Q3W, for up to 24 months (starting from the first dose), or until PD, death, intolerable toxicity, withdrawal of ICF, or other reasons specified in the protocol. Administration on day 1 of cycle 1 should be on the day of randomization as possible, and no later than 48 h after randomization. Treatment can be delayed for up to 1 week if the administration day is in a holiday.
17. The regimen of administration for placebo is the same as the one for IBI308.
18. Oxaliplatin 130 mg/m^2 IV D1 Q3W, capecitabine 1000 mg/m^2 Bid PO × 14d Q3W. 6 weeks later, maintenance therapy with capecitabine in combination with IBI308/placebo will be performed for up to 24 months (starting from the first dose) until PD, death, intolerable toxicity, withdrawal of ICF, or other reasons specified in the protocol. Administration on day 1 of cycle 1 should be on the day of randomization as possible, and no later than 48 h after randomization, synchronized with dosing of IBI308. Treatment can be delayed for up to 1 week if the administration day is in a holiday. During treatment, missed doses or underdose of capecitabine should not be additionally administered. The initial dose should be administered at the next scheduled time.
19. Subjects are required to provide at least 5 slices of archival or new tumor tissue samples (within 6 months prior to screening and signing of ICF and 3 months of section) during screening to test PD-L1 expression. Those screened to be eligible must provide another 5 slices from the same paraffin block, for companion diagnostic test of PD-L1 expression.
20. PK samples are collected for the first 100 subjects at the following time points: within 1 h before and immediately after (+ 5 min) IBI308 or placebo infusion in cycle 1, and within 1 h before IBI308 or placebo infusion in cycle 2/4/12 (trough concentrations for cycles 1/3/11). Tests will be conducted in the central laboratory.
21. Immunogenicity samples are collected within 1 h prior to IBI308/placebo infusion in combination with chemotherapy in cycle 1/2/4/8/12/16, then every 8 cycles (cycles 24, 32, and so on) thereafter, and during the first safety follow-up. If an infusion-related reaction occurs during IBI308 or placebo administration, blood samples should be taken near the start of the event, end of event, and around 30 days after the reaction, for immunogenicity analysis. Tests will be conducted in the central laboratory.
22. The end-of-treatment visit should be conducted within 7 days after the end of treatment is confirmed.

23. First safety follow-up: performed within 30 days (±7 days) after the last dose of study drug (IV) or before initiation of a new anti-tumor treatment. If the safety follow-up is less than 7 days from the end-of-treatment visit, then the safety follow-up (first) may be replaced by the end-of-treatment visit and do not required to be repeated. However, all procedures for the safety follow-up should be completed (immunogenicity).
24. Second safety follow-up: performed within 90 days (± 7 days) after the last dose of study drug (IV). All AEs, irAEs, and SAEs (related or not related to study drug) that occur before initiation of a new anti-tumor therapy should be collected. If a new anti-tumor therapy is initiated, information on all irAEs and that on SAEs considered related to the study drug or study procedure will be collected. If patients are unable to return to the study site for the second safety follow-up, the telephone follow-up will be acceptable.
25. Survival follow-up: Q60D (± 15 days) after the first safety follow-up. This follow-up is allowed to be completed by telephone.

TABLE OF CONTENTS

List of Tables

List of Figures

List of Abbreviations and Definitions

Abbreviations	English definition
ADA	Anti-drug antibody
AE	Adverse event
ALB	Albumin
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
ANC	Absolute neutrophil count
APTT	Activated partial thromboplastin time
AST	Aspartate aminotransferase
AUC	Area under curve
β-HCG	β human chorionic gonadotropin
CKD-EPI	Chronic kidney disease epidermiology collaboration equation
CK	Creatine kinase
CK-MB	Creatine kinase isoenzymes
CPS	Combined positive score
CRA	Clinical research associate
CRO	Contract research organization
CR	Complete remission
CT	Computed tomography
CTCAE	Common terminology criteria for adverse events
Cr	Creatinine
DCR	Disease control rate
DoR	Duration of response
DPD	Dihydropyrimidine dehydrogenase
EC	Ethics committee
ECOG PS	Eastern cooperative oncology group performance status
ECG	Electrocardiogram
eCRF	Electronic case report form
EDC	Electronic data capture
EORTC QLQ-C30	European organisation for research and treatment of cancer quality of life questionnaire — core 30
FBG	Fasting blood glucose

Abbreviations	English definition
FT3	Free triiodothyronine
FT4	Free thyroxine
GCP	Good clinical practice
GFR	Glomerular filtration rate
γ-GT	γ-glutamyltransferase
HBcAb	Hepatitis B core antibody
HBeAb	Hepatitis B e antibody
HBeAg	Hepatitis B e antigen
HBsAb	Hepatitis B surface antibody
HBsAg	Hepatitis B surface antigen
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
HGB	Hemoglobin
HR	Hazard ratio
ICF	Informed consent form
iDMC	Independent data monitoring committee
Ig	Immunoglobulin
INR	International normalized ratio
irAE	Immune-related adverse event
ITT	Intention to treat
IV	Intravenous
IWRS	Interactive web response system
MDRD	Modification of diet in renal disease
MRI	Magnetic resonance imaging
NAb	Neutralizing antibody
NSAIDS	Nonsteroidal antiinflammatory drugs
NSCLC	Non-small cell lung cancer
ORR	Objective response rate
OS	Overall survival
PD	Progressive disease
PD-1	Programmed cell death 1

Abbreviations	English definition
PD-L1	Programmed cell death ligand 1
PD-L2	Programmed cell death ligand 2
PFS	Progression-free survival
PK	Pharmacokinetics
PLT	Platelet
PPS	Per-protocol set
PR	Partial response
PT	Prothrombin time
RBC	Red blood cell
RECIST	Response evaluation criteria in solid tumors
SAE	Serious adverse event
SAP	Statistical analysis plan
SOC	System organ class
SD	Stable disease
SS	Safety set
TBIL	Total bilirubin
TEAE	Treatment emergent adverse event
TP	Total protein
TSH	Thyroid stimulating hormone
ULN	Upper limit of normal
UGLU	Urine glucose
UPRO	Urine protein
URBC	Urine red blood cell
UREA	Urea
UWBC	Urinary white blood cell
WBC	White blood cell

1 BACKGROUND

1.1 Disease Background

Gastric cancer (GC) is one of the most common malignant tumors globally. According to the World Health Organization GLOBOCAN database, the number of new GC cases in 2012 was 952,000 (6.8% of all new cancer cases), making GC the fifth most common cancer in the world. More than 70% (677,000) of GC cases occurred in developing countries. Half of the global total cases were diagnosed in East Asia, mainly in China. As the third leading cancer deaths worldwide [1], GC results in 723,000 annual deaths [2].

At present, surgical resection is still the only radical treatment of GC. However, patients are staged at the initial diagnosis to be in the middle or advanced stage, and are thus unresectable, or even a large portion of patients develop recurrence or metastases after surgery. In this case, the primary treatment is the systemic chemotherapy. The 5-year survival rate of advanced or metastatic GC is 5–20% and the median overall survival (OS) is approximately 1 year. The first-line treatment is mainly based on the platinum-based dual- or triple-drug chemotherapy [3-8].

Over the past more than ten years, the treatment methods of various malignant tumors have made rapid progress, achieving a milestone of revolution from traditional chemotherapy to molecular targeted therapy, and now immunotherapy, having gradually improved the prognosis. However, there has been little progress in the area of GC. Other than HER2-positive GC which can benefit from the first-line treatment with trastuzumab, multiple phase III studies for the first-line treatment of advanced GC have failed to demonstrate the efficacy.

The phase III EXPAND study [9] enrolled 904 patients with unresectable and locally advanced, or metastatic GC to compare the efficacy of cetuximab in combination with capecitabine and cisplatin (XP regimen) vs. XP regimen alone. As the primary endpoint, the progression-free survival (PFS) was 4.4 months and 5.6 months respectively ($p = 0.32$) and OS was 9.4 months and 10.7 months respectively ($p = 0.9547$). There were no significant differences between the two groups. In fact, the cetuximab in combination with capecitabine and cisplatin (XP regimen) seemed to show lower efficacy.

Similar results were found in the REAL-3 study. In this randomized, open-label phase III study, a total of 553 patients with untreated, locally advanced or metastatic GC were enrolled to compare the efficacy and safety of doxorubicin, oxaliplatin, and capecitabine (EOC regimen) in combination with or without panitumumab. The OS as primary endpoint was 8.8 months and 11.3 months, respectively ($p = 0.013$). In addition, EOC regimen in combination with panitumumab was related to an increase in adverse reactions of higher grades. This study was discontinued in 2011 by the independent Data Monitoring Committee (iDMC) due to lack of efficacy. Panitumumab is therefore not recommended in unselected GC patients [10].

In the phase III AVAGAST study, bevacizumab in combination with capecitabine, 5-fluorouracil, and cisplatin improved PFS in subjects with locally advanced or metastatic GC, compared with chemotherapy alone (6.7 months vs.5.3 months, p = 0.0037). However, there was no significant difference between the two groups in the OS as primary endpoint (12.1 months vs.10.1 months, p = 0.1002). Also, subgroup analyses revealed that regional differences in the healthcare environment may have contributed to the differences in OS [11]. Based on these conclusions, the phase III AVATAR study was conducted in Chinese patients with advanced GC. The PFS (6.3 months vs. 6.1 months, p = 0.3685) and OS (10.5 months vs. 11.4 months, p = 0.8636) were similar between bevacizumab in combination with capecitabine and cisplatin and chemotherapy alone [12].

The advent of immunotherapy brings hope to the treatment of advanced GC.

In the KEYNOTE-059 study, the potential efficacy of pembrolizumab was evaluated for the treatment of GC. This study recruited 259 patients. All of them had been treated at least twice with systemic therapy but still experienced PD, and then they received pembrolizumab 200 mg Q3W. The results showed that, the objective response rate (ORR) and median duration of response (DoR) respectively was 15.5% and 16.3 months in PD-L1 positive subjects (CPS ≥ 1), and 6.4% and 6.9 months in PD-L1-negative subjects (CPS < 10). Based on these results, in Sep. 2017, the FDA granted accelerated approval to pembrolizumab for third-line treatment in patients with PD-L1-positive recurrent or advanced GC [13]. The ongoing phase III KEYNOTE-062 trial is evaluating the efficacy of pembrolizumab alone or in combination with cisplatin and capecitabine (or 5-fluorouracil) as a first-line treatment for patients with PD-L1-positive GC [14].

ATTRACTION-2 (ONO-4538-12) is a randomized, double-blind, placebo-controlled phase III clinical trial conducted in Japan, South Korea, and Taiwan (China) that evaluated the safety and efficacy of nivolumab in patients with advanced gastric or gastroesophageal junction cancer after multi-line treatment. The primary endpoint was OS. The results showed that the median OS was 5.26 months in the nivolumab group and 4.14 months in the placebo group (p < 0.0001). nivolumab significantly reduced the risk of death by 37%. Besides, the 12-month OS in the nivolumab group was also significantly higher than that in the placebo group (26.2% vs. 10.9%). Nivolumab has thereby been approved in Japan for the treatment of advanced gastric and gastroesophageal junction cancer after failure of at least 2 systemic therapies [15]. A phase III clinical study evaluating nivolumab in combination with chemotherapy for first-line treatment of gastric and gastroesophageal junction cancer (Checkmate 648) is also underway [16].

As present, there is no evidence available demonstrating the efficacy of anti-PD-1 antibodies in combination with chemotherapy for first-line treatment of GC. Furthermore, Chinese patients with GC have their unique clinical characteristics, such as high incidence of distal GC, young onset, and more diffuse GC. Therefore, high-quality multi-center clinical studies in China are desiderated to explore the treatment strategies for GC that meet the domestic needs.

1.2 Study Drug (IBI308)

1.2.1 Mechanism of action

Immune checkpoints are a type of immune inhibitory molecules, whose Physiological function is to regulate the breadth and magnitude of the immune response, avoiding the damage and destruction of normal tissues. Cancer cells often use these immune checkpoints to avoid being attacked by immune cells. Currently, immune checkpoints CTLA-4 and PD-1/PD-L1 have been validated clinically. Immune checkpoint inhibitors that target PD-1/PD-L1 have better prospects for clinical applications due to better safety and a broader range of indications.

PD-1 is primarily expressed on activated T-cells and has two ligands, PD-L1 and PD-L2. PD-L1 is the main ligand that is expressed on activated T-cells, antigen-presenting cells, and tumor cells [17]. The binding of PD-1 with PD-L1 plays an important role in regulating the activation of T cells and maintaining peripheral immune tolerance. When T cells do not express PD-1, they interact with antigen-presenting cells to enable the activation and proliferation of T cells as well as the activation of cytokine secretion, which can kill the tumor cells. The activated T cells begin to express PD-1. After PD-1 binds to the ligand PD-L1 expressed on the surface of antigen-presenting cells or tumor cells, the inhibitory signal transmitted by PD-1 inhibits the proliferation of T cells and activates the secretion of cytokines, thus weakens the function of T cells. Most tumor cells evade the attack of immune cells through this mechanism. The activity and ability to kill cancer cells of T cells can be restored by blocking the PD-1/PD-L1 interaction with drugs [18].

FDA has approved several PD-1/PD-L1 inhibitors for the treatment of non-small cell lung cancer (NSCLC) and melanoma, which are also being studied in GC patients. The most well-known PD-1 inhibitors are pembrolizumab (Keytruda®) and nivolumab (Opdivo®), and the approved PD-L1 inhibitors include avelumab (Bavencio®), durvalumab (Imfinzi®), and atezolizumab (Tecentriq®).

Recombinant fully human anti-PD-1 monoclonal antibody (R&D code: IBI308) injection is a recombinant fully human IgG4 monoclonal antibody. Multiple nonclinical in vitro trials have shown the ability of IBI308 to block the PD-1 pathway, and the anti-tumor activity of IBI308 in murine analogs has also been indicated in various murine tumor models. The nonclinical study results indicated the development prospect of IBI308 in blocking the PD-1.

1.2.2 Clinical study results of IBI308

A phase Ia dose-escalation trial was initiated in Sep. 2016 to evaluate 4 dose levels (1 mg/kg, 3 mg/kg, 200 mg, and 10 mg/kg) of IBI308. Pharmacokinetic (PK) evaluation of IBI308 at 1 mg/kg was conducted in subjects with multiple tumors (n = 3). Preliminary results showed that IBI308 at 1 mg/kg reached the maximum drug exposure right after the completion of the single-

dose infusion. The drug distribution was rapid after reaching the peak concentration, followed by a slow elimination ($t_{1/2}$ was about 17.3 d), which is the typical two-compartment PK characteristics of a monoclonal antibody. The elimination half-life is similar to the physiological half-life of IgG4.

The pharmacodynamic results showed that: IBI308 at the dose of 1 mg/kg could rapidly (24 h) saturate the occupancy of peripheral PD-1 (95.8 ± 2.3%) and maintain the PD-1 occupancy with decreasing concentrations throughout the study (28d, C28d: 3.70 ± 0.15 μg/mL). Steady state was expected to be achieved after continual dosing of 1 mg/kg IBI308 for 84 days (Q2W, 6 doses). On the premise of no significant variation in drug clearance profile in the subject, the expected steady-state trough concentration was around 13 μg/mL and the peripheral PD-1 receptor occupancy could be continuously maintained. The phase Ia trial has enrolled 9 patients (3 for each group) in 3 treatment groups (1 mg/kg, 3 mg/kg, and 200 mg), and evaluated the dose-limiting toxicities specified in the protocol for each group. No dose-limiting toxicities were observed. Clinical studies of IBI308 for the treatment of lymphomas and solid tumors were conducted subsequently.

As of Aug. 31, 2018, a total of 540 subjects have received at least 1 dose of IBI308. Among these subjects, 34.4% had NSCLC; 19.8% had esophageal cancer; 17.8% had Hodgkin lymphoma; others had NK/T-cell lymphoma, neuroendocrine neoplasms, melanoma, liver cancer, etc. These subjects were included in the safety analysis. 88.15% of subjects completed at least 2 cycles of treatment, 76.48% completed at least 3 cycles of treatment, 63.33% completed at least 4 cycles of treatment, and 55.74% completed at least 5 cycles of treatment. The median treatment duration was 17.4 weeks. A total of 90.7% of subjects (490/540) experienced an AE during treatment, the most common (≥ 10%) treatment-emergent adverse events (TEAEs) included: anemia (27.4%), fever (23.9%), AST increased (16.3%), ALT increased (15.7%), asthenia (13.9%), cough (13.0%), WBC count decreased (11.7%), neutrophil count decreased (11.7%), proteinuria (11.5%), constipation (10.9%) and loss of appetite (10.4%). A total of 36.5% (197/540) subjects had a grade 3 or greater TEAE, among which the most common (≥ 1%) included: lung infection (4.8%), anemia (4.6%), decreased neutrophil count (3.3%), increased lipase (2.6%), decreased platelet count (2.4%), pneumonitis (1.9%), hypertension (1.9%), hyponatremia (1.9%), increased gamma-glutamyltransferase (1.9%), decreased lymphocyte count (1.9%), infectious pneumonia (1.7%), upper gastrointestinal bleeding (1.5%), decreased WBC count (1.5%), leukopenia (1.3%), hypokalemia (1.3%), and upper respiratory infection (1.1%). A total of 71.3% of all subjects (385/540) experienced treatment-related adverse events (TRAEs), among which the most common (≥ 10%, by PT) included fever (13.1%), AST increased (10.6%), and ALT increased (10.2%). A total of 15.7% (85/540) subjects had a grade 3 or greater TRAE, among which the most common (≥ 1%) were increased lipase (2.4%), lung infections (2.0%), pneumonitis (1.7%), and platelet count decreased (1.1%).

1.3 Risk/Benefit Assessment

1.3.1 Potential risks

Considering the mechanism of action of IBI308 and the clinical safety information of products with similar mechanisms, the main AEs during this clinical trial will possibly be the immune-mediated inflammation resulted from the activation of immune system, e.g. pneumonia, colitis, hepatitis, renal insufficiency, and endocrine system inflammation. According to the available clinical data, anti-PD-1 monoclonal antibodies are well-tolerated despite of high incidence of adverse reactions. Treatment discontinuation due to adverse reactions only occur in a small number of subjects, and most events resolve after appropriate interventions. Early symptoms of immune-related adverse events (irAEs) are variable. Therefore, the investigator must closely monitor early signs and symptoms of irAEs during the study, make correct judgments timely, adjust the dose according to Section 5.2 in the protocol, and provide effective treatment measures to reduce risks to subjects. Besides, subjects with autoimmune diseases should be excluded to avoid deterioration of the original disease due to the activation of immune system.

1.3.2 Potential benefits

Firstly, subjects in this study will be treated with oxaliplatin and capecitabine, which is recognized worldwide as an effective first-line chemotherapy of advanced GC. Therefore, subjects in both IBI308 group and placebo group will receive a standard treatment that is potentially effective. In addition, the IBI308 group will also include the study drug (IBI308). Pharmacological and safety data from a phase Ia clinical trial showed that IBI308 had clear pharmacological activity and good tolerability in subjects with advanced cancers. Similar drugs have shown anti-tumor activity and good safety for multi-line treatment in subjects with advanced GC, supporting clinical studies in Chinese patients with advanced GC.

2 STUDY OBJECTIVES

2.1 Primary Objectives

- To compare the overall survival (OS) of IBI308 vs. placebo in combination with chemotherapy, for first-line treatment of unresectable, locally advanced, recurrent, or metastatic gastric or gastroesophageal junction adenocarcinoma (G/GEJ AC);
- To compare the OS of IBI308 vs. placebo in combination with chemotherapy, for first-line treatment in PD-L1-positive subjects with unresectable, locally advanced, recurrent, or metastatic G/GEJ AC.

2.2 Secondary Objectives

- To compare the progress-free survival (PFS), objective response rate (ORR), disease control rate (DCR), and duration of response (DoR) between the two groups;
- To compare the safety between the two groups.

2.3 Exploratory Objectives

- To compare changes in quality of life between the two groups;
- To evaluate the pharmacokinetic (PK) characteristics of IBI308 in combination with chemotherapy in patients with unresectable, locally advanced, recurrent, or metastatic G/GEJ AC;
- To evaluate the correlation between biomarkers in tumor tissue and efficacy, including PD-L1 expression level;

3 STUDY DESIGN

3.1 Overall Design

This is a randomized, double-blind, multi-center phase III clinical trial evaluating the efficacy and safety of IBI308 vs. placebo in combination with oxaliplatin and capecitabine (XELOX), for first-line treatment in patients with unresectable, locally advanced, recurrent, or metastatic G/GEJ AC.

Subjects will be treated with IBI308 (weight < 60 kg: 3 mg/kg IV Q3W; weight ≥ 60 kg: 200 mg IV Q3W) or placebo, in combination with XELOX regimen (oxaliplatin 130 mg/m^2 IV Q3W, capecitabine 1000 mg/m^2 Bid PO × 14d Q3W), for up to 6 chemotherapy cycles (1 cycle = 3 weeks). Then subjects will receive IBI308 or placebo, in combination with capecitabine (1000 mg/m^2 Bid PO × 14d Q3W), for maintenance therapy until PD, intolerable toxicity, initiation of new anti-tumor therapy, withdrawal ofconsent, loss to follow-up or death, or any other reason for treatment discontinuation (whichever comes first) judged by the investigator. Treatment with IBI308 or placebo, in combination with capecitabine, will last for up to 24 months (starting from the first dose). If a drug is discontinued for any reason during the treatment, other drugs will be permitted to be continued.

Subjects with unresectable, locally advanced, recurrent, or metastatic G/GEJ AC will be randomized to IBI308 group or placebo group in a 1:1 ratio. A total of 650 subjects will be enrolled, of which 325 subjects will be in the IBI308 group and 325 subjects will be in the placebo group. Randomization stratification factors include the Eastern Cooperative Oncology Group Performance Status (ECOG PS) score (0 or 1), liver metastasis (positive or negative), and PD-L1 expression (CPS < 10 or ≥ 10). (CPS refers to combined positive score, which is the sum

of PD-L1 expression in tumor cells and tumor-infiltrating lymphocytes). The primary endpoint of the study is the OS in the intention-to-treat (ITT) population or in the PD-L1 positive subjects (CPS ≥ 5). OS is defined as the time from randomization to death for any cause. Subjects who are still alive at the time of analysis are censored at the last date of survival.

In this study, clinical tumor imaging evaluation will be performed according to RECIST v1.1. During the study, tumor imaging evaluation will be performed Q6W (± 7 days) initially, then once Q12W (± 7 days) after 48 weeks until PD, initiation of new anti-tumor therapy, withdrawal of ICF, loss to follow-up, death, or end of the study (whichever occurs first).

An interim analysis will be performed during the study and the results and report will be submitted to the iDMC. The iDMC will determine the treatment efficacy based on estimated effective boundaries and provide advices to the sponsor on whether the study can be continued. The iDMC charter will be finalized and approved by the iDMC and sponsor prior to the interim analysis. The responsibilities of iDMC members and related procedures will be defined in the iDMC charter.

After the study treatment is discontinued and completed, safety follow-up and overall survival follow-up will be performed Q60D.

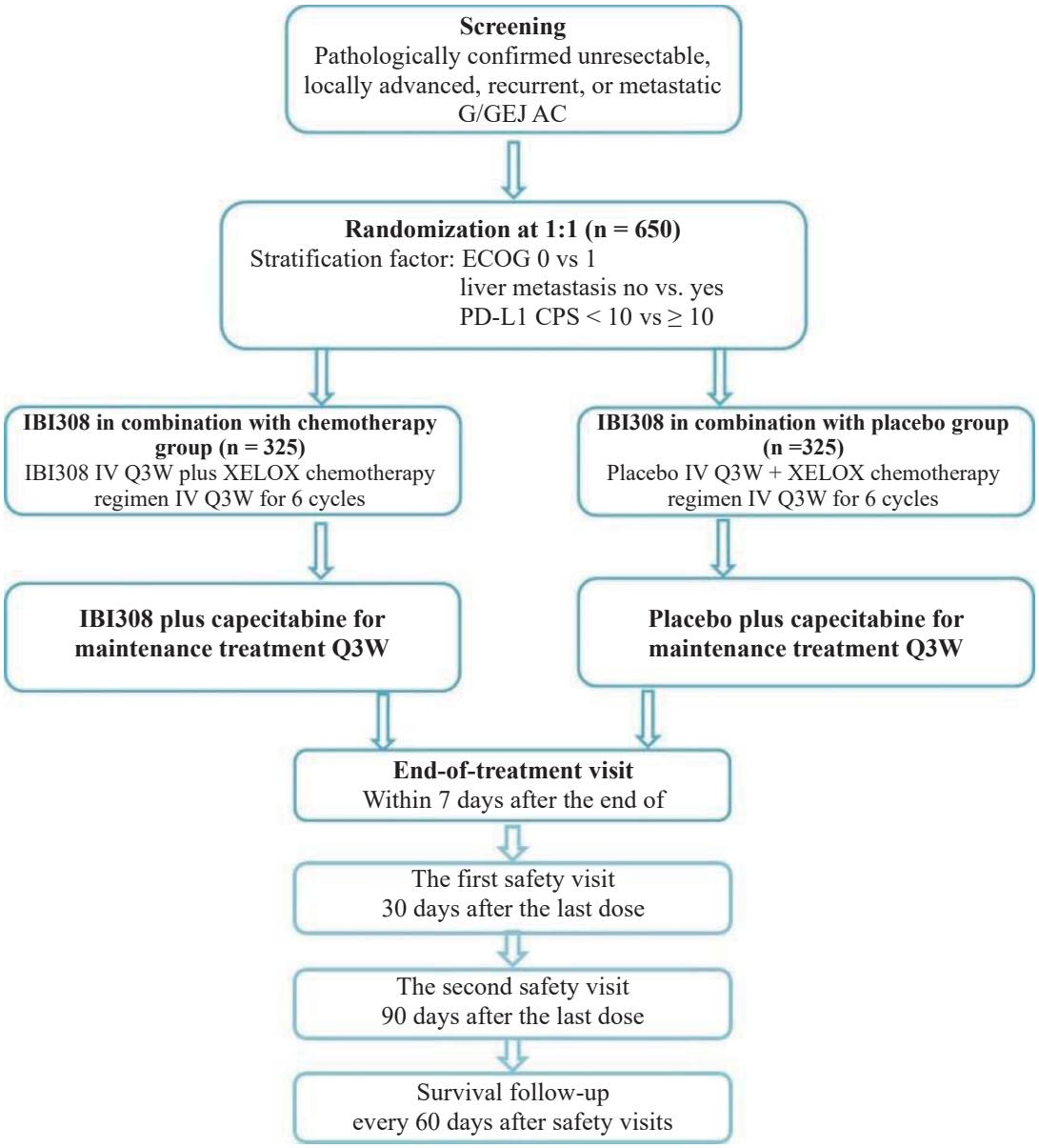

Figure 1. Schematic of CIBI308E301 study design and administration

3.2 Design Principles

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

Anti-PD-1 mAb has shown its unique efficacy for the treatment of a variety of tumors and some efficacy for the treatment of advanced gastrointestinal tract tumors after multi-line treatment as well. Patients and clinicians are thus looking forward to having its efficacy demonstrated in gastrointestinal (GI) tumors. However, considering that there is no clear data on PD-L1 expression and exact efficacy when being in combination with chemotherapy in the GC population in mainland China, this study will use a 1:1 central randomization ratio, and also control the dropout rate by blinding. PD-1 antibodies have been used in clinical practice for

many years. Common adverse reactions are similar among different tumors, and the incidence of SAEs is low. Therefore, blinding will not pose challenges on conducting the study, and observing and managing the toxicities.

3.2.2 Rationale for a CPS ≥ 5 as the defined PD-L1 positivity

In current studies of PD-1 monoclonal antibodies, immunohistochemistry is commonly used to detect the level of PD-L1 expression. However, the threshold for positivity varies because the detection reagents used are different. For example, 22C3 is used to identify PD-L1-positive patients for treatment with pembrolizumab, with tumor proportion score (TPS) ≥ 1% or 50% as the threshold for PD-L1 positivity in lung cancer. The relationship between PD-L1 expression and treatment efficacy in lung cancer has been confirmed in prospective clinical studies. The threshold for PD-L1 positivity in GC has not been uniformed yet.

The advanced gastric cancer clinical study KEYNOTE-059 included patients with a combined positive score (CPS) ⩾ 1, and both KEYNOTE-061 and KEYNOTE-062 suggested that patients with CPS ⩾ 10 appeared to benefit from anti-PD-1 monoclonal antibody; while CPS ⩾ 5 was used as the primary study endpoint in another CheckMate-649 study for advanced gastric cancer, and it was confirmed that the PD-L1-positive population benefited more than the whole population.

Taking into account the published clinical data in gastric cancer studies and the distribution of PD-L1 expression levels in the Chinese population, we sought to explore the efficacy of the combination of chemotherapy with cidilizumab in these patients with PD-L1 expression CPS ⩾ 5 in advanced gastric cancer, and this study defined PD-L1CPS ⩾ 5 as the positive cut-off value.

3.2.3 Rationale for oxaliplatin and capecitabine as the first-line chemotherapy

A platinum compound in combination with fluorouracil forms the backbone of first-line chemotherapy regimen of locally advanced or metastatic GC. The REAL-2 study showed the non-inferiority of oxaliplatin to cisplatin and capecitabine to 5-fluorouracil. The EOX group (epirubicin + oxaliplatin + capecitabine) had longest OS of 11.2 months. Also, oxaliplatin has less renal toxicities, no requirement for hydration, and lower emetic potential compared to cisplatin; capecitabine has no requirement for continuous intravenous (IV) infusion and is administered orally, which enable better quality of life for patients at home. Thus, XELOX is recognized as an effective and safe regimen as both a first-line treatment and an adjuvant therapy.

3.3 Independent Data Monitoring Committee

The iDMC is established to review an interim analysis of the primary efficacy endpoint (OS) and safety endpoints. The data analysis report required by iDMC will be provided by an independent statistician. The iDMC will determine the treatment efficacy based on estimated effective boundaries and provide advices to the sponsor on whether the study can be continued. The personnel composition, responsibilities, and procedures of the IDMC are detailed in the IDMC regulations.

3.4 Definition of Study Completion

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

The study is completed when the last subject has completed the survival follow-up, or been treated for 24 months and completed the safety follow-up (whichever occurs first).

3.5 Criteria for Study Discontinuation

This study may be interrupted or discontinued prematurely if there are sufficient grounds to do so. The party interrupting or discontinuing the study should provide written notification to the subjects, investigators, funding agencies, and regulatory authorities, and document the reasons for interruption or discontinuation. If the study is discontinued prematurely or interrupted, the principal investigator must notify the subjects, Ethics Committee (EC), and sponsor immediately, and provide the reasons for discontinuation or interruption. Where applicable, the investigator should contact the subjects and inform them of the changes of the visit schedule.

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

- Unexpected, significant, or unacceptable risks to the subject are identified;
- The study should be discontinued or interrupted based on the efficacy rationale;
- The subjects are unable to meet protocol requirements for compliance;
- The data are incomplete and/or insufficient for evaluation;
- The primary endpoint has been met.

The study may be resumed only if the safety, protocol compliance, and data quality issues have been addressed, and the requirements of the sponsor, EC and/or National Medical Products Administration are met.

4 STUDY POPULATION

4.1 Inclusion Criteria

1. Histopathologically confirmed unresectable, locally advanced, recurrent, or metastatic G/GEJ AC (including signet ring cell carcinoma, mucinous adenocarcinoma, and hepatoid adenocarcinoma).
2. Ages of ≥ 18 years old.
3. ECOG PS score of 0 or 1.
4. Time from the completion of previous (neo) adjuvant chemotherapy/adjuvant radiotherapy to disease recurrence > 6 months.
5. Time from the completion of palliative therapy for local lesions (non-target lesions) to randomization > 2 weeks.
6. Having at least one measurable or evaluable lesion according to RECIST v1.1.
7. Can provide archived (within 6 months prior to screening and signing of ICF) or fresh tissues for PD-L1 expression analysis with obtainable results.
8. Sufficient organ and bone marrow functions, as defined below:
    1) Routine blood test: absolute neutrophil count (ANC) ≥ 1.5×10^9/L, platelets (PLTs) ≥ 100×10^9/L, and hemoglobin (HGB) ≥ 9.0 g/dL. G-CSF, GM-CSF, Meg-CSF, TPO, EPO, red blood cell (RBC), and platelet transfusion should not be performed within 7 days prior to the test.
    2) Hepatic function: total bilirubin (TBIL) ≤ 1.5 × upper limit of normal (ULN), alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ≤ 2.5 × ULN in patients without liver metastasis. Patients with liver metastasis: TBIL ≤ 1.5 × ULN; ALT and AST ≤ 5 × ULN.
    3) Renal function: glomerular filtration rate (GFR) ≥ 60 mL/min (calculated using the CKD-EPI formula detailed in Appendix 4).
    4) Adequate coagulation function, defined as international normalized ratio (INR) ≤ 1.5 or prothrombin time (PT) ≤ 1.5 × ULN; if the patient is receiving anticoagulant therapy, as long as the PT is within the proposed range for anticoagulants;
    5) Urinalysis: urine protein < 2+; if urine protein ≥ 2+, 24-h urine protein should be < 1.0 g.
9. Estimated survival ≥ 12 weeks.

10. Patients (female patients of childbearing age or male patients whose partners are of childbearing age) must take effective contraceptive measures during the entire course of the treatment and 6 months after the treatment (see Section 4.3).
11. Patients who have signed ICFs, and are able to comply with the follow-up visits and relevant procedures required in the protocol.

4.2 Exclusion Criteria

1. Known sign of active hemorrhage in lesions.
2. Cardia or pylorus obstruction affecting eating and gastric emptying, or causing difficulty in swallowing tablets.
3. Diagnosed with HER2-positive G/GEJ AC.
4. Previous systemic therapy of advanced or metastatic G/GEJ AC.
5. An accumulated cisplatin dose ≥ 300 mg/m^2 in previous neo (adjuvant) treatment.
6. Peripheral neurotoxicity has not resolved to grade 1 after previous treatment.
7. Known dihydropyrimidine dehydrogenase (DPD) enzyme deficiency (or prior grade 3 or higher mucosal toxicities in fluorouracil treatment).
8. Known allergic reactions (prior grade 3 or higher allergic reactions) to ingredients of any monoclonal antibody or chemotherapeutic agents (capecitabine and/or oxaliplatin).
9. Prior exposure to any anti-PD-1 or anti-PD-L1, anti-PD-L2, anti-CD137, anti-CTLA-4 antibody, or any other antibody or drug that specifically targets T-cell costimulation or immune checkpoint pathways.
10. Enrolled in another interventional clinical study, unless only involved in an observational study (non-interventional) or in the follow-up phase of an interventional study.
11. Received systemic treatment with Chinese herbal medicines for cancer indications or immunomodulators (including thymosins, interferons, and interleukins) within 2 weeks prior to the first dose of study drug;
12. Received immunosuppressive drugs within 4 weeks prior to the first dose of study drug, excluding local glucocorticoids administered by nasal, inhaled, or other topical routes, or systemic glucocorticoids of physiological doses (no more than 10 mg/day of prednisone or equivalents), or glucocorticoids to prevent allergies to contrast media.
13. Received a live attenuated vaccine within 4 weeks prior to the first dose of study drug, or planned to receive this vaccine during the study period.

Note: Seasonal inactivated influenza virus vaccines within 4 weeks prior to the first dose of investigational drug are permitted, but live attenuated influenza vaccines are not;

14. Received major surgery (craniotomy, thoracotomy, or laparotomy) within 4 weeks prior to the first dose of study drug, or will receive major surgery during the course of the trial; received exploratory laparoscopy within 2 weeks before the first dose of study drug.
15. Anti-tumor therapy-related toxicity (excluding alopecia, events that are not clinically significant, or asymptomatic laboratory abnormalities) that has not yet resolved to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) v5.0 grade 0 or 1 prior to the first dose of study drug.
16. Known symptomatic central nervous system (CNS) metastasis and/or carcinomatous meningitis. Patients with brain metastases received prior treatment are eligible if the diseases are stable (no imaging evidence of progression for at least 4 weeks prior to the first dose of study drug, and no evidence of new brain metastasis or enlargement of the primary brain metastatic lesion upon repeated imaging), and corticosteroids are not required for at least 14 days prior to the first dose of study drug. This exception excludes carcinomatous meningitis, regardless of whether the disease is clinically stable.
17. Ascites that can be detected in physical examination, ascites that has been treated with prior procedures, or currently requires treatment. Asymptomatic patients with small amount of ascitic fluid demonstrated by imaging are eligible.
18. Moderate-sized bilateral pleural effusion or large-sized unilateral pleural effusion, or pleural effusion that has caused respiratory dysfunction requiring drainage.
19. Patients with bone metastasis at risk of paraplegia.
20. Known or suspected autoimmune diseases or a history of these diseases within the past 2 years (subjects with vitiligo, psoriasis, alopecia, or Grave's disease who do not require systemic treatment within 2 years, or those with hypothyrodism only requiring thyroid hormone replacement, or those with type I diabetes mellitus only requiring insulin replacement treatment can be enrolled).
21. Known history of primary immunodeficiency diseases.
22. Known to have active pulmonary tuberculosis.
23. Known history of allotransplantation or allogeneic hematopoietic stem cell transplantation.
24. Known history of human immunodeficiency virus (testing positive for HIV).
25. Active or poorly clinically controlled serious infections.

26. Symptomatic congestive cardiac failure (NYHA Classes II–IV) or symptomatic or poorly controlled arrhythmia.
27. Uncontrolled hypertension (systolic blood pressure ≥ 160 mmHg or diastolic blood pressure ≥ 100 mmHg) despite standard treatment.
28. Any arterial thromboembolic event occurs within 6 months prior to enrollment, including myocardial infarction, unstable angina, cerebrovascular accident, or transient cerebral ischemic attack.
29. Significant malnutrition (gain loss by 5% within 1 month, gain loss by > 15% within 3 months, or food intake decrease by 1/2 or above within 1 week before signing of ICF), excluding those with 4 weeks and above of malnutrition correction before the first dose of study drug.
30. History of deep venous thrombosis, pulmonary embolism, or other serious thromboembolic events within 3 months prior to enrollment (implantable port or catheter-related thrombosis, or superficial venous thrombosis are not considered as "serious" thromboembolisms).
31. Uncontrolled metabolic disorders, non-malignant organ or systemic diseases, or cancer-related secondary diseases that may lead to higher medical risks and/or survival evaluation uncertainties.
32. Hepatic encephalopathy, hepatorenal syndrome, or cirrhosis with Child-Pugh grade B or C.
33. Tumor-related bowel obstruction (within 3 months before signing of ICF) or history of the following diseases: inflammatory bowel disease or extensive bowel resection (partial colectomy or extensive small bowel resection accompanied with chronic diarrhea), Crohn's disease, and ulcerative colitis.
34. Known acute or chronic active hepatitis B (positive HBsAg and HBV DNA viral load ≥ 200 IU/mL or ≥ 10^3 copies/mL), or acute or chronic active hepatitis C (positive anti-HCV antibody and positive HCV RNA).
35. Known infections with active syphilis requiring treatment.
36. History of GI perforation and/or fistula within 6 months prior to the enrollment, excluding resection of primary gastric cancer lesion due to perforation in gastric cancer cases.
37. Interstitial lung disease requiring corticosteroids.
38. History of other primary malignant tumors, excluding:

- Malignant tumors that have achieved complete response (CR) for at least 2 years prior to enrollment and will require no treatment during the study;

- Adequately treated nonmelanoma skin cancer or lentigo maligna with no signs of disease recurrence;
- Adequately treated carcinoma in situ with no signs of recurrence.

39. Pregnant or breastfeeding female patients.
40. Acute or chronic diseases, psychiatric disorders, or laboratory abnormalities that may lead to the following consequences: increased study drug-related risks, or interference with interpreting study results, and considered ineligible for participating in the study by the investigator.

4.3 Restrictions During the Study

For women of childbearing age who are sexually active with male partners who have not undergone sterilization, and men who have not undergone sterilization and are sexually active with women of childbearing age, they and their partners must use one of the acceptable methods of contraception listed in **Table 2** from screening to 180 days after the last dose, and discuss with a responsible physician about the discontinuation of contraception after this time point. Periodic abstinence, calendar-based method, and withdrawal method are not the acceptable forms of contraception. Women of childbearing age is defined as females who have experienced menarche, have not undergone surgical sterilization (bilateral tubal ligation, bilateral salpingectomy, or panhysterectomy), and are not postmenopausal.

Table 2. Effective methods of contraception (one of the followings must be used)

Barrier methods	Intrauterine devices (IUDs)	Hormonal methods
Male condom with spermicide	Copper-T IUD	Implant
Cervical cap with spermicide	Progesterone-T IUD[a]	Hormonal contraceptive injection
Diaphragm with spermicide	Levonorgestrel-releasing intrauterine system (e.g. Mirena®)[a]	Combined oral contraceptive pill Low-dose oral contraceptive pill Contraceptive patch

[a]Also considered as a hormonal method

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

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

menorrhea > 1 year, or surgical sterilization (bilateral ovariectomy or hysterectomy), are considered menopausal.

4.4 Criteria for Discontinuation/Withdrawal

4.4.1 Treatment discontinuation

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

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

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

- Treatment discontinuation required by the subject or his/her legal representative;
- Occurrence of an AE that requires discontinuation due to protocol-specified reasons (refer to Section 5.2).
- Development of another malignant tumor that requires active treatment.
- Concurrent disease that interferes further treatment.
- Treatment discontinuation of subjects determined by the investigator.
- Positive serum pregnancy test results, with the pregnancy clearly confirmed.
- Poor compliance of the subject.
- Unnecessary risks of investigational drug continuation to the subject determined by the investigator and/or sponsor according to subject's disease status and condition.
- Completion of 24-months treatment with the investigational drug.

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

4.4.2 Treatment interruption

Treatment may be interrupted, as determined by the investigator, for subjects who have achieved significant tumor response after treatment and for whom radical surgical resection is feasible. According to the clinical practice, the surgery will be performed 4 weeks after the interruption.

Treatment will be resumed depending on the subject's status. In order to provide the best treatment for the subject, a multidisciplinary discussion covering oncology, general surgery, and medical imageology, etc. is required prior to the surgery to determine the possibility of recovery by radical surgery. If the radical surgery is found infeasible during the surgery, palliative resection for GC will not be performed.

If the purpose of radical surgery can be achieved based on intra-operative status, surgery process, and post-operative pathology, the completion of post-operative adjuvant treatment will mean the discontinuation of the study.

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

4.4.3 Subject withdrawal

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

The investigator has the right to request the withdrawal of a subject from the study for the followings:

- Poor compliance of the subject;
- A clinical AE, laboratory abnormality, or other medical condition indicating that the continuation is not in the best interest of the subject;
- An exclusion criterion (new or previously unnoticed) is met and continuation of the study is not allowed.

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

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

4.4.4 Loss to follow-up

A subject is considered lost to follow-up when he/she fails to return to the study site for a scheduled visit for 2 consecutive times and the site staff is unable to contact with the subject.

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

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

The subject is considered lost to follow-up and to withdraw from the study if the subject is still out of contact.

5 STUDY DRUGS AND OTHER TREATMENTS

The investigational drugs include IBI308, placebo, oxaliplatin, and capecitabine. The first dose of investigational drugs should be started on the day of randomization (day 1 of cycle 1), and no later than 48 h after the randomization. The sponsor should be notified if the first dose is not administered after 48 h. Every effort should be made to start the study treatment on the day of randomization. As determined by the investigator and for administrative reasons, treatment can be delayed for up to 1 week if the administration day in the rest treatment cycles is a holiday.

Table 3. Dosage and administration

Investigational drug	Dose	Frequency	Route of administration	Treatment cycle	Usage
IBI308[1]	Weight < 60 kg: 3 mg/kg	Q3W	Intravenous infusion	Q21D, administered on day 1	Test group
	Weight ≥ 60 kg: 200 mg	Q3W	Intravenous infusion	Q21D, administered on day 1	Test group
Placebo[1]	Weight < 60 kg: 3 mg/kg	Q3W	Intravenous infusion	Q21D, administered on day 1	Control group
	Weight ≥ 60 kg: 200 mg	Q3W	Intravenous infusion	Q21D, administered on day 1	Control group
Oxaliplatin[2]	130 mg/m^2	Q3W	Intravenous infusion	Q21D, administered on day 1, 6 consecutive cycles	Test/Control group
Capecitabine[2]	1000 mg/m^2	Q3W	Orally administered, 30 min after a meal	Q21D, 14 consecutive days	Test/Control group

1. IBI308/placebo should be infused prior to the chemotherapy. For subjects < 60 kg, every dose of IBI308/placebo should be calculated based on the actual weight. The protocol allows for a deviation of ± 5% of the total infusion dose each time.

2. If the weight fluctuation is less than 10% compared to baseline (the day of the first dose), use the baseline weight to calculate the body surface area, and then calculate the chemotherapy dose based on the body surface area. Otherwise, use the actual weight within 3 days before the scheduled administration day to calculate the chemotherapy dose. For convenience, the protocol allows for a deviation of ± 5% of the total infusion dose each time.

All the drugs in **Table 3** are provided by the sponsor, and the product/batch numbers of all procured drugs are accessible. The study sites are responsible for recording the batch numbers, manufacturers, and expiry dates.

5.1 Treatment Regimens of Investigational Drugs

5.1.1 IBI308

The main active ingredient of IBI308 is the recombinant fully human anti-PD-1 monoclonal antibody. The concentration is 10 mg/mL. IBI308 is a clear, colorless liquid and is free of foreign matter, floccules, and precipitates. The excipients include 140 mmol/L mannitol, 25 mmol/L histidine, 20 mmol/L dihydrate sodium citrate, 50 mmol/L sodium chloride, 0.02 mmol/L disodium edetate (ethylenediaminetetraacetic acid disodium salt), and 0.2 mg/mL polysorbate 80, pH 6.0.

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

The preparation and infusion of IBI308 are as follows:

1 Withdraw the required dose of IBI308 (weight < 60 kg: 3 mg/kg IV Q3W; weight ≥ 60 kg: 200 mg IV Q3W), and transfer it into an IV infusion bag containing 9 mg/mL (0.9%) sterile sodium chloride solution. The final concentration of the solution should be between 1.5–2 mg/mL. Record the time that the solution is prepared.

2 The IV bag is gently inverted to mix the solution, ensuring the uniformity of the contents. No vigorous shaking is allowed to avoid foam. If large amount of foam forms, stand the IV bag until the foam disappears.

3 Administer with a 0.2~5.0 μm in-line filter (suggested infusion time is 30–60 min). Document the start and stop time of infusion.

Note: Before preparation, make sure that the IBI308 injection is clear without any quality issue

such as turbidity or precipitation. Make sure that the time from withdrawing IBI308 from the first vial to the end of infusion is no more than 24 h (the prepared solution should be stored at 2–8 °C in the refrigerator). Avoid mixing with other drugs. Do not administer as an IV push.

5.1.2 Other investigational drugs

5.1.2.1 Placebo

All the personnel and patients at the study sites and the sponsor are blinded. Placebo will be administered according to the guidelines for IBI308 administration in Section 5.1.1.

5.1.2.2 Oxaliplatin

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

Oxaliplatin is lyophilized powder in a 50 mg vial. The preparation is completed with 5% glucose solution (do not prepare or dilute the product with saline solution). Add 10 mL of 5% glucose solution into the 50 mg vial to adjust the concentration of oxaliplatin to 5.0 mg/mL. Withdraw the prepared solution from the vial and immediately dilute with 250–500 mL of 5% glucose solution to 0.2 mg/mL or higher (normally, the physicochemical properties of the solution remain stable at 2–8 °C for 24 h). It is recommended oxaliplatin is infused into peripheral veins or central veins within 2–6 h (if acute laryngospasm occurs when administration of oxaliplatin is completed within 2 h, extend the infusion duration to 6 h for subsequent administration).

Special precautions:

- Do not use injection equipment containing aluminum.
- Do not use without dilution.
- Do not prepare or dilute the product with saline solution.
- Do not mix or administer simultaneously with other drugs through the same infusion line. The infusion line should be flushed after the oxaliplatin infusion is completed.
- The infusion line should be flushed prior to oxaliplatin infusion.
- Only the recommended solvent (5% dextrose solution) can be used.
- Do not use the prepared solution if any precipitation appears, and the prepared solution should be destroyed according to regulations regarding the disposal of hazardous articles.

5.1.2.3 Capecitabine

Capecitabine is provided by the sponsor after re-labeling. The study site should store and

administer the drug according to the approved prescribing information. The following information is for reference.

Capecitabine is provided as a 500 mg tablet. The initial dose is 1000 mg/m^2 bid PO × 14d Q3W. Take orally within 30 min after breakfast and dinner (12-h interval), respectively, with 200 mL of water (not juice). The dose will be based on the subject's body surface area at baseline (mg/m^2), but the maximum dose should not exceed 4000 mg/day. Missed doses or under-doses of capecitabine should not be additionally administered. Subjects who interrupt the treatment due to adverse reactions can resume taking this drug when the adverse reactions resolve to grade 0–1. Do not take the missed doses.

5.2 Dose Adjustments

5.2.1 General principles

- The subject's hematologic, hepatic, and renal function must meet the requirements for administration of investigational drug prior to day 1 of each cycle. All the toxicities must resolve to NCI CTCAE v5.0 grade 0–1 or baseline levels (excluding alopecia, grade 2 fatigue, grade 2 immune-related endocrine AEs, and grade 2 anemia).
- If the treatment is delayed due to oxaliplatin- or capecitabine-related toxicities, IBI308 administration should also be delayed until the toxicities resolve to the levels acceptable for administration, synchronized with chemotherapy; if IBI308 administration is delayed due to immune-related toxicities, the investigator should discuss with the sponsor to determine whether oxaliplatin and capecitabine can be administered as scheduled.
- IBI308 treatment is allowed to be interrupted for up to 12 weeks. It can be delayed due to toxicities for up to 6 weeks.
- All the dose adjustments should be documented, including the reasons and actions taken.

5.2.2 IBI308 administration adjustments

Dose adjustments of IBI308 are not permitted throughout the study. Refer to **Table 4** for IBI308 administration adjustments (only for IBI308-related AEs determined by the investigator). If the administration delay occurs in a 3-week cycle of treatment for IBI308, all the subsequent administration should be delayed to ensure that a dosing interval of 21 ± 3 days.

IBI308 administration under special circumstances:

- An administration delay is not required for grade 3 lymphocytopenia.
- An administration delay is not required for any grade 3 drug-related amylase or lipase

abnormalities that are not related to symptoms or clinical manifestations of pancreatitis.

- Administration can be resumed for grade 3–4 drug-related endocrine AEs, such as adrenocortical insufficiency, hypophysitis, hyperthyroidism, hypothyroidism, and type I diabetes, that are adequately controlled with physiologic hormone replacement therapy (corticosteroids or thyroid hormone).

Table 4. IBI308 administration adjustments

Drug-related toxicities	Severity level	Management
1. Skin toxicities		
Rash/inflammatory dermatitis	Grade 1	Continue
	Grade 2	Consider interruption
	Grade 3	Interrupt and consult a dermatologist to decide whether to resume the treatment
	Grade 4	Interrupt and consult a dermatologist to decide whether to resume the treatment after resolving and prednisone requirement ≤ 10 mg/day
Bullous dermatosis	Grade 1	Continue
	Grade 2–3	Interrupt and consult a dermatologist to decide whether to resume the treatment
	Grade 4	Permanent discontinuation
Serious skin adverse reactions: SJS, TEN, AGEP, and DRESS	Grade 1 (not applicable)	/
	Grade 2	Interrupt and monitor
	Grade 3	Interrupt and consult a dermatologist
	Grade 4	Permanent discontinuation
2. GI toxicities		
Colitis	Grade 1	Continue, or interrupt until resolve to grades 0–1
	Grade 2	Interrupt until resolve to grade 1
	Grade 3	First occurrence: interrupt until resolve to grade 1 Second occurrence: permanently discontinue
	Grade 4	Permanent discontinuation
Hepatitis	Grade 1	Continue and monitor
	Grade 2	Interrupt, resume after resolving to grades 0–1 and prednisone requirement ≤ 10 mg/day
	Grade 3–4	Permanent discontinuation
3. Pulmonary toxicities		
Pneumonia	Grade 1	Interrupt if deterioration confirmed by imaging
	Grade 2	Interrupt until resolve to grade 1 or below
	Grade 3–4	Permanent discontinuation

Drug-related toxicities	Severity level	Management
4. Endocrine toxicities		
Primary hypothyroidism	Grade 1	Continue and monitor closely
	Grade 2	Continue and monitor closely
	Grade 3–4	Interrupt until resolve to baseline level
Hyperthyroidism	Grade 1	Continue and monitor closely
	Grade 2	Continue, control the symptoms, and monitor closely
	Grade 3–4	Interrupt until resolve to grades 0–2
Primary adrenocortical insufficiency	Grade 1–2	Consider interruption until the subject is stable under hormone replacement therapy
	Grade 3–4	Interrupt until the subject is stable under hormone replacement therapy
Hypophysitis	Grade 1–2	Consider interruption until the subject is stable under hormone replacement therapy
	Grade 3–4	Interrupt until the subject is stable under hormone replacement therapy
Diabetes	Grade 1	Continue and monitor closely
	Grade 2	Continue, control the blood glucose, and monitor closely
	Grade 3–4	Interrupt until the blood glucose is controlled and resolve to grades 0–2
5. Musculoskeletal toxicities		
Inflammatory arthritis	Grade 1	Continue
	Grade 2	Interrupt until the symptoms are controlled and prednisone requirement is ≤ 10 mg/day
	Grade 3–4	Interrupt, consult a rheumatologist to decide whether to resume the treatment after resolving to grades 0–1
Myositis	Grade 1	Continue
	Grade 2	Interrupt until the symptoms are controlled and CK is normal
	Grade 3–4	Interrupt until resolve to grades 0–1 without immunosuppression; permanently discontinue if there are signs of myocardial involvement
Polymyalgia rheumatica-like syndrome	Grade 1	Continue
	Grade 2	Consider interruption until symptoms are controlled
	Grade 3–4	Interrupt, consult a rheumatologist to decide whether to resume the treatment after resolving to grades 0–1

Drug-related toxicities	Severity level	Management
6. Nephrotoxicities		
Nephritis	Grade 1	Consider interruption, make judgment based on other possible causes and the baseline renal function
	Grade 2	Interruption
	Grade 3	Permanent discontinuation
	Grade 4	Consult a nephrologist
Symptomatic nephritis: follow-up	Grade 1	Resume routine creatinine monitoring if resolve to baseline values
	Grade 2	If resolve to grade 1, taper corticosteroid dose for at least 3 weeks
	Grade 3–4	If resolve to grade 1, taper corticosteroid dose for at least 4 weeks
7. Neurotoxicities		
Myasthenia gravis	Grade 1 (not applicable)	/
	Grade 2	Interrupt until resolve
	Grade 3–4	Permanent discontinuation
Guillain-Barré syndrome	Grade 1 (not applicable)	/
	Grade 2–4	Permanent discontinuation
Peripheral neurotoxicity	Grade 1	Lower the criteria for interruption and monitor the symptoms for 1 week; closely monitor the symptoms if continuing the treatment
	Grade 2	Interrupt until resolve to grade 1
	Grade 3–4	Permanent discontinuation
Autonomic neuropathy	Grade 1	Lower the criteria for interruption and monitor the symptoms for 1 week; closely monitor the symptoms if continuing the treatment
	Grade 2	Interrupt until resolve to grade 1
	Grade 3–4	Permanent discontinuation
Aseptic meningitis	Grade 1–4	Interruption
Encephalitis	Grade 1–4	Interruption
Transverse myelitis	Grade 1–4	Permanent discontinuation
8. Hematotoxicities		
Autoimmune hemolytic anemia	Grade 1	Continue and monitor closely
	Grade 2	Interrupt and consider permanently discontinuing
	Grade 3–4	Permanent discontinuation
Acquired thrombotic thrombocytopenic purpura	Grade 1–4	Interruption
Hemolytic uremic syndrome	Grade 1–2	Continue and monitor closely

Drug-related toxicities	Severity level	Management
Aplastic anemia	Grade 3–4	Permanent discontinuation
	Grade 1–2	Interrupt, treat with growth factors, and monitor closely
	Grade 3–4	Interrupt, treat with growth factors, and monitor daily
Lymphocytopenia	Grade 1	Continue
	Grade 2–3	Continue and monitor the count of whole blood cells and CMV weekly
	Grade 4	Interruption
Immune thrombocytopenia	Grade 1	Continue and monitor closely
	Grade 2–4	Interrupt, resume the treatment after resolving to grade 1
Acquired hemophilia	Grade 1–2	Interruption
	Grade 3–4	Permanent discontinuation
9. Cardiovascular toxicities		
Myocarditis, pericarditis, arrhythmia, ventricular insufficiency with heart failure and vasculitis	Grade 1	Interruption
	Grade 2–4	Permanent discontinuation
Venous thromboembolism	Grade 1–3	Continue
	Grade 4	Permanent discontinuation
10. Ocular toxicities		
Uveitis/iritis	Grade 1	Continue
	Grade 2	Interrupt and consult an ophthalmologist
	Grade 3–4	Permanent discontinuation
Episcleritis	Grade 1	Continue
	Grade 2	Interrupt and consult an ophthalmologist
	Grade 3–4	Permanent discontinuation
Blepharitis	No grade available	Continue, unless the symptoms are persistent and serious

SJS: Stevens-Johnson syndrome; TEN: toxic epidermal necrolysis; AGEP: acute generalized exanthematous pustulosis; DRESS: drug rash with eosinophilia and systemic symptoms

IBI308 is allowed to be interrupted for up to 12 weeks. If the symptoms do not resolve within 12 weeks and treatment cannot be resumed, the subject must permanently discontinue IBI308 treatment and enter the follow-up phase of the study. except for the following two cases:

- IBI308 interruption > 12 weeks due to glucocorticoid reduction for immune-related adverse events (irAEs). Consult the sponsor's medical manager prior to resuming IBI308. Tumor imaging evaluation for efficacy shall not be affected by treatment interruption and should be performed as scheduled.

- IBI308 interruption > 12 weeks due to AEs possibly-unrelated or unrelated to IBI308. Consult the sponsor's medical manager prior to resuming IBI308. Tumor imaging evaluation for efficacy shall not be affected by treatment interruption and should be performed as scheduled.

5.2.3 Management of IBI308-related infusion reactions

IBI308 may cause severe or life-threatening infusion reactions, including severe hypersensitivity reactions or allergic reactions. Signs and symptoms usually occur during or after drug infusion and usually resolve within 24 h after the infusion completion. Refer to **Table 5** for the guidelines for management of IBI308-related infusion reactions.

Table 5. Guidelines for management of IBI308-related infusion reactions

NCI CTCAE grade	Treatment	Premedications for subsequent infusions
Grade 1 Mild reaction; infusion interruption not indicated; intervention not indicated	According to subject's medical indications, monitor the vital signs closely until the subject is stable as determined by the investigator.	None
Grade 2 Treatment or infusion interruption required, but responds promptly to timely symptomatic treatment (e.g. antihistamines, nonsteroidal anti-inflammatory drugs [NSAIDS], anesthetics, IV fluids); prophylactic medications indicated for ≤ 24 h	**Stop the infusion and monitor symptoms.** Other appropriate treatments include but are not limited to: IV fluids Antihistamines NSAIDS Acetaminophen Anesthetics According to subject's medical indications, monitor the vital signs closely until the subject is stable as determined by the investigator. If symptoms resolve within 1 h after interrupting the infusion, then the infusion will be resumed at 50% of the original infusion rate (e.g. from 100 mL/hr to 50 mL/hr). Otherwise, interrupt the treatment until symptoms resolve. Premedications should be given for subsequent infusions.	The following premedications are recommended within 1.5 h (± 30 min) prior to IBI308 infusion: Diphenhydramine 50 mg PO (or equivalent antihistamines). Acetaminophen 500–1000 mg PO (or antipyretics at equivalent effective dose).

NCI CTCAE grade	Treatment	Premedications for subsequent infusions
	If grade 2 toxicities occur despite of adequate premedications, the investigational drug should be permanently discontinued.	
Grade 3 or 4 Grade 3: Prolonged (i.e. not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae (e.g., renal impairment, pulmonary infiltration) Grade 4: Life threatening; pressors or ventilatory support indicated	**Discontinue the infusion.** Other appropriate treatments include but are not limited to: Epinephrine** IV fluids Antihistamines NSAIDS Acetaminophen Anesthetics Oxygen Pressors Corticosteroids According to subject's medical indications, monitor the vital signs closely until the subject is stable as determined by the investigator. Hospitalization may be indicated. **Epinephrine should be used immediately for allergic reactions. **The investigational drug should be permanently discontinued.**	Not applicable
Appropriate first-aid equipment should be provided in the ward and physicians should be available at all times during the administration. For more information, refer to CTCAE v5.0 (http://ctep.cancer.gov).		

5.2.4 Dose adjustments of chemotherapy

5.2.4.1 Dose adjustments for chemotherapy-related hematotoxicities

Treatment for the next cycle can begin only if ANC is $\geq 1.5 \times 10^9$/L, PLT is $\geq 75 \times 10^9$/L, and Hb is ≥ 8.0 g/dL. Treatment can be delayed due to toxicities for up to 6 weeks.

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

Table 6. Dose adjustments of chemotherapeutics

	Initial dose	−1 dose level	–2 dose level
Oxaliplatin	130 mg/m^2	100 mg/m^2	75 mg/m^2
Capecitabine	1000 mg/m^2	750 mg/m^2	500 mg/m^2

Table 7. Dose adjustments of capecitabine

Body surface area (m^2)	Standard dose (1000 mg/m^2) bid			−1 dose (75%)			–2 dose (50%)		
	Total daily dose (mg)	Number of tablets (500 mg/tablet)		Total daily dose (mg)	Number of tablets (500 mg/tablet)		Total daily dose (mg)	Number of tablets (500 mg/tablet)	
		Morning	Evening		Morning	Evening		Morning	Evening
[1.0,1.24)	2000	2	2	1500	2	1	1000	1	1
[1.25,1.49)	2500	3	2	1500	2	1	1000	1	1
[1.50,1.74)	3000	3	3	2000	2	2	1500	2	1
[1.75,1.99)	3500	4	3	2500	3	2	1500	2	1
2.0–	4000	4	4	3000	3	3	2000	2	2

Note: When the capecitabine dose needs to be adjusted due to an AE, the adjustment should be based on the dose level at which this AE occurs.

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

Toxicity	First occurrence		Second occurrence	
	Capecitabine	Oxaliplatin	Capecitabine	Oxaliplatin
Grade 4 neutropenia	−1 dose level	−1 dose level	−1 dose level	–2 dose level
Grade 4 thrombocytopenia	–2 dose level	–2 dose level	Discontinue the treatment	Discontinue the treatment
Grade 3 thrombocytopenia	−1 dose level	−1 dose level	–2 dose level	–2 dose level
Grade 3 neutropenic fever (ANC < 1.0 with fever ≥ 38.5 °C)	−1 dose level	−1 dose level	–2 dose level	–2 dose level
Grade 4 neutropenic fever (ANC < 0.5 with fever ≥ 38.5 °C or life-threatening sepsis)	–2 dose level	–2 dose level	Discontinue the treatment	Discontinue the treatment

Note: The dose adjustments of chemotherapeutics in Table 8 are recommended ones. The specific adjustments should be determined by the investigator according to the clinical practice.

5.2.4.2 Recommended dose adjustments for chemotherapy-related non-hematotoxicities

- **Management of common capecitabine toxicities**

1) Grade 2/3 hand-foot syndrome

Provide symptomatic treatment (emollients are recommended). Refer to **Table 7** and **Table 11** for dose adjustments of capecitabine.

2) Grade 2/3 diarrhea, nausea, and emesis

Interrupt capecitabine and provide symptomatic treatment. Loperamide is recommended for the treatment of diarrhea. If the symptoms are well-controlled after 2 days, resume the treatment at 100% of the initial dose. If more time is required to control symptoms, adjust the dose according to **Table 7** and **Table 11**. Capecitabine can be resumed after diarrhea resolves to grade 0–1 and until 24 hours have passed since the last dose of loperamide.

When capecitabine-related nausea and emesis occur, adequate secondary prophylactic treatment should be provided. If AEs occur despite of prophylactic treatment, adjust the dose according to **Table 7** and **Table 11**.

3) Grade 2/3 stomatitis

If grade 2/3 stomatitis occurs, immediately interrupt capecitabine until symptoms resolve or toxicity reduces to grade 1. Provide symptomatic treatment. Adjust capecitabine dose according to **Table 7** and **Table 11**.

4) Cardiotoxicity

If capecitabine-related grade 2 cardiotoxicities occur, permanently discontinue capecitabine treatment.

- **Management of common oxaliplatin toxicities**

1) Grade 3/4 nausea and emesis

If grade 3/4 nausea or emesis occurs, prophylaxis and/or treatment with antiemetics should be provided immediately. Reduce the dose to 75% of the initial dose for subsequent treatment cycles.

2) Neurotoxicity

Neurotoxicities are dose-limiting toxicities of oxaliplatin, mainly manifested in peripheral sensory nerves as dysesthesia and/or paresthesia in distal extremities, with or without algospasm, which is often cold-induced. Symptoms usually alleviate in treatment intervals, but gradually worsen with the increase of treatment cycles. Dose adjustments or treatment discontinuation is dependent on the duration of symptoms, degree of pain, and/or severity of dysfunction.

Table 9. Grading scales and dose adjustments of oxaliplatin-related sensory neurotoxicities

Grade	Description of toxicities	Duration		Dose between two cycles
		1–7 days	> 7 days	
Grade 1	Numbness or dysesthesia, which resolves quickly, no dysfunction	Initial dose	Initial dose	Initial dose
Grade 2	Numbness or dysesthesia, which interferes slightly with extremity function but not self-care activities	Initial dose	Initial dose	−1 dose level
Grade 3	Numbness or dysesthesia with pain or interfered with extremity function, limiting self-care activities	First occurrence: −1 dose level Second occurrence: −2 dose levels	First occurrence: −1 dose level Second occurrence: −2 dose levels	Discontinue (continue capecitabine)
Grade 4	Numbness or dysesthesia, disabled extremity function, or being life-threatening	Discontinue (continue capecitabine)	Discontinue (continue capecitabine)	Discontinue (continue capecitabine)
Laryngopharyngeal dysesthesia			See below	

Note: The dose adjustments of chemotherapeutics in Table 9 are recommended ones. The specific adjustments should be determined by the investigator according to the clinical practice.

- **Laryngopharyngeal dysesthesia**

Laryngopharyngeal dysesthesia (LPD) is a rare adverse reaction manifested as a loss of sensation of breathing without any objective evidence of respiratory distress (laryngospasm, bronchospasm, or hypoxia). This neurotoxicity can be triggered or exacerbated by exposure to coldness, and should be distinguished from allergic reactions caused by oxaliplatin. If a subject develops LPD, oxygen saturation should be evaluated via a pulse oximeter and, if normal, reassurance. Benzodiazepines or other anxiolytics should be considered. Subject's status should be monitored closely until the event is resolved. Reduce the oxaliplatin infusion rate to 1/3 of the original infusion rate and monitor closely. Since this syndrome is possibly related to the infusion rate, the infusion time should be prolonged to 6 h for subsequent infusions. To minimize the risk of LPD, subjects should be instructed to avoid drinking cold liquid on the day of treatment.

3) Allergic reactions/hypersensitivity reactions

Similar to other platinum compounds, hypersensitivity reactions may occur after repeated doses of oxaliplatin (around 11%). Possible manifestations include bronchospasm, hypotension, and even hemolytic anemia. Premedication with corticosteroids and antihistamines may be useful to prevent the development of an allergic reaction for some subjects, but not always, especially for those with a history of allergy to oxaliplatin.

Table 10. Management of oxaliplatin-related allergic reactions/hypersensitivity reactions

Ring & Messmer Anaphylaxis Grading Scale/NCI CTC AE v5.0			
Grade	**Clinical manifestations**	**Clinical interventions for first occurrence**	**Recurrence after prophylaxis**
1	Transient fever or rash; drug fever < 38 °C;	Interventions not indicated, oxaliplatin infusion completed, bedside monitoring performed.	Permanent discontinuation
2	Non-life-threatening cardiovascular reactions (tachycardia and hypotension), GI dysfunction (nausea), and respiratory dysfunction	Interrupt oxaliplatin infusion, treat with diphenhydramine 25–50 mg and dexamethasone 10 mg IV. Once symptoms have resolved, resume oxaliplatin infusion at a slower rate (20 mL/h for 15 min, then at 40 mL/h for 15 min, and if no further symptoms develop, continue at the original rate until the infusion is completed).	Permanent discontinuation
3	Anaphylactic shock and life-threatening airway smooth muscle spasm	Interrupt oxaliplatin infusion, treat with diphenhydramine and dexamethasone IV (see above). Use epinephrine or bronchodilators if indicated. Permanently discontinue oxaliplatin infusion.	
4	Respiratory and/or cardiac arrest	Interrupt oxaliplatin infusion, rescue; permanently discontinue oxaliplatin infusion.	

Note: The dose adjustments of chemotherapeutics in Table 10 are recommended ones. The specific adjustments should be determined by the investigator according to the clinical practice.

The following premedications should be given prior to oxaliplatin administration for subjects with grade 1 or 2 acute allergic reactions related to oxaliplatin determined by evaluation:

- Give dexamethasone 20 mg PO or IV 6 and 12 h prior to oxaliplatin administration;
- Or dexamethasone 20 mg PO or IV, diphenhydramine 50 mg IV, and one of the followings: cimetidine 300 mg IV, ranitidine 50 mg IV, or famotidine 20 mg IV 30–60 min prior to oxaliplatin administration.

If oxaliplatin-related hypersensitivity reactions cannot be prevented with these prophylactic measures, then oxaliplatin should be discontinued. Capecitabine in combination with IBI308/placebo will be continued.

4) Interstitial lung disease

If there are unexplainable respiratory symptoms, such as dry cough, dyspnea, crackles, or pulmonary infiltration with radiographic evidence, treatment should be interrupted immediately until further respiratory examinations rule out interstitial pneumonia.

5) Abnormal hepatic function

If the abnormal hepatic function results or portal hypertension cannot be certainly attributed to hepatic metastasis, oxaliplatin-induced hepatic vascular anomalies may be a possible cause.

Table 11. Dose adjustments of capecitabine/oxaliplatin for non-hematotoxicities

	Grade 2	Grade 3	Grade 4
First occurrence	Interrupt until resolve to grade 0–1, then resume at the same dose level, provide prophylactic treatment if possible	Interrupt until resolve to grade 0–1, then resume at a −1 dose level, provide prophylactic treatment if possible	Discontinue, unless the investigator determines that it is for the best interest of the subject to resume at −2 dose level after the toxicity reduces to grade 0–1 (must be approved by the sponsor)
Second occurrence	Interrupt until resolve to grade 0–1, then resume at −1 dose level	Interrupt until resolve to grade 0–1, then resume at –2 dose level	
Third occurrence	Interrupt until resolve to grade 0–1, then resume at –2 dose level	Permanently discontinue	
Fourth occurrence	Permanently discontinue		

Note: The dose adjustments of chemotherapeutics in Table 11 are recommended ones. The specific adjustments should be determined by the investigator according to the clinical practice.

5.3 Principles of Managing Immune Checkpoint Inhibitor Toxicities

The mechanism of action of IBI308 is to stimulate T-cell activation and proliferation. The result is an immune hyperfunction leading to autoimmune disease involving multiple systems. Autoimmune AEs such as immune-related pneumonitis, diarrhea/enterocolitis, renal insufficiency, skin rash, hepatitis, endocrine disorders, and peripheral or central neuritis have been observed in the clinical application of other immune checkpoint inhibitors such as ipilimumab, nivolumab, pembrolizumab, and atezolizumab. Once subjects developed the above AEs in this study, monitoring on signs and symptoms as well as relevant examinations should be performed to identify the cause. If an alternative cause is not found (such as disease progression, concomitant medications, or infections) and glucocorticoids and/or other immunosuppressants are required, then any AE described above is considered related to IBI308-induced immune hyperfunction, and should be diagnosed as an irAE (except for endocrine events such as hyperthyroidism/hypothyroidism, hypophysitis, type 1 diabetes mellitus, and adrenal insufficiency which may not require immunosuppressants but are still considered as immune hyperfunction related to IBI308).

See "NCCN Guidelines for Management of Immunotherapy-Related Toxicities Version 1.2019" for dose adjustments and toxicity management of major potential irAEs, other potential irAEs, and infusion reactions.

5.4 Concomitant Treatments

5.4.1 Prohibited treatments

The following treatments are prohibited throughout the study:

- Any systemic chemotherapy and biotherapy (except for cytokine drugs to treat chemotherapy-induced AEs), as well as herbal and proprietary Chinese medicines, with anti-tumor effects other than IBI308, oxaliplatin, and capecitabine.
- Immunomodulators, including but not limited to non-specific immunomodulators (such as thymosin, interferon, interleukin [excluding IL-11 used to increase the platelet count], immunoglobulin, and gamma globulin) as well as herbal and proprietary Chinese medicines with immunomodulating effects; immunoglobulin and gamma globulin are permitted for the treatment of immune-related AEs.
- Corticosteroids. Inhaled steroids for subjects with asthma or chronic obstructive pulmonary disease (COPD) are permitted; temporary use of corticosteroids for dyspnea are permitted; corticosteroids are permitted for the treatment of immune-related AEs; corticosteroids of physiologic dose are permitted after consulting the sponsor.

Note: Prophylactic corticosteroids as pretreatment of allergic reactions (e.g., premedication prior to IV contrast agent; if patients develop allergic reactions to chemotherapy, the pretreatment with corticosteroids will be allowed pre-dose in the next cycle of treatment) are permitted.

- Inoculation with live vaccine within 30 days prior to the first dose of investigational drugs and throughout the study. Live vaccines include but are not limited to measles, mumps, rubella, chicken pox, yellow fever, rabies, Bacillus Calmette Guerin, and typhoid (oral) vaccines. Seasonal inactivated influenza virus vaccines are permitted, but intranasal live attenuated influenza vaccines are not.

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

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

- During each visit, subjects must be asked about any new medications received.
- To minimize the risk of drug-drug interactions, every measure must be taken to limit the number of concomitant medications that are really necessary.

- Drugs of hepatotoxicity (i.e. those with warnings in the prescribing information) should be avoided during the treatment. The investigators are encouraged to review every potential hepatotoxic drug via http://www.livertox.nih.gov/.
- Prohibited drugs listed in the exclusion criteria are not permitted.

5.4.2 Permitted treatments

- Medications that meet the protocol requirements, as determined by the investigator (e.g. concomitant medication used for disease-related symptoms and treatment-related AEs).
- Subjects who need medications for a long time due to pre-existing diseases, such as hypertensive and diabetes mellitus, can continue the use of drug.
- Locoregional surgery or radiotherapy (such as radiotherapy to relieve pain from bone metastasis and symptoms of brain metastasis) used for isolated lesions (excluding target lesions), which is adopted to control symptoms and does not affect efficacy judgment.
- Supportive care for relieving tumor-related symptoms, such as bisphosphonate treatment for bone metastases.
- Use of locoregional corticosteroids, such as dermal, ocular, nasal, and inhaled corticosteroids.
- Prophylactic antiviral therapy is permitted for hepatitis B carriers. Refer to treatment guidelines for dosage and administration.

5.4.3 Drug-drug interactions

- IBI308: No interaction information is currently available.
- Oxaliplatin: No PK interaction between oxaliplatin at 85 mg/m^2 and 5-fluorouracil has been observed in subjects administered Q2W. However, increase of plasma 5-fluorouracil concentrations by approximately 20% has been observed in subjects receiving oxaliplatin at 130 mg/m^2 Q3W. In vitro studies showed that the following drugs did not displace platinum from plasma proteins: erythromycin, salicylate, sodium valproate, granisetron, and paclitaxel. Besides, oxaliplatin was not metabolized by, nor did it inhibit cytochrome P450 isoenzymes. P450-mediated drug-drug interactions are therefore not anticipated. Since platinum compounds are primarily eliminated through the kidneys, clearance of these products may be decreased by combination with potentially nephrotoxic compounds, though this has not been specifically studied.

- Capecitabine:

- Coumarin anticoagulants: Altered coagulation parameters and/or hemorrhage have been reported in subjects receiving capecitabine in combination with coumarin-derivative anticoagulants such as warfarin and phenprocoumon. These events occurred within several days to several months after capecitabine treatment and, in a few cases, within 1 month after discontinuing capecitabine. In a drug-drug interaction study with a single 15–20 mg dose of warfarin followed by capecitabine, the mean AUC of S-warfarin was increased by 57% and INR was increased by 91%. For subjects receiving capecitabine concomitant with oral coumarin-derivative anticoagulant therapy, the anticoagulant parameter (INR or PT) should be monitored frequently, and the anticoagulant dose should be adjusted accordingly. Cytochrome P-450 2C9 (CYP2C9) substrates: No formal drug-drug interaction studies between capecitabine and other known medications metabolized by CYP2C9 have been conducted. Care should be exercised when capecitabine should be carefully coadministered with these medications.
- Phenytoin: The co-administration of capecitabine and phenytoin has been reported to result in elevated serum phenytoin concentration. Formal drug-drug interaction studies with phenytoin have not been conducted, but the mechanism of interaction is presumed to be inhibition of the CYP2C9 isoenzyme by capecitabine (see Coumarin anticoagulants). The level of phenytoin should be carefully monitored in subjects coadministered with capecitabine and phenytoin.
- Drug-food interactions: In all clinical trials, subjects are instructed to administer capecitabine within 30 minutes after a meal. As all safety and efficacy data currently available are based on the administration with food, it is recommended that capecitabine should be administered with food.
- Antacids: The effects of an aluminum hydroxide- and magnesium hydroxide-containing antacid (Maalox) on the PK of capecitabine was studied in subjects with malignant tumors. Serum concentration of capecitabine and one of its metabolites (5'-DFCR) increased slightly. No effect was observed on the other major metabolites (5'-DFUR, 5-FU, and FBAL) of capecitabine.
- Sorivudine and its analogues: It has been reported that there is a clinically significant drug-drug interaction between sorivudine and 5-fluorouracil due to inhibition of dihydropyrimidine dehydrogenase by sorivudine. This interaction leads to an increase in the toxicity of fluoropyrimidine, which can be fatal. Therefore, capecitabine should not be coadministered with sorivudine and its analogues (such as brivudine). There must be a 4-week waiting period from the end of treatment with sorivudine and its analogues (such as brivudine) to the start of treatment with capecitabine.

- Oxaliplatin: There are no clinically significant differences between the exposure of capecitabine and its metabolites, as well as free and total platinum when oxaliplatin is combined with capecitabine (with or without bevacizumab).

Study treatment will be given at the study sites. Treatment compliance will be monitored by medication dispensing and return records, medical records, and eCRFs.

5.5 Drug Management

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

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

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

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

5.5.1 Dispensation

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

5.5.2 Return and destruction

In this trial, the containers of used IBI308/placebo should be returned, and those of chemotherapeutic agents can be destroyed on-site according to the appropriate guidelines and operating procedures established by study sites and local agencies.

Upon the completion or discontinuation of the study, all unused or expired study drugs must be returned to the sponsor for destruction. Arrangements for the return of IBI308 will be made by the CRA designated by the sponsor.

5.6 Study Drug-Related Records

The designee of the study sites should make timely records of receiving, dispensing, using, storing, destroying, returning, and damaging the study drugs in accordance with the relevant regulations and guidelines as well as the requirements of operation processes of this study.

5.7 Complaint Handling

To ensure the safety and proper monitoring of the subjects, and facilitate the improvement of trial process and drug product, the sponsor will collect complaints related to the study drugs.

Complaints regarding concomitant medications will be directed to the manufacturer according to the prescribing information of the drugs.

The investigator or designee should complete the following procedures for product complaints in accordance with applicable requirements of the study:

- A drug complaint form specific for clinical trials will be used to document product complaints and relevant description completely.
- The completed product complaint form will be submitted to the sponsor or designee by fax within 24 h.

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

6 STUDY PROCEDURE

6.1 Enrollment and Randomization

6.1.1 Enrollmentand randomization

The investigator will enroll the subjects by the following steps:

1. Obtain the ICF signed by the subjects prior to any study-related procedures.
2. Confirm the subjects' eligibility by the principal investigator or trained designee after reviewing the inclusion/exclusion criteria.
3. Randomize the subjects using the IWRS in a 1:1 ratio by randomization stratification factors including ECOG PS score (0 or 1), liver metastasis (positive or negative), and PD-L1 expression (CPS < 10 or ≥ 10).

Subjects who have failed to meet the criteria (screen failures) can be re-screened. If re-screening is considered, the investigator must contact the sponsor's medical manager. Each subject can be re-screened once. The subjects must sign the ICF again and receive a new identification number when they are re-screened.

6.1.2 Enrollment error handling

The inclusion/exclusion criteria must be followed strictly. If an ineligible subject is enrolled, the sponsor's medical manager and investigator must discuss whether to allow the subject to continue participating in the study and whether to use the study drug. If as determined by the investigator, allowing the subject to continue with the study is appropriate medically, which is also agreed with by the sponsor's medical manager, then the subject will continue participating in the study and receive the study drug; If as determined by the investigator, allowing the subject to continue the study is appropriate medically, which is not agreed with by the sponsor's medical manager, then the subject should not continue participating in the study (regardless of receiving the investigational drugs or not). The investigator must not allow the subject to continue with the study until receive the written approval from the sponsor.

6.2 Study Plan and Schedule

6.2.1 Screening period

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

- Signing of ICF
- Confirming the inclusion/exclusion criteria
- Recording the demographics, medical history, and previous medications
- Recording vital signs, height, and body weight
- Recording information on HP infection at the confirmed diagnosis of gastric cancer (including test methods if any)
- Physical examination
- ECOG PS score
- 12-lead ECG (within 7 days prior to the first dose)
- Routine blood test/blood chemistry/urinalysis (within 7 days prior to the first dose)
- Coagulation function (within 7 days prior to the first dose)
- Pregnancy test (within 3 days prior to the first dose)

- HIV antibody, HBV antibody (test HBV DNA in subjects positive for HBsAg or just positive for HBcAb), treponema pallidum antibody, and HCV antibody (test HCV RNA for subjects with positive HCV antibodies). Results obtained at the study site within 28 days prior to randomization are also accepted)
- Thyroid function (results obtained at the study site within 28 days prior to randomization are accepted)
- AE evaluation
- Concomitant medications
- Tumor imaging evaluation
- Archived or fresh tumor tissue samples (both primary and metastatic ones within 6 months prior to screening and signing of ICF) are tested for PD-L1 expression and biomarkers.

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

6.2.1.1 Medical history

A medical history should be obtained by the investigator or qualified designee. Medical history includes all active diseases and diseases diagnosed within the past 10 years, including history of smoking, alcohol, surgery, and drug allergy. All the autoimmune diseases should be documented, regardless of the date of onset. Detailed information regarding G/GEJ AC should be documented separately by EDC and not listed as medical history, and information on history of HP infections and HER2 expressions (including IHC and FISH test results) in pathological tissues.

6.2.1.2 Previous medications

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

6.2.1.3 Concomitant medications

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

6.2.2 Baseline (prior to day 1 of cycle 1)

- IWRS randomization (the first dose must be administered within 48 h after randomization)

- Recording the vital signs
- Body weight and height (if applicable)
- ECOG PS score
- AE evaluation
- Concomitant medications
- EQ 5D-5L
- EORTC QLQ-C30
- EORTC QLQ-STO22
- Administration of investigational drugs (on day 1 of cycle 1 as possible, and no later than 48 h after randomization)
- PK sampling (if applicable)
- Immunogenicity

6.2.3 Treatment visits

- Recording the vital signs
- If the weight fluctuation is less than 10% compared to baseline (date of the first dose), then use the baseline weight to calculate the chemotherapy dose (except for IBI308). Otherwise, use the weight on the scheduled day of administration to calculate the chemotherapy dose
- Physical examination
- ECOG PS score
- 12-lead ECG
- Routine blood test/blood chemistry/urinalysis
- Thyroid function
- HBV DNA and/or HCV RNA (if applicable)
- AE evaluation
- Concomitant medications
- Tumor imaging evaluation (if applicable)
- Administration of investigational drugs (tumor imaging evaluation should be performed prior to administration)

- EQ 5D-5L (if applicable)
- EORTC QLQ-C30 (if applicable)
- EORTC QLQ-STO22 (if applicable)
- PK sampling (if applicable)
- Immunogenicity (if applicable)
- Survival condition

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

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

6.2.4 End-of-treatment visit

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

- Recording the vital signs
- Physical examination
- Body weight
- ECOG PS score
- 12-lead ECG
- Routine blood test/blood chemistry/urinalysis
- Coagulation function
- Thyroid function
- Pregnancy test
- Tumor imaging evaluation (if applicable)
- AE evaluation
- Concomitant medications
- Survival condition
- EQ 5D-5L
- EORTC QLQ-C30
- EORTC QLQ-STO22

6.2.5 Safety follow-up

Two safety follow-ups will be performed. The first safety follow-up will be conducted 30 days (± 7 days) after the last dose while the second one 90 days (± 7 days) after the last dose. The follow-up items are as follows:

- Recording the vital signs
- Physical examination
- Weight (during the first safety follow-up only)
- ECOG PS score
- 12-lead ECG (during the first safety follow-up only)
- Routine blood test/blood chemistry/urinalysis (during the first safety follow-up only)
- AE evaluation
- Recording concomitant medications (during the first safety follow-up only)
- Subsequent anti-tumor therapy (if applicable)
- Survival condition
- EQ 5D-5L (during the first safety follow-up only)
- EORTC QLQ-C30 (during the first safety follow-up only)
- EORTC QLQ-STO22 (during the first safety follow-up only)
- Immunogenicity (during the first safety follow-up only)

If the safety follow-up is less than 7 days from the end-of-treatment visit, then the first safety follow-up may be replaced by the end-of-treatment visit and do not required to be repeated. However, immunogenicity sampling should be completed.

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

6.2.6 Survival follow-up

After completing the first safety follow-up, the subject should be contacted with (telephone follow-up is allowed) once Q60D (± 15 days) to obtain the survival information, any subsequent systemic anti-tumor therapy, and PD information. Long-term follow-up should be continued until death or end of study.

6.2.7 Subsequent anti-tumor therapy

The investigator or qualified designee will collect all the information on new anti-tumor therapy initiated after the last dose of the investigational drugs and the corresponding efficacy. If the subject initiates a new anti-tumor therapy within 30 days after the last dose, then the safety follow-up must be performed before initiation of the new therapy.

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

6.2.8 Unscheduled visits

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

7 STUDY EVALUATION

7.1 Efficacy Evaluation

Tumor evaluations are performed based on RECIST v1.1. Refer to Appendix 3 for the evaluation methods. All the decisions made during the study will be based on the imaging evaluations, subjects' clinical status, and relevant examinations by the local investigators.

7.1.1 Tumor imaging and disease evaluations

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

During the screening, the investigator of the study site will confirm the presence of measurable or evaluable lesions based on RECIST v1.1, determining the eligibility of the subject.

7.1.2 Tumor imaging during the study

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

After the first dose of investigational drugs, tumor imaging evaluation will be performed Q6W (± 7 days) initially, then Q12W (± 7 days) after 48 weeks until PD, initiation of a new anti-tumor therapy, withdrawal of ICF, loss to follow-up, death, or end of study (whichever occurs first).

The subject may continue the treatment if PD cannot be confirmed, especially for non-target lesions and new lesions, until the occurrence of clinical symptoms (i.e. clinically unstable) or the next scheduled evaluation time point when the imaging evaluation will be performed again. If repeated scans confirm PD, then the PD should be recorded using the date of the initial scan.

Clinically unstable disease is defined as follows:

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

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

If the tumor imaging and administration are scheduled on the same day, imaging should be completed first to determine the efficacy before deciding whether to administer the investigational drugs.

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

The tumor imaging following the radical surgery will be performed according to the clinical practice. This imaging is recommended to be done 4 weeks after the surgery and Q12W (± 7 days) thereafter.

If there is an interval of more than 4 weeks between last imaging evaluation and end-of-treatment visit, imaging evaluation at this visit as well as Q6/12W (± 7 days) thereafter should be performed for subjects, who are required to discontinue the treatment for reasons other than imaging-confirmed PD, until one of the followings occurs: initiation of a new anti-tumor therapy, PD, withdrawal of ICF, or death. A scan at the end of treatment is not mandatory if it has been less than 4 weeks since the last tumor imaging evaluation.

7.2 Safety Evaluation

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

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

Refer to Sections 8.3 and 8.4 for details regarding AE evaluation and documentation.

Refer to the schedule of visits in **Table 1** for the time of examination. Refer to Appendix 2 for ECOG PS scoring criteria.

7.2.1 Physical examination

7.2.1.1 Comprehensive physical examination

A comprehensive physical examination is performed by the investigator or designee during the screening. A complete physical examination includes: evaluations of general conditions, respiratory tract, cardiovascular system, abdomen, skin, head and neck (including ears, eyes, nose, and throat), lymph nodes, thyroid, musculoskeletal system (including spine and limbs), genitalia/anus (if required), and nervous system. All the clinically significant abnormalities should be documented as the disease history. In addition, the comprehensive physical examination should be performed according to instructions specified in the study schedule. After the first dose of investigational drugs, any new clinically significant abnormality should be documented as an AE.

7.2.1.2 Targeted physical examination

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

7.2.1.3 ECOG PS score

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

7.2.1.4 Vital signs

Vital signs are examined in accordance with the schedule of visits in Table 1, Vital signs include temperature, pulse, respiratory rate, and blood pressure. The subject's blood pressure and pulse in the supine position should be measured after a rest for at least 5 min. The time and date of collection and measurement should be documented in the appropriate section of the eCRF. Temperature, pulse, respiratory rate, and blood pressure should be measured prior to the administration of investigational drugs.

Additional monitoring of vital signs is allowed based on standard clinical practice or clinical needs.

Additional records for vital signs may be collected in eCRF when an AE/SAE occurs (if applicable). The time and date of collection and measurement should be documented in the appropriate section of the eCRF.

7.2.1.5 12-Lead ECG

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

The subjects are required to rest in supine position for at least 5 minutes prior to 12-Lead ECG. All 12-lead ECGs should be performed while the subjects are resting in the supine position. Further ECG (or other related tests) is performed if clinically indicated, such as a cardiac AE. The investigator should review the ECG on the day it is performed, and document the results on the ECG. The same method of evaluation is used throughout the study.

The investigator should evaluate all the ECG as either a clinically significant or insignificant abnormality. For a clinically significant abnormality, the investigator should document the result as an AE in the eCRF.

7.2.2 Routine laboratory safety evaluation

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

7.2.2.1 Laboratory safety evaluation (routine blood test, urinalysis, and blood chemistry)

Refer to **Table 12** for laboratory tests including routine blood test, urinalysis, blood chemistry, and coagulation function.

Table 12. Routine laboratory safety evaluation

Routine blood test	RBC, HGB, WBC, PLT, LYM, ANC
Blood chemistry	TBIL, ALT, AST, γ-GT , ALP, ALB, TP, LDH, UREA, Cr, Na, K, Cl, Mg, Ca, P, amylase, CK, CK-MB and FBG
Urinalysis	pH, UWBC, UPRO, URBC and UGLU
Coagulation function	PT, INR
Thyroid function	FT3, FT4, TSH
Viral serological test	HBsAg, HBsAb, HBcAb, HBeAg, HBeAb, HBV DNA, anti-HCV antibody, treponema pallidum antibody, HCV RNA, and anti-HIV antibody

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

7.2.2.2 Pregnancy test

Urine or serum human chorionic gonadotropin (hCG) pregnancy tests should be performed in women of childbearing age (refer to Section 4.3 for definition) within 3 days prior to the first dose of investigational drugs. For the result of urine hCG of positive or inconclusive, a serum β-hCG pregnancy test is performed. Result of the serum pregnancy test is determinative. If one subject has a positive serum β-hCG result and is confirmed to be pregnant, the subject will be ineligible and should discontinue participating in the study. A repeated test is performed for the suspected pregnancy during the study.

7.3 Immunogenicity

Immunogenicity samples will be collected within 1 h prior to IBI308/placebo infusion in cycles 1/2/4/8/12/16, then every 8 cycles (cycle 24, 32, and so on) thereafter, and during the safety follow-up. If an infusion-related reaction occurs during IBI308 infusion, blood samples should be taken near the start of the event, end of event, and around 30 days after the reaction, for comparative analysis of immunogenicity. Blood samples are analyzed at the central laboratory.

ADA titer should be tested for each subject. ADA-positive samples should be further tested for neutralizing antibodies (NAbs). For ADA and NAb assays, 5 mL of whole blood is collected using vacutainers with clot activator. Serum is then separated, dispensed in aliquots, and frozen. Refer to the "Laboratory Manual" provided by the sponsor-designated central laboratory for sampling methods, sample storage, transport, and analysis.

7.4 Pharmacokinetics

PK samples are collected for the first 100 subjects at the following time points: within 1 h before and immediately (+ 5 min) after IBI308 or placebo infusion in cycle 1, and within 1 h before 308 or placebo infusion in cycle 2/4/12 (trough concentrations for cycle 1/3/11).

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

7.5 Quality of Life Evaluation

Quality of life evaluation will be performed on the day of the first dose, during each imaging evaluation, and during the safety follow-up as per EQ 5D-5L, EORTC QLQ-C30, and EORTC QLQ-STO22 rating scale. Refer to "Quality of Life Evaluation Manual" provided by the sponsor for detailed evaluation scales and requirements.

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

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

The EORTC QLQ-STO22 is the main tool used for evaluating the quality of life in patients with GC, and is often used in conjunction with QLQ-C30. The 5 symptom scales are dysphagia, pain, reflux, eating restriction, and anxiety; 4 single item scales are dry mouth, taste problem, body image, and hair loss. There are 4 levels for each item: not at all, a little, quite a bit, and very much, scored 1–4 points.

7.6 Biomarker Analysis

If permitted by the Ethics Committee (EC), subjects are required to provide at least 5 slices of acceptable tumor tissue samples during screening to test PD-L1 expression. Those screened to be eligible must provide another 5 slices from the same paraffin block, or companion diagnostic test of PD-L1 expression. Acceptable tumor tissues include archival ones or 4–5 μm sections prepared from fresh specimens collected during screening. Specimens within 6 months prior to screening and signing of ICF and sections within 3 months are acceptable.

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

7.7 Storage and Destruction of Biological Samples

Samples will be disposed or destroyed, pooled and anonymized. Additional analyses of pooled and anonymized samples may be performed to further evaluate and validate the analytical method. Results of these analyses may be published separately from the clinical study report.

Reproducibility (if performed) will be assessed simultaneously with the biological analysis of the samples. The results of these evaluations will not be published in the clinical study report, but will be presented separately in a biological analysis report.

8 SAFETY REPORTS AND ADVERSE EVENT MANAGEMENT

8.1 Definition of Adverse Events

An adverse event (AE) is defined as any adverse medical event that is observed after the signing of the informed consent, regardless of whether or not considered as related to the investigational drug. AEs include but are not limited to the followings:

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

8.2 Definition of Serious Adverse Event

A serious adverse event (SAE) refers to an AE meeting at least one of the followings:

- Death, except for the cases caused by PD.
- Life-threatening (a "life-threatening" event is defined as an AE when the subject is at immediate risk of death at the time of this event, but does not include the case that may lead to death only when the event worsens).

- Requires hospitalization or prolonged hospitalization, excluding the followings:
  - ✓ Hospitalization at a rehabilitation institution
  - ✓ Hospitalization at a sanatorium
  - ✓ General emergency admission
  - ✓ Same-day surgery (e.g., outpatient/same-day/ambulatory surgery)
  - ✓ Hospitalizations or prolonged hospitalizations unrelated to worsening of an AE are not considered as SAEs. Hospitalization due to pre-existing disease, without new AEs or exacerbation of pre-existing disease (e.g., hospitalization to examine laboratory abnormalities that have been persistent before the study); hospitalization for administrative reasons (e.g., annual routine physical examinations); hospitalizations during the study as specified in the protocol (e.g., hospitalization performed in accordance study protocol); elective hospitalization unrelated to worsening of AEs (e.g., elective surgery); scheduled treatment or surgical procedures, which should be documented in the entire study protocol and/or individual subject's baseline information; and hospitalization merely due to the use of blood products.
- Resulting in permanent or severe disability/incapacity.
- Resulting in congenital abnormalities/birth defects.
- Other important medical events: events that are not fatal or life-threatening, and does not require hospitalization, but may jeopardize the subject and may require medical or surgical interventions to prevent one of the above outcomes based on appropriate medical judgment.

8.3 Criteria for Severity Levels of AEs

The severity level of AEs is evaluated using the 5-level criteria of NCI CTCAE Version 4.03.

AEs not included in NCI CTCAE Version 5.0 are graded in accordance with the following CTCAE grading principles:

- Grade 1 mild; asymptomatic or mild signs; clinical or diagnostic observations only; medical intervention not indicated.
- Grade 2 moderate; minimal, local or non-invasive intervention required; limiting age-appropriate instrumental activities of daily living (e.g., cooking, shopping, using telephone and managing money).

- Grade 3 severe or clinically significant but not immediately life-threatening; hospitalization or prolonged hospitalization indicated; disabling; limiting self-care activities of daily life (e.g., bathing, dressing and undressing, feeding self, using toilet, and taking medications), but not bedridden.
- Grade 4 life-threatening consequences; urgent intervention indicated.
- Grade 5 death related to AE.

8.3.1 Correlation between AEs and investigational drug

The relationship between the investigational drug and AEs can be determined by the classification and the criteria in the followings:

Table 13. Detailed rules for AE evaluation

CTCAE v5.0 Grade	**Grade 1**	**Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; medical intervention not indicated**
	Grade 2	**Moderate; minimal, local or non-invasive intervention required; limiting age-appropriate instrumental activities of daily living**
	Grade 3	**Severe or medically significant but not immediately life-threatening; hospitalization or prolonged hospitalization indicated; disabling; limiting self-care activities of daily life, but not bedridden**
	Grade 4	**Life-threatening consequences; urgent intervention indicated**
	Grade 5	**Death related to AE**
Severity	A SAE refers to any one of the following events at any dose or during the use of investigational drugs:	
	†**Leading to death**;	
	†**Life-threatening**; or as determined by the investigator, the subject is at immediate risk of death at the time of the event (Note: this does not include an AE that may lead to death if the event worsens);	
	†**Leading to permanent or serious disability/insufficiency**; (substantial disruption of the subject's ability to conduct normal life);	
	†**Hospitalization or prolonged hospitalization**; (defined as an inpatient admission, regardless of the length of stay, even if the hospitalization is a prophylactic measure for continuous observation. Note: Hospitalization due to pre-existing disease that does not worsen during the trial (including elective surgery) is not considered as a SAE. A pre-existing disease refers to clinical conditions diagnosed prior to the treatment with investigational drugs and documented in the subject's medical history);	
	†**Congenital anomalies/birth defects**; (for the offspring of the subject using the product, regardless of the time of diagnosis);	
	Other important medical events; events that are not fatal or life-threatening, and does not require hospitalization, but may jeopardize the subject and may require medical or surgical interventions to prevent one of the above outcomes (marked with †) based on appropriate medical judgment.	
Duration	The start and end dates of AEs should be documented. Indicate the appropriate length of time and units if the duration is less than 1 day.	
Measures taken	Is the AE lead to discontinuation of the investigational drugs?	

Relationship with the investigational drug	Is the AE caused by the investigational drug? A medically qualified investigator is required to assess the causality relationship between the investigational drug and AEs. To ensure that causality is assessed by a medically qualified investigator, the investigator must sign/date (initials) the source document or worksheet to support the causality assessment on the AE form. This signed document must be retained within the period required by the regulations. The following criteria serve as a reference guide to assist the investigator in assessing the relationship between the investigational drug and AEs based on available information. **The following factors are used to assess the relationship between the investigational drug and AEs;** if the correlation between each criterion and the corresponding factor increases (in terms of quantity and/or intensity), the likelihood that the AE is caused by the investigational drug increases;	
	Exposure	Is there any evidence that the subject is exposed to the investigational drug, e.g., a credible medical history, an acceptable compliance evaluation (drug count and daily log), expected pharmacological effect, and in vivo drug/metabolite measurement samples?
	Time course	Does the AE have a reasonable time relationship with the administration of the investigational drug? Is the time of AE consistent with the criteria for drug-induced AEs?
	Possible causes	Does the AE cannot be explained by other pathogenies, such as underlying disease, other drugs/vaccines, or other hosts or environmental factors
	Dechallenge	Is the investigational drug discontinued or dose/exposure/frequency reduced? If yes, doses the AE resolve or improve? If yes, then it is a positive dechallenge. If no, then it is a negative dechallenge. Note: The above is not applicable if the followings occur: (1) the AE results in death or permanent disability; (2) the AE resolves/improves despite continuing treatment with the investigational drug; (3) the study is single-dose; (4) only one dose of the investigational drug is administered.
	Rechallenge	Is the subject re-exposed to the investigational drug? If yes, does the AE reoccur or worsen? If yes, then it is a positive rechallenge. If no, then it is a negative rechallenge. Note: The above is not applicable if the following occurs: (1) the initial AE results in death or permanent disability, or (2) the study is single-dose, or (3) only one dose of the investigational drug is administered. Note: A rechallenge is not recommended for a SAE that is possibly caused by the investigational drug or if re-exposure to the investigational drug may result in potentially serious risks to the subject. However, if continuing study treatment is beneficial to the subject and no replacement treatment is available, a rechallenge can be performed after the approval is obtained from the sponsor's Medical Director.

	Consistency with the characteristics of investigational drug	Is the clinical/pathological manifestation of the AE consistent with pharmacological or toxicological data of the investigational drug or other similar drugs?
Based on his/her best clinically judgment, the medically qualified investigator will consider the above factors and report the results of the causality assessment in the CRF/worksheet.		
Causality documentation	**The following table can be used to assess the causality (not all the criteria are required to be met)**	
Related	Evidence of exposure to investigational drugs. A reasonable time relationship between the occurrence of the AE and administration of the investigational drug. The AE is more likely to be attributed to the investigational drug, rather than other causes.	
Unrelated	The subject does not receive the investigational drug, or the time relationship between the occurrence of the event and the administration of the investigational drug is unreasonable, or other explanations are more likely to be attributed to (still applicable to overdosed subjects without relevant AEs).	

8.4 AE Documentation

The investigator should document AEs or SAEs using medical terminology/concepts. Avoid colloquialisms/abbreviations. All the AEs (including SAEs) should be documented in the AE form of the eCRF.

8.4.1 AE collection and collection duration

The investigator should learn about AEs by asking the subjects non-leading questions.

All the AEs, including SAEs and irAEs (including those related and unrelated to investigational drugs), that occur from the signing of the ICF to 90 days after the last dose are collected, regardless of whether it is observed by the investigator or self-reported by the subject.

If a new anti-tumor therapy is initiated within 90 days after the last dose, information on all irAEs and that on SAEs considered related to the investigational drugs or study procedures will be reported.

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

8.4.2 Follow-up of AEs

The AE should be followed until the event returns to the baseline or grade 0–1, or until the investigator believes that no further follow-up is required for reasonable reasons (e.g., the event cannot be resolved or has already been improved). If the event cannot be resolved, a reasonable explanation should be documented in the eCRF. The outcome of an AE/SAE and date should be documented in the eCRF and medical record, regardless of whether the event is related to the investigational drug.

8.4.3 Contents of AE documentation

The investigator documents every AE, including the diagnosis (document signs and symptoms including the laboratory abnormalities when there is no diagnosis), time and date of occurrence (if applicable), CTCAE grade of severity and changes in severity (events of grade 3 or above), whether it is a SAE, whether it is an AE of special interest (AESI), measures taken for the investigational drugs, treatment for the AE and outcome of the event, and relationship between the event and investigational drug.

For a SAE, the investigator should also provide the date when the AE meets the criteria for a SAE, the date when the investigator is informed of the SAE, the reason of being a SAE, date of hospitalization, date of hospital discharge, possible cause of death, date of death, whether an autopsy has been performed, causality assessment of the study procedures, causality assessment of other drugs, and other possible causes of the SAE. The investigator should provide the

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

Descriptions of the AE are as follows:

Diagnosis, symptoms, and signs

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

AEs secondary to other events

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

Ongoing or recurrent AEs

An ongoing AE refers to an event that does not resolve and is ongoing between two evaluation time points. These AEs should only be documented once in the eCRFs. The initial severity level should be documented, and the information should be updated if the event exacerbates.

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

Laboratory test abnormalities

All clinically significant laboratory test abnormalities are reported as AEs. The investigator has responsibilities for reviewing all the laboratory test abnormalities and determining whether the abnormalities should be reported as AEs.

Death

During the entire course of the study, all the deaths that occur within 90 days after the last dose are documented in the "Death Report Form" in the eCRFs and reported to the sponsor promptly, regardless of the causality with the investigational drug.

For a death with a known cause, record the cause of death as an AE and the outcome of the AE as "death" and submit an SAE report; for a death with an unknown cause, record the cause as "unknown cause of death" in the AE form of eCRF, and submit an SAE report. The exact cause of the death will be further investigated.

If the death is definitely caused by tumor progression, then it should not be documented and reported as an AE/SAE; nonetheless, the investigator should document the death in the "Death Report Form" of the eCRF and inform the sponsor promptly.

Pre-existing medical conditions

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

Hospitalization and prolonged hospitalization, or surgery

Any AE leading to hospitalization or prolonged hospitalization shall be recorded and reported as SAE, with the following exceptions:

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

However, elective surgery/therapy required due to worsening of a pre-existing medical condition during the study (e.g. surgery/therapy required earlier than scheduled) should be considered as an AE.

Progressive disease

A progressive disease is defined as the worsening of subject condition caused by the primary tumor that the investigational drug is targeting, the appearance of new lesions, or the progression of the primary lesion. PD will not be reported as an AE. Any deaths, life-threatening events, hospitalization or prolonged hospitalization, permanent or significant disability/incapacity, congenital anomaly/birth defects, or other important medical events caused by PD will not be reported as SAEs.

Overdose

A dose exceeding 10% the dose specified in the study protocol is called overdose. The occurrence of overdose must be documented in the eCRF.

New anti-tumor therapy

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

8.5 Expedited Reporting of SAEs and Pregnancy

SAE reporting:

All the SAEs that occur since the signing of ICF until 90 days (inclusive) after the last dose must be reported within 24 h. The investigator must fill out the "SAE Report Form" given by the sponsor, regardless of whether it is the initial report or a follow-up report. Besides, the investigator must report the SAE to the sponsor (drugsafety@innoventbio.com) within 24 h after being informed of the event, as well as to regulatory authorities and EC in accordance with the laws and regulations of China.

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

The investigator must submit the completed SAE report form to the sponsor within 24 hours of noticing the event. The investigator should urgently perform visit on missing information and provide a complete SAE report for events that result in death or are life-threatening. The investigator should also report the events to the national regulatory authorities and EC in accordance with regulations.

Pregnancy

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

During the study, if a female subject exposed to the investigational drug becomes pregnant, she must be excluded from the study. The investigator must report to the sponsor within 24 h after being informed of the event and submit the "Innovent Clinical Study Pregnancy Report/Follow-Up Form".

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

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

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

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

8.6 Abnormal Hepatic Function

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

Table 14. Liver injuries required to be reported as SAEs

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

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

Other than repeated AST and ALT tests, albumin, creatine kinase, TBIL, direct and indirect bilirubin, γ-GT, PT/INR, and ALP should also be tested. Detailed medical history includes history of alcohol, acetaminophen, soft drugs, various supplements, traditional Chinese medicine, chemical drug exposure, family diseases, occupational exposure, sexual behavior, travel, contact with patients with jaundice, surgery, blood transfusion, hepatic diseases or allergies, cardiac diseases, and immune diseases. Further tests may include the detection of acute hepatitis A, B, C and E, hepatic imaging (such as biliary tract), autoantibodies, and echocardiography. If a retest shows consistency with the criteria outlined in **Table 14** and there are no other possible causes, the possibility of drug-induced liver injury should be considered before all the results of etiological tests are accessible. These potentially drug-induced liver injuries should be reported as SAEs.

8.7 Management of Drug-Related Toxicities

8.7.1 Immune-related adverse event

Since the mechanism of action of IBI308 involves T-cell activation and proliferation, irAEs are likely to be observed during this study. Signs and symptoms of irAEs should be monitored. If there are no alternative causes (e.g., infections), signs or symptoms of the subjects during the study may be related to the immune system.

Refer to Section 5.2 for dose adjustments of IBI308 and principles of AE management. For irAE management principles, please refer to guidelines for management of immunotherapy-related toxicities.

8.8 Unblinding

8.8.1 Emergency unblinding

This is a randomized, double-blind study. Subjects are randomized to either IBI308 or placebo group in double-blind form. The investigator, subjects, medical personnel and assistants, and sponsor or its designee do not know the exact drug given other than the chemotherapy. During the study, if there is a need for unblinding (e.g., occurrence of an SAE), the responsible investigator will submit a request, and the sponsor and principal investigator will decide together whether to carry out unblinding. If emergency unblinding is required, the investigator can discuss with the sponsor and submit an unblinding request. After approval, the subject's treatment allocation will be known through the interactive web response system (IWRS).

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

8.8.2 Accidental unblinding

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

In addition, there may be ethical concerns for continuing the study treatment for the subject. If the subjects continue the study treatment after unblinding, the investigator must obtain special approval from the sponsor's CRA for the subject to continue participating in the study.

9 STATISTICS

9.1 Statistical Analysis Plan

A detailed statistical analysis plan (SAP) will begin to be written after the first enrollment and will be finalized prior to database locking and unblinding. All analyses and the expression methods for the results will be detailed in the SAP.

9.2 Hypothesis and Sample Size Calculation

This is a superiority trial. The primary efficacy endpoints are the OS in the ITT population and in the PD-L1-positive population. The superiority hypothesis test is:

Null hypothesis H0: HR ≥ 1

Alternative hypothesis Ha: HR < 1

This study is a phase III clinical study. The primary efficacy endpoints are OS in PD-L1-positive population and OS in ITT population. The test will be performed in a fixed order. The test of OS in ITT population will be performed only when the PD-L1-positive population reaches statistically significant, so as to strictly control the overall type I error of hypothesis test on the two populations for OS efficacy endpoints.

For OS in the PD-L1-positive population, assuming the hazard ratio (HR) of IBI308 to placebo, in combination with chemotherapy, is 0.7 (median OS is 15.7 and 11 months, respectively), 287 OS events are required to be at a level of 0.05 (two sided) with 85% power. For OS in the ITT population, assuming that the HR of IBI308 to placebo, in combination with chemotherapy, is 0.75 (median OS is 14.7 and 11 months, respectively), 515 OS events are required to be at a level of 0.05 (two sided) with 90% power.

The above calculations are based upon a 0.5% censoring rate of each month. The study will take 18 months to enroll 650 subjects, with 325 in each group. 515 OS events are estimated to be observed within 46 months. Based on the above assumptions, the PD-L1-positive population accounted for 56.2% (i.e., 365) of the ITT population with 287 OS events observed at the final analysis in the PD-L1-positive population.

In this study, hypothesis tests will be performed in a fixed order. The superiority test will be performed on the OS of PD-L1 positive population first, and the OS test will be performed on the ITT population after the OS of PD-L1 positive population reaches statistical significance. This study plans to conduct an interim analysis of OS in both the PD-L1-positive population and the ITT population when the number of OS events is at least 70% (i.e., 361 in the ITT population and 201 in the PD-L1-positive population), and the test level will follow the Lan-Demets approach to approximate the O'Brien-Fleming boundary. At the interim analysis, with a nominal test of 0.0148, the minimum detectable difference (MDD) in OS was HR = 0.709 in the PD-L1-

positive population and HR = 0.774 in the ITT population. At the final analysis, the nominal test level was 0.0455 with MDD for OS of HR = 0.790 for the PD-L1 positive population and HR = 0.838 for the ITT population. The exact alpha value of the OS analysis will be adjusted according to the Lan-DeMets approximation of the O'Brien-Fleming boundary based on the number of OS events that occur in real time to ensure an overall OS detection level of $\alpha = 0.05$. At the same time, this study plans to conduct an interim analysis of safety data at 200 PFS events to monitor the overall safety of clinical trial subjects.

The enrollment rate and dropout rate observed as well as OS distribution when blinded will be used to predict and determine the cut-off time points for interim OS analysis and final OS analysis.

9.3 Statistical Populations

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

Modified ITT set (mITT): all enrolled subjects who are randomized and have measurable lesions at baseline. Treatment groups are analyzed based on results of the randomization. This analysis set is used for ORR analysis.

Safety analysis set (SS): all randomized subjects who received at least one dose of study treatment. Subjects are analyzed based on the actual treatment received during the study. The SS is used for all the safety evaluations. Treatment groups are analyzed based on the actual allocations.

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

9.4 Statistical Analysis Methods

9.4.1 General statistical analysis

Variable data will be summarized using the mean, standard deviation, median, maximum, and minimum; attributes data will be described using frequency and percentage.

All statistical analyses will be carried out using SAS 9.2 or above.

Other than the primary efficacy endpoint presented in Section 9.4.1.1, the significance level of comparisons between groups, i.e. Nominal $\alpha = 0.05$ (two-sided), then the difference between treatment groups is considered statistically significant if $p \leq 0.05$.

9.4.1.1 Analysis of primary efficacy endpoint

The primary endpoint is OS of ITT population or PD-L1-positive subjects.

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

The median OS and corresponding 95% CI will be estimated via the Kaplan-Meier method, and survival curves will be plotted. A stratified log-rank test will be used to compare the PFS between groups. The HR and corresponding 95% CI will be estimated with a stratified Cox proportional hazards model.

9.4.1.2 Analysis of secondary efficacy endpoints

- PFS will be analyzed using the ITT analysis set

PFS is the time from randomization to the first date of progression (by imaging), or to death due to any cause. Subjects who do not have PD or die will be censored on the date of their last imaging evaluation. Subjects who do not receive any imaging evaluation after baseline will be censored on the date of randomization.

The median PFS and corresponding 95% CI will be estimated via the Kaplan-Meier method, and survival curves will be plotted. A stratified log-rank test will be used to compare the PFS between groups. The HR and corresponding 95% CI will be estimated with a stratified Cox proportional hazards model.

- ORR: the proportion of subjects in the mITT analysis set who have achieved CR or partial response (PR).

The ORRs and corresponding 95% CIs of the IBI308 group and placebo group will be estimated. The difference and corresponding 95% CI of ORRs between the treatment groups will also be computed.

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

The DCRs and corresponding 95% CIs of the IBI308 group and placebo group will be estimated. The difference and corresponding 95% CI of DCRs between the treatment groups will also be computed.

- DoR: subjects who have achieved CR or PR: from the first date of response to PD or death. Subjects who neither have PD or die will be censored at the date of their last tumor imaging evaluation.

The median DoR will be estimated via the Kaplan-Meier method and survival plots will be plotted.

9.4.2 Safety analysis

The safety analysis will be performed based on SS. Safety parameters include AEs, laboratory tests, vital signs, ECG, and immunogenicity. Unless otherwise stated, all the safety analyses will be summarized by treatment groups.

9.4.2.1 Drug exposure

The drug exposure, duration of treatment (number of treatment cycles) of the subjects will be summarized. Unless otherwise stated, all the safety analyses will be summarized by treatment groups.

9.4.2.2 Adverse event

All the AEs will be coded according to MedDRA.

The incidence (frequency) of AEs, TEAEs, treatment-related AEs (TRAEs), irAEs, SAEs resulting in treatment discontinuation will be summarized. The severity distribution of TEAEs, TRAEs, and irAEs will be summarized, by system organ class (SOC)/PT in MedDRA, according to NCI CTCAE v5.0.

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

9.4.2.3 Laboratory test

Abnormalities in hematology and blood chemistry will be assessed through laboratory indexes. Each laboratory test result will be graded according to NCI CTCAE v5.0. The number of subjects with laboratory abnormalities at baseline will be presented by severity grade. Laboratory indexes measured on the day of the first dose of investigational drugs (day 1 of cycle 1) will be considered as baseline measurements. The treatment period for all laboratory indexes begins on day 1 of study treatment.

The frequency of laboratory abnormalities of each subject during the treatment period will be summarized by severity grade. The worst grade (most severe) for each subject will be used if the same laboratory index is found to be abnormal repeatedly. All the laboratory indexes will be summarized by the worst NCI grade.

Cross-classification tables describing changes in frequency of any given laboratory index before and after treatment based on NCI CTCAE v5.0 grades will be provided.

Lists of subjects with laboratory abnormalities ≥ NCI CTCAE v5.0 grade 4 will be provided.

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

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

9.4.2.4 ECG

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

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

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

Abnormal changes from baseline in physical examination will be tabulated.

9.4.2.6 Immunogenicity indicators

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

9.4.3 Compliance analysis

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

The proportion of subjects who are given 80–110% of the dose of the investigational drug specified in the protocol will be summarized.

The proportions of the subjects who complete the study and who complete different treatment cycles as per protocol will also be summarized.

9.4.4 Subjects' baseline characteristics and concomitant medications

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

9.4.5 Interim analysis

In this study, hypothesis tests will be performed in a fixed order. The superiority test will be performed on the OS of PD-L1 positive population first, and the OS test will be performed on the ITT population after the OS of PD-L1 positive population reaches statistical significance.This study plans to conduct an interim analysis of OS in both the PD-L1-positive population and the ITT population when the number of OS events is at least 70% (i.e., 361 in the ITT population and 201 in the PD-L1-positive population), and the test level will follow the Lan-Demets

approach to approximate the O'Brien-Fleming boundary.At the interim analysis, with a nominal test of 0.0148, the minimum detectable difference (MDD) in OS was HR = 0.709 in the PD-L1-positive population and HR = 0.774 in the ITT population.At the final analysis, the nominal test level was 0.0455 with MDD for OS of HR = 0.790 for the PD-L1 positive population and HR = 0.838 for the ITT population.The exact α value of OS analysis will be adjusted according to the number of OS events occurring in real time to approximate the O'Brien-Fleming boundary according to the Lan-DeMets method, so as to ensure the overall detection level of OS α = 0.05.At the same time, this study plans to conduct an interim analysis of safety data at 200 PFS events to monitor the overall safety of clinical trial subjects.The interim analysis will be performed under blind conditions, and the unblinded results will only be delivered to the iDMC. Refer to Section 3.3 for details regarding the iDMC.

9.4.6 Subgroup analysis

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

9.4.7 Multiple comparisons and adjustments

In this study, a fixed order test will be used to control the overall α of 0.05 (two sided). The superiority test will be performed on the OS of PD-L1 positive population firstly, and then the OS test will be performed on the ITT population after the OS of PD-L1 positive population reaches statistical significance. The overall type I error for hypothesis testing on both populations for the efficacy endpoints of OS was tightly controlled through a fixed order testing approach.

The final multiplicity comparison strategy will also be defined and specified in the statistical analysis plan and iDMC charter prior to database lock (under blind data) to ensure that the overall test level with an α of 0.05 (two sided).

9.4.8 Eligible subject data lists

In addition to subjects' data list, tumor evaluation (date of evaluation, lesion status, evaluation results) and efficacy endpoints of subjects who have achieved CR and PR will be listed separately.

Data including the PFS and OS of all the subjects at the end of the study (date of progression, date of death, PFS, and OS) will be also be presented.

9.4.9 Exploratory analysis

To compare changes in quality of life between the two groups;

Study the PK characteristics of IBI308 in combination with chemotherapy in patients with unresectable, locally advanced, recurrent, or metastatic G/GEJ AC; (including but not limited to)

descriptive statistics will be used to analyze IBI308 trough concentration in week 1/3/11;

To descriptive statistic the expression level and distribution of PD-L1, and explore the potential relationship between PD-L1 expression and efficacy.

9.5 Methods for Controlling Bias

9.5.1 Randomization and blinding

This is a double-blind study. The investigator, subjects, and sponsor remain blinded to the treatment allocations during the study. Refer to Section 8.8 if unblinding is required due to AEs.

In this study, subjects are randomized through the IWRS, stratified by ECOG PS score (0 or 1), hepatic metastasis (positive or negative), and PD-L1 expression (CPS < 10 or ≥ 10). The investigator or qualified designee will log in to the IWRS through their respective passwords. The system will assign each subject a unique random number and the corresponding treatment group: IBI308 + chemotherapy or placebo + chemotherapy. Subjects allocated to the IBI308 + chemotherapy group will receive IBI308 in combination with XELOX regimen; subjects allocated to the placebo + chemotherapy group will receive placebo in combination with XELOX regimen. The independent statistician responsible for the randomization process will use the block randomization method to generate a random assignment table (subjects' randomization numbers) in a 1:1 ratio of IBI308 + chemotherapy to placebo + chemotherapy. The subjects' random numbers will be submitted to the randomization system in electronic form. The sponsor's investigational drug supply team will package the investigational drugs according to the medication randomization list.

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

9.5.2 Blinding maintenance evaluation

This is a double-blind study. Treatment allocation to either IBI308 or placebo must be blinded. Other than situations that require emergency unblinding as outlined in Section 8.8, the investigators, subjects, and sponsor must remain blinded to the treatment allocations during the study.

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

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

10 QUALITY ASSURANCE AND QUALITY CONTROL

In accordance with the "Good Clinical Practice" (GCP) guidelines, the sponsor is responsible for the implementation and maintenance of quality assurance and quality control systems as per appropriate standard operating procedures, to ensure that the implementation of the clinical trial and the collection, recording, and reporting of authentic data comply with the requirements in the protocol, GCP, and corresponding regulations.

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

10.1 Clinical Monitoring

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

Before the start of the study, the CRA will assess the qualifications of each study site, and report issues related to facilities, technical equipment, or medical staff to the sponsor. During the study, the CRA is responsible for the monitoring of whether the written ICFs from all subjects have been obtained and whether the data records are correct and complete. Also, the CRA will compare the data entered into the eCRFs with the source data, and inform the investigator of any error or omission. Besides, the CRA will also control the compliance with the protocol and study procedures at each study site, arrange for the supply of investigational drugs, and ensure that the drugs are kept under proper conditions.

The monitoring visit will be conducted in accordance with applicable statutes and regulations. Each site receives regular monitoring visits from the time the subjects are enrolled. After each visit to the investigator, the CRA should submit a written report to the sponsor.

10.2 Quality Assurance Audits

During the course of the study, the sponsor or the representative authorized by the sponsor may perform quality assurance audits on the study sites, database and related study documents. At the same time, the corresponding regulatory authorities may also inspect the study sites, database and related study documents at their own discretion. The investigator must inform the sponsor immediately when an inspection notice is received from the regulatory authorities.

The sponsor's quality assurance department should conduct an audit on the clinical study sites. Audit includes the supply of drugs, required trial documents, records of informed consent

process, as well as the consistency of medical report forms with the source documents. The content and scope of the audits can also be increased as the circumstance may require. After reasonable notice, the investigator should allow auditors commissioned by the sponsor to conduct audits related to the trial and inspections conducted by the regulatory authorities. The primary purpose of an audit or an inspection is to verify that the rights or health of the subjects have been protected, the signing of the ICF and the correct implementation of the trial process, and all data related to the evaluation of the investigational drug have been processed, reported and pre-planned. In addition, the protocol, facility, ethical SOPs, GCP and applicable regulatory requirements are consistent. The investigator should have direct access to all trial documents, source records and source data.

11 DATA MANAGEMENT AND RECORD KEEPING

This study will use an electronic data acquisition (EDC) system, and the study data will be recorded in the eCRFs by the investigator or its authorized personnel. Before the initiation of the study site or data entry, the investigator and authorized personnel will be properly trained and appropriate security measures will be taken for the computers and other equipment.

Data entry into the eCRFs should be completed as soon as possible during or after the visit. The eCRFs should be updated at any time to ensure that they reflect the latest developments of the subjects. To avoid differences in outcome evaluations by different evaluators, it is recommended that baseline and all subsequent efficacy and safety evaluations of a given subject should be performed by the same individual. The investigator shall review the data to ensure the accuracy and correctness of all data entered into the eCRFs. During the study, the investigator should document any evaluations that are not conducted, or any information that is not available, applicable, or known. The investigator needs to sign all verified data electronically.

The CRA will review the eCRF, and evaluate its completeness and consistency. The CRA will also compare the eCRF with the source documents to ensure the consistency of critical data. All data entry, correction and modification will be performed by the investigator or the designee. The data in the eCRFs are submitted to the data server and any modification to the data should be recorded in the audit trail, including reasons, operator names, time and dates of modifications. The roles and permission levels of the personnel responsible for data entry will be determined in advance. The CRA or data manager will submit data queries in the EDC system, and study personnel shall respond to the queries. The EDC system will record the audit trail of each query, including the name of the investigator, as well as the time and date.

Unless otherwise specified, the eCRF should be considered simply as a form for data collection and not a source document. The source documents are all records used by the investigator or hospital, which are related to the subjects and are able to demonstrate the presence,

inclusion/exclusion criteria, and participation of the subjects, including laboratory records, ECG results, pharmaceutical records, and subject folders. Permanent copies of study visit records will be considered as source documents and used to record data of enrolled subjects. Data in the eCRFs should be from the source documents and consistent with source data.

The investigator should be responsible for maintaining all source documents and offering the documents to the CRA for review during each visit. In addition, the investigator must submit a complete eCRF for each enrolled subject, regardless of the duration of participation. The protocol numbers and subject numbers of all supporting documents (such as laboratory records or hospital records) submitted with the eCRFs should be carefully verified. All the personal privacy information (including the subjects' names) should be deleted or made illegible to protect the privacy of the subjects. The investigator should verify that the record has been reviewed and that the data are accurate with an electronic signature. The electronic signature is completed with the investigator's user ID and password. The system automatically attaches the date and time of the signature. The investigator shall not share the user ID and password with other personnel. If data in the eCRF need to be modified, the procedures defined by the EDC system have to be followed. All modifications and reasons for the changes are recorded in the audit trail.

AEs, and concurrent diseases/medical history will be coded. The dictionary used for coding will be described in the "Clinical Study Report".

Clinical trial documents (protocol and revisions, completed eCRFs, signed ICFs) are to be kept and managed in accordance with the GCP. The study sites should keep these documents for 5 years after the end of the study.

The study documents should be retained properly for future access or data traceability. Safety and environmental risks should be considered when retaining documents.

The documents associated with the study may only be destroyed with the written consent of the sponsor and the investigator. The investigator/study site may transfer the study documents to other parties that comply with the record-keeping requirements or to another location that meet record-keeping requirements only after notifying the sponsor and obtaining the written consent.

12 ETHICS

12.1 Ethics Committee

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

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

12.2 Implementation of Ethics

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

The GCP is an international ethical and scientific specification for designing, conducting, recording and reporting clinical trials that involve the participation of human subjects. This study will be conducted in accordance with the GCP and relevant national regulations and in accordance with the relevant ethical principles of the Declaration of Helsinki to protect the rights, safety, and health of the subjects.

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

12.3 Informed Consent Form

Before the start of any study procedure, the ICF should be used to explain to potential participants the potential risks and benefits of this study. The ICF should be in a language that is simple and be easy to understand. The ICF statement should clarify that ICF is voluntarily signed and the risks and benefits of participating in this study should be clearly outlined. The subject may withdraw from the study at any time. The investigator may only enroll a subject after fully explaining the details of the study, answering questions to the subject's satisfaction, giving the subject sufficient

time for consideration, and obtaining written ICF from the subject or his/her legal representative. All signed ICFs must be kept in the investigator's files or in the subject's folder.

The investigator is responsible for explaining the contents of the ICF and obtaining the ICF signed and dated by the subject or his/her legal representative prior to starting the study. The investigator should provide the subject with a copy of the signed ICF. The investigator must document the informed consent process in the source document of the trial.

12.4 Protection of Subjects' Data

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

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

12.5 Protocol deviations

The protocol deviation refers to any non-compliance with the study protocol, the International Conference on Harmonization Good Clinical Practice (ICH GCP), or operating manual. Non-compliance may come from the subjects, investigators, or study site personnel. Deviations should be corrected promptly.

13 PUBLISHING OF STUDY DATA

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

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

The sponsor has the right to announce or publish information or data related to the trial or to report it to the drug administration. The sponsor must obtain the consent of the investigator if the

name of the investigator is included in the content of the announcement, publication or advertising.

14 REFERENCES

1. http://globocan.iarc.fr,2012.
2. Goetze OT, Al-Batran SE, Chevallay M et al. Updates Surg. 2018 Jun; 70(2):173-179.
3. Cunningham D, Okines AFC, Ashley S. Capecitabine and Oxaliplatin for Advanced Esophagogastric Cancer. New England Journal of Medicine 2010, 362:858-859.
4. Waddell T, Chau I, Cunningham D, Gonzalez D, Okines AFC, Wotherspoon A, et al. Epirubicin, oxaliplatin, and capecitabine with or without panitumumab for patients with previously untreated advanced oesophagogastric cancer (REAL3): a randomised, open-label phase 3 trial. The Lancet Oncology 2013, 14:481-489.
5. Ajani JA, Ilson DH, Daugherty K, Pazdur R, Lynch PM, Kelsen DP. Activity of taxol in patients with squamous cell carcinoma and adenocarcinoma of the esophagus. J Natl Cancer Inst 1994, 86:1086-1091.
6. Ilson DH, Ajani J, Bhalla K, Forastiere A, Huang Y, Patel P, et al. Phase II trial of paclitaxel, fluorouracil, and cisplatin in patients with advanced carcinoma of the esophagus. J Clin Oncol 1998, 16:1826-1834.
7. Lorenzen S, Schuster T, Porschen R, Al-Batran SE, Hofheinz R, Thuss-Patience P, et al. Cetuximab plus cisplatin-5-fluorouracil versus cisplatin-5-fluorouracil alone in first-line metastatic squamous cell carcinoma of the esophagus: a randomized phase II study of the Arbeitsgemeinschaft Internistische Onkologie. Ann Oncol 2009, 20:1667-1673.
8. Zhang X, Shen L, Li J, Li Y, Li J, Jin M. A phase II trial of paclitaxel and cisplatin in patients with advanced squamous-cell carcinoma of the esophagus. Am J Clin Oncol 2008, 31:29-33.
9. Lordick F, Kang YK, Chung HC et al. Capecitabine and cisplatin with or without cetuximab for patients with previously untreated advanced gastric cancer (EXPAND): a randomised, open-label phase 3 trial. Lancet Oncol. 2013 May; 14(6):490-9.
10. Waddell T, Chau I, Cunningham D et al. Epirubicin, oxaliplatin, and capecitabine with or without panitumumab for patients with previously untreated advanced oesophagogastric cancer (REAL3): a randomised, open-label phase 3 trial. Lancet Oncol. 2013 May; 14(6):481-9.
11. Sawaki A, Yamada Y, Yamaguchi K et al. Regional differences in advanced gastric cancer: exploratory analyses of the AVAGAST placebo arm. Gastric Cancer. 2018 May; 21(3):429-438.
12. Shen L, Li J, Xu J, Bevacizumab plus capecitabine and cisplatin in Chinese patients with inoperable locally advanced or metastatic gastric or gastroesophageal junction cancer: randomized, double-blind, phase III study (AVATAR study). Gastric Cancer. 2015 Jan; 18(1):168-76.

13. Fuchs CS, Doi T, Jang RW et al. Safety and Efficacy of Pembrolizumab Monotherapy in Patients With Previously Treated Advanced Gastric and Gastroesophageal Junction Cancer: Phase 2 Clinical KEYNOTE-059 Trial. JAMA Oncol. 2018 May 10; 4(5).
14. https://www.clinicaltrials.gov/ct2/show/NCT02494583?term=KEYNOTE-062&rank=1.
15. Kang YK, Boku N, Satoh T et al. nivolumab in patients with advanced gastric or gastro-oesophageal junction cancer refractory to, or intolerant of, at least two previous chemotherapy regimens (ONO-4538-12, ATTRACTION-2): a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet. 2017 Dec 2; 390(10111):2461-2471.
16. https://www.clinicaltrials.gov/ct2/show/NCT03143153?term=Checkmate648&rank=1.
17. Zou W, Chen L. Inhibitory B7-family molecules in the tumour microenvironment. Nat Rev Immunol 2008, 8:467-477.
18. Chen L, Han X. Anti-PD-1/PD-L1 therapy of human cancer: past, present, and future. Journal of Clinical Investigation 2015, 125:3384-3391.

15 APPENDIX

Appendix 1: Signature Page for Investigator

Protocol Title: A Randomized, Double-Blind, Multi-Center Phase III Clinical Trial Evaluating the Efficacy and Safety of IBI308 or Placebo in Combination with Oxaliplatin and Capecitabine (XELOX), for First-Line Treatment of Unresectable, Locally Advanced, Recurrent, or Metastatic Gastric or Gastroesophageal Junction Adenocarcinoma

Protocol No.: CIBI308E301

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

Instructions for the Investigator: Please sign and date this signature page, type the investigator's name and job title, as well as the name of the study site, and return this document to Innovent Biologics (Suzhou) Co., Ltd.

I have read the entire contents of this study protocol and shall perform the study as required:

Investigator's signature: _____ Date: _____

Name (Print): _____

Job title: _____

Name/Address of study site: _____

_____

_____

Appendix 2: ECOG PS Scoring Criteria

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

References

Oken MM, Creech RH, Tormey DC, Horton J, Davis TE, McFadden ET, and Carbone PP. Toxicity and Response Criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol 1982; 5:649-655.

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 the baseline level, tumor lesions/lymph nodes will be categorized into measurable and non-measurable ones according to the following definitions:

1.1.1 Measurable lesion

Tumor lesion: At least one diameter line that can be accurately measured (recorded as the maximum diameter), and its minimum length is as follows:

- 10 mm as indicated by CT scan (CT slice thickness ≤ 5 mm)
- 10 mm caliper measurement by clinical exam (lesions which cannot be accurately measured with calipers should be recorded as non-measurable)
- 20 mm by chest X-ray
- Malignant lymph nodes: measurable with pathological enlargement and a short diameter of a single lymph node by CT scanning of ≥ 15 mm (it is recommended that the slice thickness measured by CT scanning should be no more than 5 mm). At baseline and follow-up, only the minimum diameter will be measured and followed up.

1.1.2 Non-measurable lesion

All other lesions, including small lesions (with the maximum diameter of < 10 mm or the minimum diameter of a pathological lymph node of ≥ 10 mm to < 15 mm) and non-measurable lesions. Non-measurable lesions include: meningeal disease, ascites, pleural or pericardial effusion, inflammatory breast cancer, cancerous lymphangiitis of the skin/lung, abdominal masses that cannot be diagnosed and followed up by imaging, and cystic lesions.

1.1.3 Special considerations for lesion measurement

Bone lesions, cystic lesions, and lesions previously treated with local therapy must be specified:

Bone lesions:

- Bone scan, PET scan, or plain films are not suitable for measuring bone lesions, but can be used to confirm the presence or disappearance of bone lesions;
- In case of osteolytic lesions or mixed osteolytic/osteogenic lesions that have a definite soft tissue composition with the soft tissue composition meeting the above measurability definition, these lesions can be considered as measurable lesions provided that they can be evaluated using tomographic imaging techniques such as CT and MRI;

- Osteogenic lesions are non-measurable lesions.

Cystic lesions:

- A lesion that meets the definition criteria for simple cysts in radiography should not be considered as a malignant lesion because it is a simple cyst by definition, which should be neither a measurable lesion nor a non-measurable lesion;
- If such lesion is cystic metastatic and meets the above measurability definition, it can be regarded as a measurable lesion. However, if noncystic lesions are present in the same patient, these are preferred for selection as target lesions.

Lesions with prior local treatment:

- Tumor lesions situated in a previously irradiated area, or in an area subjected to other loco-regional treatment, are usually not considered measurable unless there has been demonstrated progression in the lesion. The conditions under which these lesions are measurable should be detailed in the study protocol.

1.2 Description of Measurement Method

1.2.1 Measurement of lesions

When performing clinical evaluation, all tumor measurements should be recorded in metric notation. All baseline assessments of tumor lesion size should be possibly completed within 21 days (3 weeks) before the start of treatment.

1.2.2 Assessment method

The same technique and method should be used for baseline assessment and subsequent measurement of lesions. Except for lesions that cannot be evaluated by imaging, while the clinical examination is applicable only, other lesions must be evaluated by imaging.

Clinical lesions: Clinical lesions will only be considered measurable when they are superficial and ≥ 10 mm diameter as assessed using calipers (e.g. skin nodules). For subjects with skin lesions, it is recommended to use color photos containing the size of the lesion measured by ruler as an archive. When the lesion can be evaluated by both imaging and clinical examination, imaging evaluation should be used whenever possible 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 when progression is an important endpoint, particularly in identifying new lesions. Chest X-ray examination is only applicable when the boundary of the measured lesion is clear and the lungs are well ventilated.

CT and MRI: CT is the best currently available and repeatable method for efficacy evaluation. The measurability definition in this guideline is based on the thickness by scanning of ≤ 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 measurement method to measure the lesion size. Ultrasonic examination can not be repeated after the measurement due to its operational dependency, and cannot guarantee 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 trial, CT or MRI should be used for confirmation. If there is concern about radiation exposure at CT, MRI may be used instead of CT in selected instances.

Endoscopy and laparoscopy: These techniques are not recommended for objective evaluation of tumors, but they can be used to confirm the CR results when biopsy specimens are obtained, or to confirm the relapse in trials where the endpoint is defined as a relapse or surgical resection after CR.

Tumor markers: Tumor markers cannot be used alone to evaluate objective tumor response. However, if the marker level exceeds the ULN at baseline, it must be returned to normal when used to evaluate a CR. Since the tumor markers are varied from diseases, it needs to be considered when writing measurement criteria in the protocol. Specific criteria for CA-125 response (recurrent ovarian cancer) and PSA (recurrent prostate cancer) response have been published. In addition, the International Gynecologic Cancer Society (IGCS) has prepared the criteria for CA-125 progression, which will soon be added to the objective evaluation criteria for tumors in the first-line treatment of ovarian cancer.

Cytological/histological technologies: Under certain circumstances specified in the protocol, these technologies can be used to identify PR and CR (e.g., residual benign tumor tissue is often present in the lesions of germ cell tumors). When exudation may be a potential side effect of a certain therapy (such as treatment with a taxane compound or an angiogenesis inhibitor), and the tumor can be measured meeting the criteria for response or disease stabilization, the occurrence of tumor-related exudation during treatment or aggravation can be confirmed by cytological technologies to distinguish response (or SD) and PD.

2 ASSESSMENT OF TUMOR REMISSION

2.1 Assessment of All Tumors and Measurable Lesions

In order to evaluate the objective response or possible future progress, it is necessary to perform a baseline assessment of the total tumor burden of all tumor lesions, which then should be used as the references for the subsequent measurement results. In clinical protocols with objective

response as the primary treatment endpoint, only subjects with measurable lesions at baseline can be enrolled. Measurable lesion is defined by the presence of at least one measurable lesion. For trials with PD (time of PD or degree of progression on a fixed date) as the primary endpoint of treatment, the inclusion criteria for subjects with or without measurable lesions must be specified in the protocol.

2.2 Baseline Documentation of Target and Non-Target Lesions

When there are more than one measurable lesions in the baseline assessment, all lesions should be recorded and measured, and the total number should not exceed 5 (not more than 2 per organ), since the target lesion represents all involved organs (i.e., for subjects with 1 or 2 involved organs only, at most 2 or 4 target lesions can be selected for baseline measurement).

Target lesions must be selected based on size (the maximum diameter), and can represent all involved organs, and measurements must have well repeatability. Sometimes when the largest lesion cannot be measured repeatedly, the lesion with the maximum diameter may be selected again.

Special attention should be paid to the lymph nodes defined as normal tissues that can be identified by imaging, even if there is no signs of tumor metastasis. Pathological nodes which are defined as measurable and may be identified as target lesions must meet the following criteria: the minimum diameter by CT scanning of ≥ 15 mm. Only the minimum diameter should be measured at the baseline. Usually, radiologists will use the minimum diameter of a nodule to determine whether the nodule has metastasized. The nodule size is generally expressed in 2-D data of imaging (either an axial plane in CT or one of the axial, sagittal, or coronal plane in MRI). The minimum value is the minimum diameter. For example, a 20 mm × 30 mm abdominal nodule with a minimum diameter of 20 mm can be considered as a malignant, measurable nodule. In this example, 20 mm is the measured value of the nodule. Nodules with a diameter of ≥ 10 but < 15 mm should not be considered as target lesions. Nodules with a diameter of < 10 mm should not be classified as pathological nodules, requiring no further records or observations.

The sum of the calculated diameters of all target lesions (including the maximum and the minimum diameters of non-nodular lesions) will be reported as the sum of the diameters at the baseline. If the lymph node diameter is included, as mentioned above, only the minimum diameter is counted. The sum of the baseline diameters will be used as a reference value for the disease at the baseline.

All the remaining lesions, including pathological lymph nodes, can be considered as non-target lesions and no measurement is required, but such lesions should be recorded during baseline assessment. For examples, such lesions can be recorded as "presence", "absence", or "definitive

progression" in rare cases. Extensive target lesions can be recorded with target organs (such as massively enlarged pelvic lymph nodes or large-scale liver metastases).

2.3 Response Criteria

2.3.1 Assessment of target lesions

Complete response (CR): All target lesions should be disappeared, with the minimum diameter of all pathological lymph nodes (including target and non-target nodules) reducing to < 10 mm.

Partial response (PR): The sum of target lesion diameters is reduced by at least 30% compared to the baseline level.

PD: The minimum value of the sum of all measured target lesion diameters throughout the study should be used as a reference, with increases in the diameter of at least 20% compared to the baseline level (if the baseline measurement is the minimum value, it should be used as a reference); otherwise, the absolute value of the sum of the diameter must be increased by 5 mm (the appearance of one or more new lesions is also considered to be PD).

SD: Due to neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, the minimum sum of diameters can be taken as reference in this study.

2.3.2 Considerations for non-target lesion assessment

Lymph nodes: Even if the lymph nodes are identified as target lesions of a decrease of less than 10 mm, the actual minimum diameter value corresponding to the baseline must be recorded for each measurement (consistent with the anatomical plane at baseline measurement). In other words, if the lymph node is a target lesion, even if the criteria for CR are reached, a CR cannot be determined due to the definition of < 10 mm of the minimum diameter of a normal lymph node. Target lymph node lesions that need to be specifically recorded in specific locations in the eCRF by other recording methods: For CR, the minimum diameter of all lymph nodes must be < 10 mm; for PR, SD, and PD, the actual measured minimum diameter of the target lymph node will be included in the sum of the target lesion diameters.

Target lesions that are too small to be measured: In clinical studies, all lesions (nodules or non-nodules) recorded at baseline should be recorded again in subsequent assessments, even if these lesions are very small (as small as 2 mm, for example). However, in some cases, the lesion may be too small so that the CT scan image is very blurry, and it is difficult for the radiologist to define the measurement value. Therefore, such lesion may be reported as "too small to be measured". In this case, it is very important to record a value on the eCRF. If it is the opinion of the radiologist that the lesion has probably disappeared, the measurement value should be recorded as 0 mm. If the lesion does exist but with a blurry image so that an exact measurement value cannot be obtained, the default recording should be 5 mm. (Note: This is unlikely to occur

in lymph nodes, because a lymph node normally has a measurable size, or it is often surrounded by fat tissues as in the retroperitoneal cavity; but if the measurement value of such node cannot be obtained, the default recording should also be 5 mm). The default value of 5 mm is determined by the cutting thickness of the CT scan (which will not change due to different cutting thickness values of CTs). Since the same measurement value is hardly possible to occur twice, providing the aforesaid default value can reduce the risk of erroneous assessment. But it needs to be reiterated that if the radiologist can provide the exact measured size of the lesion, the actual value must be recorded, even if the diameter of the lesion is less than 5 mm.

Separated or combined lesions: When a non-nodular lesion is presented in parts, the maximum diameter of each separated part is added to calculate the sum of the lesion diameters. Similarly, for combined lesions, they can be distinguished by the plane between the combined parts, and then calculate the maximum diameter of each. However, if the combination is inseparable, the maximum diameter should be taken as the maximum diameter of the entire combined lesion.

2.3.3 Assessment of non-target lesions

This section defines the response criteria for non-target lesions. While some non-target lesions may actually be measurable but without measurement requirements, such lesions should be assessed only qualitatively at time points specified in the protocol.

CR: All non-target lesions are disappeared and the levels of tumor markers are recovered to normal. All lymph nodes must be non-pathological in size (with the minimum diameter of < 10 mm).

Incomplete response/non-progressive disease: At least 1 non-target lesion is found with/without persistent tumor marker levels that exceed normal levels.

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

2.3.4 Special considerations regarding the assessment of non-target lesion progression

The supplementary explanation for the non-target lesion progression is as follows: When the subject has measurable non-target lesions, if a clear definition of progress is to be made on the basis of the non-target lesions, the overall non-target lesions must have deteriorated to the extent that the treatment must be terminated even if the target lesions are evaluated as stable or PR. However, the general increase in the size of one or more non-target lesions is often insufficient to meet the criteria for PDs. Therefore, when the target lesion reachs stable or PR, it is very rare that the change of non-target lesions alone can define the overall tumor progression.

When all of the subject's non-target lesions are not measurable: This is applicable to some phase Ⅲ trials provided that the presence of a measurable lesion is not required in the inclusion

criteria. However, the overall assessment is also based on the aforesaid requirements since no measurement value can be obtained for the lesion. The assessment of the exacerbation of non-target lesions is a major challenge (by definition: all non-target lesions must not be measurable), and thus when the changes in non-target lesions lead to an increase in the overall disease load equivalent to the PD of target lesions, an effective test method should be established for assessment according to the definitive progressions of non-target lesions. For example, the lesion can be described as an increase in tumor burden equivalent to an additional 73% increase in volume (equivalent to a 20% increase in the diameter of a measurable lesion); or a peritoneal effusion from "minor" to "major"; or a lymphatic lesion from "local" to "extensive"; or lesions described in the protocol as "sufficient to cause changes in the therapy". Other examples include a pleural effusion from "trace" to "major", lymphatic involvement spreading from the primary site to a distant site, or lesions described in the protocol as "requiring changes in the treatment". If a definitive progression has been found, the subject should be generally considered as having PD at the time point of the finding. It is best to have objective criteria applicable to the assessment of non-measurable lesions. Notably, the additional criteria must be reliable.

2.3.5 New lesions

The appearance of new malignant lesions can be an indication for the progression of the disease. Therefore, it is critical to perform a certain assessment for such new lesions. Currently, there is no specific criteria for imaging tests of these lesions, while the findings for new lesions should be definitive. For example, the progression cannot be attributed to differences in imaging technologies, changes in imaging morphology, or other lesions except tumors (such as some "new bone lesions" that are simply the cure or the recurrence of the underlying lesions). This is of great importance when the patient is partially or completely responded to the treatment for his/her lesions at baseline. Specifically, a necrosis of a liver lesion may be defined as a new cystic lesion in the CT report, but it is not.

Lesions that have been detected during follow-up but not found at baseline will be considered as new lesions, and will be an indication for a PD. For example, for a subject who is found to have visceral lesions during the baseline examination, and then metastases by a head CT or MRI, the subject's intracranial metastatic lesion will be considered as the rationale for the determination of PD, even if no cranial examination is performed at baseline.

If a new lesion is not definitive due to its small size or other reasons, further treatment and follow-up evaluation are required to confirm whether it is a new lesion. If the lesion is confirmed to be a new one by repeated examinations, the time of the initial finding should be counted as the start of the PD.

Generally, the FDG-PET assessment of lesions requires additional tests for supplemental confirmation, and it is reasonable to combine the results from FDG-PET tests and those from CT tests (especially for new suspicious diseases). New lesions can be identified by FDG-PET tests based on the following procedures:

In case of negative FDG-PET test results at baseline in combination with positive results from subsequent follow-up FDG-PET tests, a PD is indicated.

In case of no FDG-PET tests at baseline in combination with positive results from subsequent FDG-PET tests:

A PD can be proved if new lesions determined by the subsequent FDG-PET test results which are positive are consistent with those determined by CT test results.

Otherwise, the CT tests should be performed again for confirmation of new lesions with positive test results of FDG-PET found in follow-ups (if confirmed, the time of abnormality found by previous FDG-PET tests should be counted as the start of the PD).

And no progression should be determined in case of consistency between the subsequent FDG-PET test results which are positive and those of existing lesions determined by CT tests.

2.4 Evaluation of Optimal Overall Efficacy

The evaluation of the best overall response refers to the best response recording from the start to the end of the study, while any necessary conditions must also be taken into account for confirmation. Sometimes, the therapeutic response will appear after the end of treatment. As a result, it should be clearly specified in the protocol that whether the efficacy evaluation after the treatment is counted in the evaluation of the best overall response. Also in the protocol, it must be specified that how any new therapy before progression affects the best response. The best response from the subjects mainly depends on the results of target and non-target lesions and the manifestations of new lesions. In addition, the response depends on the nature of the study, as well as the requirements and measurement criteria in the protocol. Specifically, the response from the subjects is the primary endpoint in non-randomized studies where the confirmation of PR or CR is required for the evaluation of the best overall response.

2.4.1 Time point response

It is assumed that there will be an efficacy evaluation at each time point defined in the protocol. Table 1 summarizes the overall efficacy evaluation at each time point for subjects with measurable lesions at baseline.

If no measurable lesions (no target lesions) are found in subjects, see Table 2 for the corresponding evaluation.

2.4.2 Description of missing evaluations and non-evaluable cases

If the imaging or measurement of the lesions of a subject cannot be performed at a specific time point, the subject should then be determined non-evaluable at that time point. If only part of the lesions of a subject can be evaluated in an evaluation, the case should then be determined as non-evaluable at that time point, unless there is evidence to prove that the missing lesions will not affect the efficacy evaluation at the specified time point. In addition, such case may be an indication for a PD. For example, a subject has 3 lesions with a sum of diameters of 50 mm at the baseline level, but only 2 are subsequently determined evaluable, with a sum of diameters of 80 mm, and then the subject will be evaluated as having a PD, regardless of the effects of the missing lesion.

2.4.3 Optimal overall response: at all time points

Once all data of the subjects are available, their optimal overall response can be determined.

Evaluation of the optimal overall response when the confirmation of complete or partial response (CR/PR) is not required in the study: The best response in the study refers to the optimal response at all time points (for example, SD is the efficacy evaluation for the subjects in cycle 1, PR for cycle 2, and PD for the last cycle. However, the optimal overall response should be evaluated as PR). When the optimal overall response is evaluated as SD, the minimum time from the baseline level specified in the protocol must be met. If not, the SD result will not be accepted and the optimal overall response from the subjects will depend on the subsequent evaluations. For example, if the response from the subjects is evaluated as SD in cycle 1 and PD in cycle 2, but the minimum time requirement of SD is not met, the optimal overall response will be evaluated as PD. Similarly, if the response from the subjects is evaluated as SD in cycle 1, followed by a loss to follow-up, the subjects will be considered non-evaluable.

Evaluation of the optimal overall response when the confirmation of CR/PR is required in the study: The complete or partial response can be determined only if the CR/PR criteria required by the study are met by each subject, and at a subsequent time point (usually 4 weeks later) specifically mentioned in the protocol, the efficacy is confirmed again. In this case, the optimal overall response can be found in the description of Table 3.

2.4.4 Special notes on efficacy evaluation

When the nodular lesions are included in the overall target lesion evaluation and the node size is reduced to "normal" scale (< 10 mm), there is still going to be a scan report on the lesion size. In order to avoid overestimating the condition indicated by the increase in nodule size, the measurement result will still be recorded even if the size is normal. As mentioned above, this suggests that the measurement results from subjects who are evaluated as CR will not be recorded as 0 in the eCRF.

If the efficacy confirmation is required during the study, the optimal overall response will be more difficult to be evaluated at the repeated "non-measurable" time points. For these missing data/evaluations, it must be stated in the analysis plan of the study that they can be explained clearly when determining efficacy. In most studies, for example, the response from a subject in PR-NE-PR can be considered as the efficacy confirmation.

When a subject experiences an overall deterioration of the health status requiring discontinuation of the treatment, but no objective evidences are obtained, it should be reported as a symptomatic progression. In addition, the cases with objective progression should be possibly assessed even after the treatment is terminated. Symptomatic deterioration is not an assessment description of objective response, but the reason for the discontinuation of the treatment. In this case, the objective response will be assessed by the target and non-target lesions shown in Tables 1 to 3.

The assessment should be based on the early progression as required by the definition, but early deaths or non-evaluable cases are defined as special cases for studies, which should be specifically described in each of the study protocol (depending on the treatment intervals and cycles).

Sometimes, it may be difficult to distinguish local lesions from normal tissues. When such definition is the basis for the assessment of CR, we recommend a biopsy before evaluating the efficacy by CR of local lesions. When the abnormal imaging results of the local lesions in some subjects are considered as indications for lesion fibrosis or scarring, the FDG-PET should be taken as criteria similar to biopsy, in order to confirm the efficacy by CR. In this case, the application of FDG-PET should be prospectively described in the protocol, and supported by the report of the specialty medical literatures. However, it must be realized that false positive results can be obtained in the CR assessment due to the limitations of FDG-PET and biopsy themselves (including the resolution and sensitivity).

Attached Table 3-1. Time Point Response — subjects with target lesions (including or not including non-target lesions)

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

Target lesion	Non-target lesion	New lesion	Overall response
Any	PD	Yes or no	PD
Any	Any	Yes	PD
CR = complete response	PR = partial response	SD = stable disease	PD = progressive disease; NE = non-measurable

Attached Table 3-2. Time Point Efficacy — subjects with non-target lesions only

Non-target lesion	New lesion	Overall response
CR	No	CR
Non-CR/non-PD	No	Non-CR/non-PD
Not completely evaluable	No	NE
PD that cannot be determined	Yes or no	PD
Any	Yes	PD

Note: "Non-CR/non-PD" is preferred over SD for non-target disease. Since SD is increasingly used as an endpoint for efficacy evaluation, the efficacy by non-CR/non-PD is determined for cases without specified measurable lesions.

For indefinite progression findings (such as very small and uncertain new lesions; and cystic or necrotic changes in the underlying lesions), the treatment can be continued until the next assessment. If a PD is confirmed in the next assessment, the date when a suspected progression is found previously will be taken as the date of the progression.

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

Overall response at the first time point	Overall response at the subsequent time points	Optimal overall response
CR	CR	CR
CR	PR	SD, PD, or PR[a]
CR	SD	If SD meets the minimum time requirement, it should be the result otherwise PD
CR	PD	If SD meets the minimum time requirement, it should be the result otherwise PD
CR	NE	If SD meets the minimum time requirement, it should be the result otherwise NE
PR	CR	PR
PR	PR	PR
PR	SD	SD
PR	PD	If SD meets the minimum time requirement, it should be the result otherwise PD
PR	NE	If SD meets the minimum time requirement, it should be the result otherwise NE
NE	NE	NE

Note: CR = complete response; PR = partial response; SD = stable disease; PD = progressive disease; NE = non-evaluable. SUP. "a": If CR is definitely confirmed at the first time point, for subjects who are found to have any disease at the subsequent time points, the evaluation results at the subsequent time points should still be PD (due to the recurrence of the disease after CR) even if the PR criteria are met according to the efficacy from the baseline. The optimal response will be determined by whether SD is observed at the minimum treatment interval. The first evaluation result may be CR in some cases, while small lesions are indicated by scanning at the subsequent time points. Consequently, the efficacy in the subjects at the first time point should actually be PR rather than CR. In this case, the initial CR result should be changed to PR, for which the optimal response will be PR.

2.5. Frequency of Tumor Re-Evaluation

The frequency of the tumor re-evaluation during the treatment will be determined according to the treatment regimen while being consistent with the type and schedule of the treatment. For the phase II trials where the therapeutic benefits are unclear, it is rational to perform a follow-up every 6–8 weeks (the time is designed at the end of a cycle), for which the time interval may be adjusted depending on special protocols or circumstances. In the protocol, it must be specified that which tissue sites are assessed at the baseline level (usually those that are most likely to be closely related to the metastatic lesion of the studied tumor type), along with the frequency to repeat the evaluation. Normally, both the target and non-target lesions should be evaluated in each assessment, while some non-target lesions may be less frequently evaluated under optional circumstances, such as bone scans that are only required when the evaluation of the efficacy by the target disease is confirmed as CR or when a progressive bone disease is suspected.

After treatment, the tumor re-evaluation will be determined by whether the response rate or the time to an event (progression/death) is used as the endpoint of the clinical trial. If the time to an event (such as TTP/DFS[1]/PFS) is used as the endpoint, the routine re-evaluation should be performed as required by the protocol. Especially in randomized comparison studies, pre-defined evaluations should be included in the schedule (e.g., 6–8 weeks during treatment, or 3–4 months after treatment) and not be affected by other factors, such as delayed treatment, dosing intervals, and any other events that may bring imbalanced treatment arms in the timing of disease evaluation.

2.6. Confirmation of Efficacy Evaluation/Response Period

2.6.1. Confirmation

For non-randomized clinical studies with efficacy as the primary endpoint, the efficacy by PR and CR must be confirmed to ensure that the efficacy results are not obtained from inaccurate evaluations. This allows reasonable explanations for the results when the historical data are available, but the efficacy results based on the historical data should also be confirmed. In all other cases, such as randomized trials (phase II or III) or studies with either SD or PD as the primary endpoint, there are no more requirements for an efficacy confirmation since it is a valueless practice when explaining the trial results. Nevertheless, eliminating the requirement for

efficacy confirmation will make the review at the study site even more important in preventing deviations, especially for unblinded studies.

In the case of SD, the measurement that meets the SD criteria specified in the protocol must be obtained at least once in the shortest time interval (generally no shorter than 6–8 weeks) after the start of the study.

2.6.2 Overall response period

The overall response period refers to the time from the first measurement consistent with the criteria for CR or PR (whichever is obtained first) to the time when the recurrence or progression of the disease is firstly recorded (the minimum measurement recorded in the study is used as a reference for determination of PD). The overall response duration refers to the time from the first measurement consistent with the criteria for CR to the time when the recurrence or progression of the disease is firstly recorded.

2.6.3 Stable disease period

The stable disease period refers to the time from the start of the treatment to the occurrence of a PD (which should be started from the time of randomization in randomized trials) while using the minimum sum in the study as a reference (if the baseline sum is the minimum value, it is used as a reference for PD calculation). The clinical association of SD period varies with different studies and diseases. For a specific trial using the proportion of patients with SD for a minimum period of time as an endpoint, it should be specified in the protocol that the minimal time interval between two measurements defined by SD.

Note: The DOR and SD as well as the progression-free survival (PFS) are influenced by the frequency of the follow-up after baseline evaluation. It is not in the scope of the guidelines to define a standard follow-up frequency. A number of factors should be considered for the follow-up frequency, such as the type and staging of the disease, treatment cycles, criteria, and specifications. When a comparison across studies is required, the accuracy limitations of the corresponding measurement endpoints should also be considered.

2.7. PFS/TTP

2.7.1 Phase II clinical trials

This guideline is mainly about the use of objective response as a study endpoint in phase II clinical trials. In some cases, the response rate may not be preferred when evaluating the potential anti-cancer activities of new drugs/new regimens. In such cases, PFS/PPF results at the cut-off time points can be considered as suitable alternative indicators for being the signal source to identify the biological activity of the new drug. However, such evaluations obviously are questionable in an uncontrolled trial given that the seemingly valuable observations may be related to the patient screening and other biological factors rather than the effect of drug intervention. Therefore, it is preferable to have a randomized control designed for the phase II clinical trials using the said evaluation as an endpoint. However, for certain tumors with consistent clinical manifestations (usually in persistent and poor conditions), it is also acceptable to have non-randomized trials. Yet in such cases without a positive control, close attention should be paid to recording for efficacy evidences when assessing the expected PFS or PPF results.

Appendix 4: Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) Equation

CKD-EPI equation and Modification of Diet in Renal Disease (MDRD) equation are the most common equations used during creatinine-based assessment of glomerular filtration rate (GFR) in adults. The computational tool of the National Kidney Disease Education Program (NKDEP) works depending on creatinine determination by traceable isotope dilution mass spectrometry (IDMS). In all labs, creatinine should be determined by traceable IDMS.

When GFR is > 60 mL/min/1.73 m^2, the CKD-EPI equation more accurately reflects the glomerular function compared to the MDRD equation. In this study, GFR is required to be ≥ 60 mL/min/1.73 m^2, so this equation is recommended:

Black:

Females: Scr ≤ 62 μmol/L (≤ 0.7 mg/dL) $GFR = 166 \times (Scr(mg/dL)/0.7)^{-0.329} \times (0.993)^{Age}$

Scr > 62 μmol/L (> 0.7 mg/dL) $GFR = 166 \times (Scr(mg/dL)/0.7)^{-1.209} \times (0.993)^{Age}$

Males: Scr ≤ 80 μmol/L (≤ 0.9 mg/dL) $GFR = 163 \times (Scr(mg/dL)/0.9)^{-0.411} \times (0.993)^{Age}$

Scr > 80 μmol/L (> 0.9 mg/dL) $GFR = 163 \times (Scr(mg/dL)/0.9)^{-1.209} \times (0.993)^{Age}$

Non-black

Females: Scr ≤ 62 μmol/L (≤ 0.7 mg/dL) $GFR = 144 \times (Scr(mg/dL)/0.7)^{-0.329} \times (0.993)^{Age}$

Scr > 62 μmol/L (> 0.7 mg/dL) $GFR = 144 \times (Scr(mg/dL)/0.7)^{-1.209} \times (0.993)^{Age}$

Males: Scr ≤ 80 μmol/L (≤ 0.9 mg/dL) $GFR = 141 \times (Scr(mg/dL)/0.9)^{-0.411} \times (0.993)^{Age}$

Scr > 80 μmol/L (> 0.9 mg/dL) $GFR = 141 \times (Scr(mg/dL)/0.9)^{-1.209} \times (0.993)^{Age}$

The online CKD-EPI calculator is available at the following website:

https://qxmd.com/calculate/calculator_251/egfr-using-ckd-epi