CLINICAL STUDY PROTOCOL

Study Title:	An Open-Label, Multi-Center, and Phase Ia/Ib Study Evaluating the Monotherapy or Combination Chemotherapy of IBI308 in the Treatment of Chinese Subjects with Advanced Malignant Tumors
Protocol Number:	CIBI308A101
Version and Date:	Jan. 31, 2019/Version 3.0
Product Name:	Sintilimab (IBI308)
Study Phase:	Phase Ia/Ib
Sponsor:	Innovent Biologics (Suzhou) Co., Ltd. No. 168 Dongping Street, Suzhou Industrial Park, Jiangsu, China
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Sponsor's Signature Page

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Project Number: CIBI308A101

Title	Name (regular script)	Signature	Date
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Protocol Synopsis

Protocol no.	CIBI308A101
Sponsor	Innovent Biologics (Suzhou) Co., Ltd.
Investigational drug	Sintilimab (IBI308)
Active ingredient	Recombinant fully human anti-PD-1 monoclonal antibody
Study title	An Open-Label, Multi-Center, and Phase Ia/Ib Study Evaluating the Monotherapy or Combination Chemotherapy of IBI308 in the Treatment of Chinese Subjects with Advanced Malignant Tumors
Study phase	Phase I
Expected study duration	Phase Ia: approximately 12 months; Phase Ib: approximately 36 months.
Study objectives	Primary study endpoints: • To evaluate the safety and tolerability of the monotherapy or combination chemotherapy of IBI308 in subjects with advanced solid tumors; • To evaluate the anti-tumor activity of the monotherapy or combination chemotherapy of IBI308 in subjects with advanced solid tumors. Secondary study endpoints: • To evaluate the pharmacokinetic (PK) characteristics of single- and repeated-administration of IBI308 in subjects with advanced solid tumors; • To evaluate the immunogenicity of IBI308 in subjects with advanced solid tumors; • To evaluate the pharmacodynamic (PD) parameters of IBI308 in subjects with advanced solid tumors. Exploratory objectives: • To explore the use of "immunerelated Response Evaluation Criteria in Solid Tumors" (irRECIST) to assess the efficacy of IBI308 in subjects with advanced solid tumors; • To explore the potential biomarkers in tumor tissues that can predict the efficacy of IBI308: including but not limited to immunohistochemistry assay of PD-L1 expression in tumor samples, whole exome sequencing to detect tumor mutation burden (TMB), multicolor immunohistochemistry, and PD-L1 and CD8 double staining assay.

Study design	This is a multi-center, open-label, phase Ia/Ib study of IBI308 monotherapy or combination chemotherapy in the treatment of Chinese subjects with advanced malignant tumors. Phase Ia study: This is designed to investigate tolerability, safety, and PK of IBI308. Around 12–24 patients with advanced solid tumors that failed standard treatment will be enrolled. The dose escalation strategy is established using the standard "3 + 3" design. Four dose levels (1 mg/kg, 3 mg/kg, 200 mg, and 10 mg/kg) will be evaluated in this section. After the completion of 1 mg/kg dose administration, subjects are randomized in a 1:1 ratio to either 3 mg/kg or 200 mg dose group for independent evaluations. Dose limiting toxicity (DLT) is observed for 28 days after the first dose for each dose group. After completion of DLT observation, subjects are treated with IBI308 Q2W (1 mg/kg, 3 mg/kg, or 10 mg/kg) or Q3W (200 mg) until PD, intolerable toxicity, withdrawal of informed consent, or other reasons requiring treatment discontinuation (whichever occurs first). The specific study visit arrangement is shown in Table 1 and Table 2. Phase Ib study: This is designed to preliminarily assess the safety and anti-tumor activity of IBI308 in the following cohorts. • Cohort A: Melanoma study, enrolling approximately 10–20 subjects with advanced melanoma. They will receive 200 mg IV Q3W of IBI308 until PD, intolerable toxicity, withdrawal of informed consent, 24 months of treatment, or other reasons for discontinuation of the study treatment (whichever occurs first). After enrollment of up to 20 subjects, the sponsor can decide whether to expand the enrollment based on PK, preliminary efficacy, and safety data. The specific study visit arrangement is shown in Table 3 and Table 6. • Cohort B: Study on malignant tumors of the digestive system or neuroendocrine tumors, enrolling approximately 50–100 subjects with such tumors who failed or became intolerable to first-line systemic standard treatment. They will receive 200 mg IV Q3W of IBI308 until PD, intolerable toxicity, withdrawal of informed consent, 24 months of treatment, or other reasons for discontinuation of the study treatment (whichever occurs first). After enrollment of 50 subjects, the sponsor will terminate the enrollment of subjects based on the progress of clinical development and preliminary efficacy and safety data of IBI308. The specific study visit arrangement is shown in Table 3 and Table 6. • Cohort C: Lung cancer study, enrolling approximately 10–20 subjects of advanced NSCLC who failed or became intolerant to first-line systemic standard treatment. They will receive 200 mg IV Q3W of IBI308 until PD, intolerable toxicity, withdrawal of informed consent, 24 months of treatment, or other reasons for discontinuation of the study treatment (whichever occurs first). The specific study visit arrangement is shown in Table 3 and Table 6. • Cohort D: Study on the safety and preliminary efficacy evaluation of first-line treatment of advanced non-squamous non-small cell lung cancer (nsNSCLC) using IBI308 in combination with chemotherapy, enrolling approximately 20 subjects. Each treatment cycle contains 3 weeks. And 200 mg IV of IBI308, 500 mg/m^2 IV of pemetrexed, and 75 mg/m^2 IV of cisplatin are given on D1 of each cycle. Up to 4

	cycles of triple drug combination therapy are given. Subsequently, the subjects experiencing no PD can receive a maintenance treatment of 200 mg IV Q3W of IBI308 and 500 mg/m^2 IV Q3W of pemetrexed until PD, intolerable toxicity, withdrawal of informed consent, 24 months of treatment, or other reasons for discontinuation of the study treatment (whichever occurs first). The specific study visit arrangement is shown in Table 4 and Table 6. • Cohort E: Study on the safety and preliminary efficacy evaluation of first-line treatment of advanced squamous cell non-small cell lung cancer (scNSCLC) using IBI308 in combination with chemotherapy, enrolling approximately 20 subjects. Each treatment cycle contains 3 weeks. The dosing regimen is IBI308 200 mg IV D1 + gemcitabine 1250 mg/m^2 IV D1, D8 + cisplatin 75 mg/m^2 IV D1. Up to 6 cycles of triple drug combination therapy are given. Subsequently, the subjects experiencing no PD can receive a maintenance treatment of 200 mg IV Q3W of IBI308 until PD, intolerable toxicity, withdrawal of informed consent, 24 months of treatment, or other reasons for discontinuation of the study treatment (whichever occurs first). The specific study visit arrangement is shown in Table 4 and Table 6. • Cohort F: Study on the safety and preliminary efficacy evaluation of first-line treatment of inoperable locally progressing, recurrent/metastatic gastric or gastroesophageal junction adenocarcinoma using IBI308 in combination with oxaliplatin/capecitabine (XELOX), enrolling approximately 20 subjects. Each treatment cycle contains 3 weeks. And 200 mg IV of IBI308 and 130 mg/m^2 IV of oxaliplatin are given on D1 of each cycle, while 2000 mg/m^2/d of capecitabine is given orally bid on D1–14. Up to 6 cycles of triple drug combination therapy are given. Subsequently, the subjects experiencing no PD can receive a maintenance treatment of 200 mg IV Q3W of IBI308 until PD, intolerable toxicity, withdrawal of informed consent, 24 months of treatment, or other reasons for discontinuation of the study treatment (whichever occurs first). The specific study visit arrangement is shown in Table 4 and Table 6. • Cohort G: Study on the safety and efficacy evaluation of first-line treatment of inoperable locally progressing, recurrent/metastatic high-grade (G3) neuroendocrine tumors using IBI308 in combination with chemotherapy, enrolling approximately 15 subjects. Each treatment cycle contains 3 weeks. The dosing regimen is IBI308 200 mg IV D1 + etoposide 100 mg/m^2 IV D1–3 + cisplatin 75 mg/m^2 IV D1. Up to 6 cycles of triple drug combination therapy are given. Subsequently, the subjects experiencing no PD can receive a maintenance treatment of 200 mg IV Q3W of IBI308 until PD, intolerable toxicity, withdrawal of informed consent, 24 months of treatment, or other reasons for discontinuation of the study treatment (whichever occurs first). The specific study visit arrangement is shown in Table 5. • Cohort H: Study on the safety and efficacy of IBI308 in combination with chemotherapy in the treatment of subjects with advanced high-grade (G3) neuroendocrine tumors who failed first-line systemic standard treatment, enrolling approximately 15 subjects. Each treatment cycle contains 3 weeks. The dosing regimen is IBI308 200 mg IV D1 + irinotecan 125 mg/m^2 IV D1, D8 + 5-fluorouracil

	(5-FU) 1000 mg/m^2 IV D1–3. Up to 6 cycles of triple drug combination therapy are given. Subsequently, the subjects experiencing no PD can receive a maintenance treatment of 200 mg IV Q3W of IBI308 until PD, intolerable toxicity, withdrawal of informed consent, 24 months of treatment, or other reasons for discontinuation of the study treatment (whichever occurs first). The specific study visit arrangement is shown in Table 5. • Cohorts G and H of the phase Ib study are newly added for the protocol 3.0. Study sites who don't participate in studies in these two cohorts will be closed after the end of clinical studies in cohorts A–F.
Dose-limiting toxicity	According to the National Cancer Institute "Common Terminology Criteria for Adverse Events" (NCI CTCAE) version 4.03, DLT is defined as any of the following IBI308-related adverse events (AEs) that occur within the first treatment cycle (Days 1–28) in the phase Ia dose-escalation study: 1. Hematological toxicity: • Grade 4 hematological toxicity lasting > 7 days. • Grade 3 thrombocytopenia with bleeding tendency or requiring platelet transfusion. • Grade 3 neutropenic fever with bacteremia or sepsis. 2. Non-hematological toxicity: • Any grade 4 immune related adverse event (irAE); • Grade 3 pneumonia. • Grade 2 pneumonia that does not recover to ≤ grade 1 within 14 days after intervention. • Other grade 3 irAEs that do not recover to ≤ grade 2 within 3 days after intervention or ≤ grade 1 within 14 days after intervention (except for asymptomatic grade 3 thyroid, adrenal gland, or pituitary insufficiency, and grade 3 inflammatory responses at the tumor site). • Other grade 3 or 4 non-hematological toxicity [excluding: grade 3 electrolyte abnormalities, grade 3 or 4 infusion-related reactions (IRRs), manageable grade 3 hypertension, grade 3 infusion site extravasation, grade 3 arthralgia/myalgia, grade 3 asthenia/fatigue, manageable grade 3 vomiting, grade 3 or 4 liver transaminase elevation lasting < 7 days]. 3. Any grade 5 AE. Note: Grade 3 or 4 IRR is not a DLT. However, if a grade 3 or 4 IRR occurs, subject needs to discontinue treatment and be replaced by a new subject. If ≥ 2 subjects experience a grade 3 or 4 IRR in any treatment group, then enrollment must be suspended. The sponsor needs to review the safety data to determine whether to continue enrolling subjects.

Inclusion criteria	1. Subjects with advanced solid tumors, including: 1) Phase Ia: Patients with locally advanced, recrrent, or metastatic solid tumors that failed standard treatment; 2) Phase Ib: Cohort A: • Patients with locally advanced, recurrent or metastatic melanoma confirmed by cytology or histology. Cohort B: • Patients with locally advanced, recurrent or metastatic esophageal squamous cell carcinoma confirmed by cytology or histology who failed or became intolerant to first-line systemic standard treatment; • Patients with locally advanced, recurrent or metastatic gastric adenocarcinoma (including gastroesophageal junction adenocarcinoma) confirmed by cytology or histology who failed or became intolerant to first-line systemic standard treatment; • Patients with locally advanced, recurrent or metastatic hepatocellular cell carcinoma (HCC) confirmed by cytology or histology who were not suitable for locoregional treatment or failed locoregional treatment and failed or became intolerant to first-line systemic standard treatment; • Patients with other advanced malignant tumors of the digestive system who failed or became intolerant to standard therapy; • Patients with advanced neuroendocrine tumors who failed, became intolerant, or refused to receive standard therapy. Metastatic neuroendocrine tumors confirmed by histopathology, including well differentiated neuroendocrine tumors and poorly differentiated neuroendocrine carcinomas; with imaging-confirmed tumor PD within 12 months before the first dose; for poorly differentiated neuroendocrine carcinomas, they should experience progression after being treated with platinum-based regimens; for well-differentiated neuroendocrine tumors, they should have received at least one systemic treatment, including somatostatin analogs, mTOR inhibitors, anti-angiogenic drugs, and chemotherapy; patients with neuroendocrine tumors or neuroendocrine carcinomas who cannot tolerate or refuse to receive the above treatment can also be enrolled. Cohort C: • Patients with locally advanced, recurrent or metastatic NSCLC confirmed by cytology or histology who failed or became intolerant to first-line systemic standard treatment, excluding patients with known epidermal growth factor receptor (EGFR) mutations and anaplastic lymphoma kinase (ALK) rearrangement.

	Cohort D: • Patients with inoperable locally advanced (stage IIIB), recurrent or metastatic (stage IV) nsNSCLC (staged according to the 7th edition of "Staging Manual in Thoracic Oncology" published by the International Association for the Study of Lung Cancer) confirmed by histology or cytology who didn't received first-line treatment, excluding patients with EGFR mutations and ALK rearrangement. • For patients with stage IIIB nsNSCLC who previously received platinum-based adjuvant or neoadjuvant chemotherapy or radical chemoradiotherapy, if local recurrence or distant metastasis occurred within 6 months after the treatment was completed, the previous platinum-based treatment will be considered to be a first-line treatment and hence the patients cannot be enrolled into the cohort. Cohort E: • Previously untreated patients with inoperable locally advanced (stage IIIB), recurrent or metastatic (stage IV) scNSCLC (staged according to the 7th edition of "TNM Staging of Thoracic Tumor" published by the International Association for the Study of Lung Cancer) who previously not received first-line treatment, excluding patients with EGFR mutations and ALK rearrangement. • For patients with stage IIIB scNSCLC who previously received platinum-based adjuvant or neoadjuvant chemotherapy or radical chemoradiotherapy, if local recurrence or distant metastasis occurred within 6 months after the treatment was completed, the previous platinum-based treatment will be considered to be a first-line treatment and hence the patients cannot be enrolled into the cohort. Cohort F: • Patients with inoperable locally advanced, recurrent or metastatic gastric or gastroesophageal junction adenocarcinoma confirmed by histopathology; • Excluding patients with known HER2 gene amplification or overexpression. • Not previously treated by chemotherapy for advanced diseases, or with progression occurring more than 6 months after the end of systemic adjuvant therapy. Cohort G: • Previously untreated patients with inoperable locally progressive, recurrent or metastatic high-grade (G3) neuroendocrine tumors confirmed by histology or cytology. • Patients must have high-grade (G3) neuroendocrine tumors with a Ki-67 index of > 20%. • Not previously treated by chemotherapy for advanced diseases, or with progression occurring more than 6 months after the end of systemic adjuvant therapy.

	Cohort H: • Patients with advanced high-grade (G3) neuroendocrine tumors confirmed by histology or cytology who failed or became intolerant to first-line systemic standard treatment. • Patients must have high-grade (G3) neuroendocrine tumors with a Ki-67 index of > 20%. • For patients who received adjuvant or neoadjuvant chemotherapy for neuroendocrine tumors, if local recurrence or distant metastasis occurred within 6 months after this treatment was completed, this treatment will be considered to be a first-line treatment and hence the patients can be enrolled into the cohort. 2. Patients who have signed ICF, and are able to complete follow-up visits and relevant procedures required in the protocol. 3. Ages ≥ 18 and ≤ 70 years. 4. Estimated survival ≥ 12 weeks. 5. Patients with at least one measurable or evaluable lesion according to "Response Evaluation Criteria in Solid Tumors" version 1.1 (RECIST V1.1). 6. An Eastern Cooperative Oncology Group Performance Status (hereinafter referred to as the ECOG PS score) score of 0 or 1. 7. 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 trial and 6 months after the treatment (see Table 24 in Section 5.7.2). 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; hemoglobin (HGB) ≥ 9.0 g/dL. 2) Hepatic function: Total bilirubin (TBIL) ≤ 1.5 × upper limit of normal (ULN); TBIL ≤ 3 × ULN for patients with HCC, liver metastasis, or a history/suspected history of Gilbert syndrome (persistent or recurrent hyperbilirubinemia, mainly manifested as high unconjugated bilirubin, with no evidence of hemolysis or liver disease); alanine aminotransferase (ALT) and aspartate transferase (AST) ≤ 2.5 × ULN for patients without HCC and liver metastases; ALT or AST ≤ 5 × ULN for patients with HCC or liver metastases. 3) Renal function: Serum creatinine (SCr) ≤ 1.5 × ULN or clearance of creatinine (CCr) ≥ 50 mL/min; urinalysis results showing urine protein < 2+; for patients whose baseline urinalysis results showing urine protein ≥ 2+, they should undergo 24-h urine collection and the protein content in the collected urine should be < 1 g. 4) Coagulation function: activated partial thromboplastin time (APTT) and international normalized ratio (INR) ≤ 1.5 × ULN. 5) Thyroid stimulating hormone (TSH) or free thyroxine (FT4) are within the normal range.

Exclusion criteria	1. Previous exposure to any anti-PD-1 or anti-PD-L1 antibody. 2. Experienced any ≥ grade 3 irAE (based on NCI CTCAE V4.03) while receiving any immunotherapy drugs in the past. Patients who were treated with ipilimumab are not enrolled unless all of the following criteria are met: • The ipilimumab-related irAE has completely recovered, and the treatment of irAE have ended 4 weeks before the first dose of IBI308; • There was at least a 12-week interval between the first dose of ipilimumab and the first dose of IBI308 and a 6-week interval between the last dose of ipilimumab and the first dose of IBI308; • The use of ipilimumab did not result in grade 4 irAEs or grade 3 irAEs requiring > 4 weeks of treatment; • A clear PD was observed after the last dose of ipilimumab. 3. 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. 4. Received any investigational drug within 4 weeks prior to the first dose of IBI308. 5. Received the last dose of anti-tumor therapy (chemotherapy, endocrine therapy, targeted therapy, immunotherapy, tumor embolization) within 3 weeks before the first dose of IBI308; received the last dose of biologics, nitrosourea or mitomycin C within 6 weeks before the first dose of IBI308 (if the biological product received was for antitumor endocrine therapy, refer to the requirement of "received the last dose within 3 weeks before the first dose of IBI308"). 6. Received immunosuppressants within 4 weeks before the first dose of IBI308, excluding locoregional glucocorticoids administered by nasal, inhaled, or other routes, or systemic glucocorticoids of physiological doses (no more than 10 mg/day of prednisone or equivalents). Glucocorticoid administration for pretreatment or special examinations is allowed. 7. Received a live attenuated vaccine within 4 weeks prior to the first dose of IBI308, or plan to receive this vaccine during the study period. 8. Received major surgery (craniotomy, thoracotomy, or laparotomy) within 4 weeks prior to the first dose of IBI308, or has unhealed wounds, ulcers, or fractures. 9. Antitumor therapy-induced toxicity (excluding alopecia) that has not yet resolved to NCI CTCAE V4.03 grade 0 or 1 prior to the first dose of IBI308. 10. Previously received whole pelvic radiotherapy. 11. Patients with known leptomeningeal metastasis; patients with other known CNS metastases that have not been effectively controlled by treatment or remain untreated. Excluding patients who were treated, are now stable, and stopped glucocorticoids and anticonvulsants ≥ 4 weeks prior to receiving the first dose of IBI308.

	12. Known active autoimmune disease (see Appendix 5) or a history of such disease within the past 2 years (patients with vitiligo, psoriasis, alopecia, or Graves' disease not requiring systemic treatment within the next 2 years, or those with hypothyroidism only requiring thyroid hormone replacement therapy, and type I diabetes only requiring insulin replacement therapy within the past 2 years may be enrolled). For patients with positive autoimmune antibodies only, they should be evaluated by the investigator to determine whether they have an autoimmune disease. 13. Known history of primary immunodeficiency diseases. 14. Known history of pulmonary tuberculosis. 15. Known history of allotransplantation or allogeneic hematopoietic stem cell transplantation. 16. Known allergy to any ingredients in IBI308; previously severe allergic reactions to other monoclonal antibodies; for Cohort D of the Phase Ib study, patients who were previously allergic to pemetrexed or cisplatin, or patients who were unable or unwilling to receive folic acid and/or vitamin B12 treatment; for Cohort E of the Phase Ib study, patients who were previously allergic to cisplatin or gemcitabine; for Cohort F of the Phase Ib study, patients who were previously allergic to capecitabine or oxaliplatin; for Cohort G of the Phase Ib study, patients who were previously allergic to etoposide or cisplatin; for Cohort H of the Phase Ib study, patients who were previously allergic to irinotecan or 5-FU. 17. Uncontrolled concurrent diseases including but not limited to: • Those infected with HIV (positive for HIV1/2 antibody). • Active or poorly clinically controlled serious infections. • Symptomatic congestive cardiac failure (New York Heart Association (NYHA) Class II–IV) or symptomatic or poorly controlled arrhythmia. • Uncontrolled hypertension (systolic blood pressure ≥ 160 mmHg or diastolic blood pressure ≥ 100 mmHg) despite of standard treatment. • Any arterial thromboembolic events occurred within 6 months prior to enrollment, including myocardial infarction, unstable angina, cerebrovascular accident, or transient cerebral ischemic attack. • Patients with esophageal or gastric varices requiring immediate intervention (such as variceal ligation or sclerotherapy) or those considered to have a high bleeding risk by the investigator, gastroenterologist, or hepatologist. Patients with signs of portal hypertension (including splenomegaly confirmed by medical imaging) or a history of variceal bleeding are required to undergo endoscopy within 3 months prior to enrollment. • Life-threatening hemorrhagic events or grade 3 or 4 gastrointestinal/variceal hemorrhage requiring blood transfusion, endoscopy, or surgical treatment within 3 months prior to enrollment. • 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). • Uncontrolled metabolic disorders, non-malignant organ or systemic diseases, or cancer-related secondary diseases that may lead to high medical risks and/or uncertainty in survival evaluation. • Hepatic encephalopathy, hepatorenal syndrome, or cirrhosis with Child-Pugh Class B or C (See Appendix 7 for Child-Pugh grading). • Bowel obstruction 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, ulcerative colitis, or chronic diarrhea. • 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 investigators. 18. Patients with acute or chronic active hepatitis B or hepatitis C infection (for patients treated with IBI308 monotherapy, they will be enrolled if their HBsAg is positive but their HBV DNA copy number is $\leq 1 \times 10^4$/mL; for patients treated with IBI308 in combination with chemotherapy, they will be enrolled only if their HBsAg is positive and their HBV DNA copy number is below the LLD. For the prevention and treatment requirements, refer to the 2015 edition of "Prevention and Treatment Guide for Chronic Hepatitis"; patients with inactive Hepatitis C are allowed for enrollment). 19. History of GI perforation and/or fistula within 6 months prior to the enrollment. 20. Interstitial lung diseases (including previous and current history, refer to Appendix 6). 21. Clinically uncontrollable third space effusion, such as pleural effusion and ascites that cannot be controlled by drainage or other methods prior to enrollment. 22. History of other primary malignant tumors, excluding: • History of radical treatment for malignant tumors with no evidence of tumor recurrence for more than 5 years prior to enrollment and with a very low risk of recurrence; • Adequately treated nonmelanoma skin cancer or lentigo maligna with no signs of disease recurrence; • Adequately treated carcinoma in situ with no signs of disease recurrence. 23. Pregnant or breastfeeding female patients.
Study drug, strengths, and administration	1. IBI308: 10 mL:100 mg, IV infusion. 2. Pemetrexed: 100 mg/vial or 500 mg/vial, IV infusion. 3. Cisplatin: 10 mg/vial, 20 mg/vial, or 30 mg/vial, IV infusion. 4. Gemcitabine: 200 mg/vial or 1 g/vial, IV infusion. 5. Capecitabine: 500 mg/tablet, oral administration.

	6. Oxaliplatin: 50 mg/vial or 100 mg/vial, IV infusion. 7. Etoposide: 50 mg/vial or 100 mg/vial, IV infusion. 8. Irinotecan: 40 mg/vial, 100 mg/vial, or 300 mg/vial, IV infusion. 9. 5-FU: 10 mL: 250 mg, IV infusion.
Evaluation criteria	**Safety evaluation:** • Incidence, relationship with investigational drug, and severity level of all adverse events (AEs), treatment emergent adverse events (TEAEs), adverse events of special interest (AESIs), and serious adverse events (SAEs) will be evaluated. • Changes in vital signs, physical examination, and laboratory tests results before, during, and after the study treatment will be evaluated. • Immunogenicity assessment: Anti-drug antibody (ADA) assay will be conducted for subjects, and ADA-positive samples will be further tested to determine whether the ADA is a neutralizing antibody (NAb). **Efficacy evaluation:** • Efficacy evaluation is based on RECIST V1.1. Objective response rate (ORR), time to response (TTR), duration of response (DOR), progression free survival (PFS), 6-month and 1-year PFS rates, disease control rate (DCR), overall survival (OS), and 6-month and 1-year survival rates after drug administration are evaluated. • The irRECIST-based evaluation of irORR, irDCR, irPFS, and irDOR is explored. **PK/PD evaluation:** • The PK characteristics of single or multiple doses of IBI308 in the human body are described, and the main PK parameters, including but not limited to area under curve (AUC), C_{max}, CL, V, and $t_{1/2}$, are determined. • Blood samples are collected to analyze PD parameters, including but not limited to PD-1 receptor saturation. • PK/PD evaluation is required only for Cohorts A–F of phase Ia and Ib studies. **Biomarker evaluation:** • Tumor tissue samples are collected for tumor biomarker analysis, including but not limited to the expression of PD-L1 in tumor specimens, whole exome sequencing to detect tumor mutation burden (TMB) in tumor tissues, multicolor immunohistochemistry, and PD-L1 and CD8 double staining assay. • Biomarkers are evaluated only in Cohorts A–F of phase Ia and Ib studies and not evaluated in Cohorts G and H of the phase Ib study.

Statistical methods	Sample size: Phase Ia: Four dose levels are assessed. The dose escalation strategy is established using the standard "3 + 3" design. Around 12–24 patients with advanced solid tumors that failed standard treatment need to be enrolled. Phase Ib: It is planned to enroll 10–20 subjects in Cohort A, 50–100 ones in Cohort B, 10–20 ones in Cohort C, 20 ones in each of Cohorts D, E, and F, and 15 ones in each of Cohorts G and H. Statistical analysis methods: The analysis method is descriptive statistics. In principle, no between-group comparison will be carried out. Continuous variables will be described using number of cases, mean, standard deviation(SD), median, minimum, and maximum. Categorical variables will use frequencies and percentages. The safety parameters (AE, laboratory tests, vital signs), PK/PD parameters, immunogenicity, and anti-tumor activity of IBI308 monotherapy or combination therapy in subjects of advanced solid tumors are summarized by tumor stages, cohorts, and types of tumor. The ORR, DCR and their 95% confidence intervals (CIs) are calculated under different dosing regimens. The median progression free survival (mPFS), median overall survival (mOS), and 6-month and 1-year PFS rates and survival rates are estimated using Kaplan-Meier. For subjects achieving objective response, DOR, TTR, and maintained response rate at the data cut-off date of analysis are calculated. Exploratory analyses: A subgroup analysis of anti-tumor activity (ORR) is carried out based on factors that are clinically considered to affect prognosis, such as gender, age, and ECOG PS score. The level of PD-L1 expression and its relationship with anti-tumor activity (ORR, DOR). The relationship between AUC and anti-tumor activity (ORR, DOR).

Table 1. Schedule of study visits in the phase Ia study

Stage	Screening period	Treatment period							End-of-treatment visit/safety follow-up[18]	Survival follow-up[19]
		Cycle 1 (28 days)						Cycle 2 and beyond		
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**N**		
Day	**−28 to −1**	**1**	**2**	**3**	**8**	**15**	**22**	**Day 1 (± 2 days)**	**End of treatment (EOT), 90 days (± 7 days) after EOT**	**Every 90 days (± 7 days)**
Standard study procedures										
Written ICF[1]	X									
Inclusion/exclusion criteria	X									
Demographics/medical history/previous medications[2]	X									
Vital signs[3]	X	X				X		X	X	
Weight/height[4]	X	X						X		
Physical examination	X					X		X	X	
ECOG PS score	X	X						X	X	
12-Lead ECG[5]	X	X						X	X	
Routine blood test/blood chemistry/urinalysis[6]	X					X		X	X	
Coagulation function[7]	X								X	
Pregnancy test[8]	X									
Thyroid function[9]	X							X	X	
Autoantibody[10]	X									
Immunogenicity (ADA, NAb)[11]		X						X	X	
HIV, HBV, and HCV[12]	X									
PK[13]		X	X	X	X	X	X	X	X	

Stage	**Screening period**	**Treatment period**							**End-of-treatment visit/safety follow-up[18]**	**Survival follow-up[19]**
		Cycle 1 (28 days)						**Cycle 2 and beyond**		
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**N**		
Day	**−28 to −1**	**1**	**2**	**3**	**8**	**15**	**22**	**Day 1 (± 2 days)**	**End of treatment (EOT), 90 days (± 7 days) after EOT**	**Every 90 days (± 7 days)**
PD[13]		X	X		X			X	X	
AE evaluation[14]	X	X	X	X	X	X	X	X	X	
Concomitant medications	X	X	X	X	X	X	X	X	X	
Survival condition										X
Subsequent anti-tumor therapy									X	X
Efficacy evaluation										
Tumor imaging evaluation[15]	X							X	X	
Study drug infusion										
IBI308[16]		X						X		
Biomarker study										
Archived or fresh tumor tissue sample[17]	X									

Note:

1. Informed consent form (ICF) should be signed by subjects prior to any procedures outlined in the protocol.
2. Previous medications include treatment for the initial diagnosis, chemotherapy, radiotherapy, and surgery. The time of the last anti-tumor treatment must be recorded.
3. Vital signs include: body temperature, pulse, respiratory rate, and blood pressure. Refer to 6.4.4.1 for specific requirements for pulse and blood pressure monitoring.
4. Height is measured during screening period only. Weight must be measured before every planned dose during the study. If the weight fluctuation is less than 10% compared to baseline (date of first dose), then the baseline weight will be used to calculate the dose. Otherwise, the actual dose will be calculated based on the weight of scheduled dosing days.

5. Time of 12-lead ECG examinations: during the screening period, within 60 min after the end of IBI308 infusion in each cycle, and during safety follow-ups.
6. Routine blood test involves red blood cell (RBC), HGB, hematocrit value (HCT), white blood cell (WBC), platelet (PLT), WBC differential count [lymphocyte count (LYM), ANC, monocyte count (MONO), eosinophil count (EOS), and basophil cell count (BASO)]. 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 and Cr)], electrolytes (Na, K, Cl, Mg, Ca, and P), amylase, and fasting blood glucose (FBG). Routine urinalysis includes pH, urinary WBC (UWBC), urine protein (UPRO), urine red blood cell (URBC), and urine glucose (UGLU). Subjects who showed urine protein of ≥ 2+ during the urinalysis in the screening period should undergo a 24-h urine protein quantitation test. The routine blood test, blood chemistry, and urinalysis are performed during screening, within 7 days prior to each dose of IBI308, on day 15 of Cycle 1, and during safety follow-up. Tests will be conducted at each study site.
7. Coagulation function test includes thrombin time (TT), PT, APTT, and INR. The test will be conducted within 7 days prior to the first dose and during the safety follow-up. Tests will be conducted at each study site.
8. Women of childbearing age should undergo a urine or blood pregnancy test within 3 days before the first dose. If the urine pregnancy test is not conclusive, then blood pregnancy test should be performed. The conclusion should be based on the blood pregnancy test. Tests will be conducted at each study site.
9. Thyroid function test includes triiodothyronine (T3), thyroxine (T4), free triiodothyronine (FT3), FT4, and TSH. The test is conducted during screening, within 7 days prior to each dose of IBI308 after Cycle 1, and during safety follow-up. Tests will be conducted at each study site.
10. Autoantibodies include: anti-nuclear antibodies (ANA), anti-dsDNA antibodies, and anti-thyroglobulin antibodies. The test is conducted during screening, and afterwards retest will be done only if deemed necessary by the investigator. Tests will be conducted at each study site.
11. Immunogenicity assays will be performed within 1 h prior to IBI308 infusion in Cycles 1, 2 and then every 2 cycles thereafter (Cycles 4, 6, 8, and so on), and during safety follow-up visits. If an infusion-related reaction occurs during IBI308 infusion, blood samples should be taken near the start and end of this event and around 30 days after the reaction and used for comparative analysis of immunogenicity. Tests will be conducted in the central laboratory.
12. Including tests for HCV and HIV antibodies, as well as HBsAg, HBsAb, HBcAb, HBeAg, and HBeAb. HBV-DNA should be further tested for subjects positive for HBsAg and/or HBcAb. The test is conducted during screening, and afterwards retest will be done only if deemed necessary by the investigator. Tests will be conducted at each study site.
13. Refer to PK/PD sampling schedule (Table 2). Tests will be conducted in the central laboratory.
14. AEs and laboratory safety assessments will be performed based on NCI CTCAE V4.03. Refer to Section 7 for definitions, recording, causality determination, severity level, reporting deadlines, and treatment of AEs and SAEs.
15. Tumor evaluations are based on RECIST V1.1 and irRECIST. There is no central imaging evaluation in this study. Tumor imaging examinations usually include contrast-enhanced CT or MRI of the chest, abdomen, and pelvic cavity. The same subject should receive the same type of imaging examination during the study. Baseline evaluation will be conducted within 28 days prior to enrollment. The investigators can evaluate imaging results within 28 days prior to enrollment. Tumor imaging evaluation should be carried out every 9 weeks (± 7 days) after first dose of the study drug. For subjects with initial

response (complete response (CR) or partial response (PR)), tumor imaging examination should be performed 4 weeks (± 7 days) later for confirmation. Subsequently, this evaluation should be performed every 12 weeks (± 7 days) until PD is suggested in the image. For subjects who are recorded as imaging PD for the first time, an imaging evaluation should be carried out 4 weeks (± 7 days) later for confirmation. If these subjects continue to receive the study drug after this confirmation, imaging evaluation will be carried out once every 9 weeks (± 7 days) until the second PD, which is defined as an increase of more than 10% in the sum of the longest diameter (mm) of target lesions compared with the first imaging PD or the occurrence of new measurable lesions. For subjects who discontinue the treatment for reasons other than imaging PD, an imaging evaluation should be carried out at the end of the treatment and every 9 weeks (± 7 days) after treatment discontinuation until start of a new anti-tumor therapy, PD, ICF withdrawal by subjects, or death.

16. The Cycle 1 for every dose group is the period of DLT observation (28 days) and the drug is only administered on day 1. Since the Cycle 2, IBI308 is intravenously infused once every 2 weeks in the 1 mg/kg, 3 mg/kg, and 10 mg/kg groups and once every 3 weeks in the 200 mg group. Some subjects who meet particular requirements are allowed to continue receiving treatment after PD ("Section 5.1.2 Continued treatment after progressive disease" of the study protocol).
17. Subjects are required to provide archived or fresh tumor tissue samples meeting test requirements during screening.
18. Treatment follow-up is performed after the end of treatment. Safety follow-up is performed 90 ± 7 days after the last dose. The study drug-related AEs need to be followed up until resolved to grade 0 or 1, stable, or withdrawal of ICF (whichever occurs first). Refer to 6.2.3 for details.
19. Survival follow-up: once every 90 days (± 7 days) after the end of treatment. Telephone follow-up is allowed.

Table 2. PK/PD sampling schedule in the phase Ia study

Stage	Screening period	Treatment period												Safety follow-up[5]
		Cycle 1 (28-day period of DLT observation)[2]									Cycle 2 and thereafter[3,4]			
Day	−28 to −1	1					2	3	8	15	22	Day 1 (± 2 days)			90 days (± 7 days)
Sampling time[1]		−1 h	During infusion	Immediately at the end of infusion	1 h after the end of infusion	6 h after the start of infusion	24h	48h	168h	336h	504h	-1h	During infusion	Immediately at the end of infusion	
Time window of blood sampling				+5min	±5min	±15min	±1h	±2h	±8h	±12h	±24h			+5min	
IBI308			X										X		
PK		X		X	X	X	X	X	X	X	X	X [3]		X [3]	X [5]
PD		X					X		X			X [4]			X [5]

Note:

1. Samples should be collected from the opposite arm of the infusion site.
2. If the dosing on Day 1 of Cycle 2 is delayed due to an AE or other reasons, additional sampling is required at 672 ± 24 h (Day 29) in Cycle 1.
3. From Cycle 2, PK blood sampling is performed every 2 cycles (Cycles 2, 4, 6, and so on). Except for cycle 4, the blood sampling time points are within 1 h before the start of the infusion and immediately after the end of the infusion (+ 5 min). In Cycle 4 (dense sampling), for the 200 mg cohort, blood is sampled within 1 h before the start of infusion, at 0 h (+ 5 min) and 1 h ± 5 min after the end of infusion, and at 6 h ± 15 min, 24 ± 1 h, 48 ± 2 h, 168 ± 8 h (Day 8), 336 ± 12 h (Day 15), and 504 ± 24 h (Day 22) after the start of infusion; and for 1 mg/kg, 3 mg/kg, and 10 mg/kg cohorts, blood is sampled within 1 h before the start of infusion, at 0 h (+ 5 min) and 1 h ± 5 min after the end of infusion, and at 6 h ± 15 min, 24 ± 1 h, 48 ± 2 h, 168 ± 8 h (Day 8), and 336 ± 12 h (Day 15) after the start of infusion.
4. From Cycle 2, PD samples are collected every 4 cycles (Cycles 6, 10, 14, and so on).
5. Both PK and PD sampling are required during safety follow-ups, but not required during survival follow-ups.

Table 3. Visit schedule for Cohorts A/B/C in the Phase Ib study

Stage	Screening period	Treatment period (21 days per cycle)						End-of-treatment visit[18]	Safety follow-up[19]	Survival follow-up[20]
		Cycle 1					Cycle 2 and beyond			
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**N**			
Day	**−28 to −1**	**1**	**2**	**3**	**8**	**15**	**Day 1 (± 2 days)**	**Within 7 days after the end of treatment is confirmed**	**90 days (± 7 days) after the end of treatment**	**Every 90 days (± 7 days)**
Standard study procedures										
Written ICF[1]	X									
Inclusion/exclusion criteria	X									
Demographics/medical history/previous medications[2]	X									
Vital signs[3]	X	X					X	X	X	
Weight/height[4]	X	X					X	X	X	
Physical examination	X						X	X	X	
ECOG PS score	X	X					X	X	X	
12-Lead ECG[5]	X	X					X	X	X	
Routine blood test/blood chemistry/urinalysis[6]	X						X	X	X	
Coagulation function[7]	X							X	X	
Pregnancy test[8]	X									
Thyroid function[9]	X						X	X	X	
Autoantibody[10]	X									
Immunogenicity (ADA, NAb)[11]		X					X		X	
HIV, HBV, and HCV[12]	X									
PK[13]		X	X	X	X	X	X		X	

Stage	Screening period	Treatment period (21 days per cycle)						End-of-treatment visit[18]	Safety follow-up[19]	Survival follow-up[20]
		Cycle 1					Cycle 2 and beyond			
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**N**			
Day	**−28 to −1**	**1**	**2**	**3**	**8**	**15**	**Day 1 (± 2 days)**	**Within 7 days after the end of treatment is confirmed**	**90 days (± 7 days) after the end of treatment**	**Every 90 days (± 7 days)**
PD[13]		X	X		X		X		X	
AE evaluation[14]	X	X	X	X	X	X	X	X	X	
Concomitant medications	X	X	X	X	X	X	X	X	X	
Survival condition										X
Subsequent anti-tumor therapy									X	X
Efficacy evaluation										
Tumor imaging evaluation[15]	X						X	X	X	
Study drug infusion										
IBI308[16]		X					X			
Biomarker study										
Archived or fresh tumor tissue sample[17]	X									

Note:

1. The ICF should be signed by subjects prior to any procedures outlined in the protocol.
2. Previous medications include: treatment for the initial diagnosis, including chemotherapy, radiotherapy, and surgery. The time of the last anti-tumor treatment must be recorded.
3. Vital signs include: body temperature, pulse, respiratory rate, and blood pressure. Weight must be measured before every planned dose during the study.
4. Height is measured during screening period only. Weight must be measured before every planned dose during the study.
5. Time of 12-lead ECG examinations: during the screening period, within 60 min after the end of IBI308 infusion in each cycle, and during safety follow-ups.
6. Routine blood test include: RBC, HGB, HCT, WBC, PLT, and white blood cell differential (LYM, ANC, MONO, EOS, BASO). Blood chemistry include: hepatic function (TBIL, ALT, AST, γ-GT, ALP, ALB, TP, LDH), renal function (Urea, Cr), blood electrolytes (Na, K, Cl, Mg, Ca, P), amylase, and FBG.

Urinalysis include: PH, UWBC, UPRO, URBC, and UGLU. Subjects who showed urine protein of ≥ 2+ during the urinalysis in the screening period should undergo a 24-h urine protein quantitation test. Routine blood test, blood chemistry test, and urinalysis are carried out during the screening period, within 7 days before each administration of IBI308, during the end-of-treatment visit, and during the safety follow-ups. Tests will be conducted at each study site.

7. Coagulation function tests include: TT, PT, APTT, and INR. They are tested within 7 days before the first dose of IBI308, during the end-of-treatment visit, and during the safety follow-ups. Tests will be conducted at each study site.
8. Women of childbearing age should undergo a urine or blood pregnancy test within 3 days before the first dose. If the urine pregnancy test is not conclusive, then blood pregnancy test should be performed. The conclusion should be based on the blood pregnancy test. Tests will be conducted at each study site.
9. Carried out during the screening period, within 3 days before each administration of IBI308 since Cycle 2, during the end-of-treatment visit, and during the safety follow-ups. T3, T4, FT3, FT4, and TSH are examined during the screening period. Starting from Cycle 2, only TSH is examined. If there are abnormalities, the examination of other thyroid function parameters will be considered. Tests will be conducted at each study site.
10. Autoantibodies include: anti-nuclear antibodies, anti-dsDNA antibodies, and anti-thyroglobulin antibodies. The test is conducted during screening, and afterwards retest will be done only if deemed necessary by the investigator. Tests will be conducted at each study site.
11. Immunogenicity examinations are carried out within 1 h before the infusion of IBI308 in Cycle 1, Cycle 2, and every 2 cycles thereafter (Cycles 4, 6, 8, and so on), and during safety follow-ups. If an infusion-related reaction occurs during IBI308 infusion, blood samples should be taken near the start and end of this event and around 30 days after the reaction and used for comparative analysis of immunogenicity. Tests will be conducted in the central laboratory.
12. Including tests for HCV and HIV antibodies, as well as HBsAg, HBsAb, HBcAb, HBeAg, and HBeAb. HBV-DNA should be further tested for subjects positive for HBsAg and/or HBcAb. The tests will be carried out at each study site during the screening period, and afterwards retest will be done only if deemed necessary by the investigator based on the clinical indications.
13. See the PK/PD sampling schedule (Table 6) for the time of PK and PD assays. For Cohort B, after the PK/PD blood samples of 20 subjects who meet the requirements of assay and analysis are collected, subsequent subjects are not required to undergo PK/PD assays. Tests will be conducted in the central laboratory.
14. AEs and laboratory safety assessments will be performed based on NCI CTCAE V4.03. Refer to Section 7 for definitions, recording, causality determination, severity level, reporting deadlines, and treatment of AEs and SAEs.
15. Tumor evaluations are based on RECIST V1.1 and irRECIST. There is no central imaging evaluation in this study. Tumor imaging examinations usually include contrast-enhanced CT or MRI of the chest, abdomen, and pelvic cavity. The same subject should receive the same type of imaging examination during the study. Baseline evaluation will be conducted within 28 days prior to enrollment. The investigators can evaluate imaging results within 28 days prior to enrollment. Tumor imaging evaluation should be carried out every 9 weeks (± 7 days) after first dose of the study drug. For subjects with initial response (CR or PR), an imaging evaluation is carried out 4 weeks (± 7 days) later to confirm the response, and the imaging evaluation is carried out every 9 weeks (± 7 days) thereafter until imaging PD is recorded. For subjects who are first recorded as imaging PD that is confirmed related to immunity by the imaging evaluation carried out 4 weeks later, if they continue to receive the study drug, imaging evaluations should be carried out every 9 weeks (± 7 days) until the recurrence of PD. The recurrence of PD is defined as the increase in the sum of the longest diameter of the tumor target lesions by > 10% on the

basis of the first imaging PD or the occurrence of a new measurable lesion. For subjects with first imaging PD but an unstable clinical situation or rapid progression who are deemed as not suitable for continued drug treatment, it is not necessary for them to undergo further imaging examinations to confirm PD. For subjects who discontinue the treatment for reasons other than imaging PD, an imaging evaluation should be carried out at the end of the treatment and every 9 weeks (± 7 days) after treatment discontinuation until start of a new anti-tumor therapy, PD, ICF withdrawal by subjects, or death.

16. IBI308 200 mg, intravenous infusion, once every 3 weeks. Some subjects who meet particular requirements are allowed to continue receiving treatment after PD ("Section 5.1.2 Continued treatment after progressive disease" of the study protocol). The treatment by IBI308 lasts for up to 24 months.
17. Subjects are required to provide archived or fresh tumor tissue samples meeting test requirements during screening.
18. The end-of-treatment visit is carried out within 7 days after the end of treatment is confirmed, as detailed in 6.2.3 of the protocol.
19. A safety follow-up should be carried out within 90 ± 7 days after the last dose or before the start of a new anti-tumor treatment (whichever occurs first). The study drug-related AEs need to be followed up until resolved to grade 0 or 1, stable, or withdrawal of ICF (whichever occurs first). Refer to 6.2.3 for details.
20. Survival follow-up: once every 90 days (± 7 days) after the drug treatment is stopped. Telephone follow-up is allowed.

Table 4. Visit schedule for Cohorts D/E/F in the Phase Ib study

Stage	Screening period	Treatment period (21 days per cycle)									End-of-treatment visit[21]	Safety follow-up[22]	Survival follow-up[23]
		Combination therapy								Combination or maintenance treatment			
		Cycle 1					Cycle 2	Cycle 3	Cycle 4	Cycle 5/7[20] and thereafter			
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**N**			
Day	**−28 to −1**	**1**	**2**	**3**	**8**	**15**	**Day 1 (± 2 days)**				**Within 7 days after the end of treatment is confirmed**	**90 days (± 7 days) after the end of treatment**	**Every 90 days (± 7 days)**
Standard study procedures													
Written ICF[1]	X												
Inclusion/exclusion criteria	X												
Demographics/medical history/previous medications[2]	X												
Vital signs[3]	X	X					X	X	X	X	X	X	
Weight/height[4]	X	X					X	X	X	X	X	X	
Physical examination	X						X	X	X	X	X	X	
ECOG PS score	X	X					X	X	X	X	X	X	
12-Lead ECG[5]	X	X					X	X	X	X	X	X	
Routine blood test/blood chemistry/urinalysis[6]	X						X	X	X	X	X	X	
Coagulation function[7]	X										X	X	
Pregnancy test[8]	X												
Thyroid function[9]	X						X	X	X	X	X	X	

Stage	Screening period	Treatment period (21 days per cycle)									End-of-treatment visit[21]	Safety follow-up[22]	Survival follow-up[23]
		Combination therapy								Combination or maintenance treatment			
		Cycle 1					Cycle 2	Cycle 3	Cycle 4	Cycle 5/7[20] and thereafter			
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**N**			
Day	**−28 to −1**	**1**	**2**	**3**	**8**	**15**	**Day 1 (± 2 days)**				**Within 7 days after the end of treatment is confirmed**	**90 days (± 7 days) after the end of treatment**	**Every 90 days (± 7 days)**
Autoantibody[10]	X												
Immunogenicity (ADA, NAb)[11]		X					X	X	X	X		X	
HIV, HBV, and HCV[12]	X												
PK[13]		X	X	X	X	X	X	X	X	X		X	
PD[13]		X	X		X		X	X	X	X		X	
AE evaluation[14]	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	
Survival condition													X
Subsequent anti-tumor therapy												X	X
Efficacy evaluation													
Tumor imaging evaluation[15]	X							X		X		X	
Study drug administration in Cohort D[16]													
IBI308		X					X	X	X	X			
Pemetrexed		X					X	X	X	X			

Stage	Screening period	Treatment period (21 days per cycle)									End-of-treatment visit[21]	Safety follow-up[22]	Survival follow-up[23]
		Combination therapy								Combination or maintenance treatment			
		Cycle 1					Cycle 2	Cycle 3	Cycle 4	Cycle 5/7[20] and thereafter			
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**N**			
Day	**−28 to −1**	**1**	**2**	**3**	**8**	**15**	**Day 1 (± 2 days)**				**Within 7 days after the end of treatment is confirmed**	**90 days (± 7 days) after the end of treatment**	**Every 90 days (± 7 days)**
Cisplatin		X					X	X	X				
Study drug administration in Cohort E[17]													
IBI308		X					X	X	X	X			
Gemcitabine		X			X		X	X	X				
Cisplatin		X					X	X	X				
Study drug administration in Cohort F[18]													
IBI308		X					X	X	X	X			
Capecitabine		X	X	X	X		X	X	X				
Oxaliplatin		X					X	X	X				
Biomarker study													
Archived or fresh tumor tissue sample[19]	X												

Note:

1. The ICF should be signed by subjects prior to any procedures outlined in the protocol.
2. Previous medications include: treatment for the initial diagnosis, including chemotherapy, radiotherapy, and surgery.
3. Vital signs include: body temperature, pulse, respiratory rate, and blood pressure.

4. Height is measured during screening period only. Weight must be measured before every planned dose during the study. If the weight fluctuation of a subject is less than 10% compared to the baseline (the day when the first dose of IBI308 is given), then the baseline weight will be used to calculate the dose. Otherwise, the actual dose will be calculated based on the weight of scheduled dosing days.
5. Time of 12-lead ECG examinations: during the screening period, within 60 min after the end of IBI308 infusion in each cycle, and during the end-of-treatment visit and safety follow-ups.
6. Routine blood test include: RBC, HGB, HCT, WBC, PLT, and white blood cell differential [LYM, ANC, MONO, EOS, BASO]. Blood chemistry include: hepatic function [TBIL, ALT, AST, γ-GT, ALP, ALB, TP, LDH], renal function [BUN, Cr], blood electrolytes (Na, K, Cl, Mg, Ca, P), lipase, amylase, and FBG. Urinalysis include: PH, UALB, UPRO, URBC, and UGLU. Any subject with urine protein ≥ 2+ from urinalysis dipstick in routine urinalysis at screening needs to undergo a 24-h urine protein test. The tests will be conducted during screening, within 7 days before the first dose of the study drug, within 3 days before each administration of the study drug starting from Cycle 2, during the end-of-treatment visit, and during the safety follow-ups. Tests will be conducted at each study site.
7. Coagulation function tests include: TT, PT, APTT, and INR. They are tested within 3 days before the first dose of IBI308, during the end-of-treatment visit, and during the safety follow-ups. Tests will be conducted at each study site.
8. Women of childbearing age should undergo a urine or blood pregnancy test within 3 days before the first dose. If the urine pregnancy test is not conclusive, then blood pregnancy test should be performed. The conclusion should be based on the blood pregnancy test. Tests will be conducted at each study site.
9. They are tested during screening, within 3 days before each administration of the study drug starting from Cycle 2, during the end-of-treatment visit, and during the safety follow-ups. T3, T4, FT3, FT4, and TSH are examined during the screening period. Starting from Cycle 2, only TSH is examined. If there are abnormalities, the examination of other thyroid function parameters will be considered. Tests will be conducted at each study site.
10. Autoantibodies include: anti-nuclear antibodies, anti-dsDNA antibodies, and anti-thyroglobulin antibodies. The test is conducted during screening, and afterwards retest will be done only if deemed necessary by the investigator. Tests will be conducted at each study site.
11. Immunogenicity examinations will be carried out within 1 h before the start of IBI308 infusion in Cycle 1, Cycle 2, and every 2 cycles thereafter (Cycles 4, 6, 8, and so on), and during safety follow-ups. If an infusion-related reaction occurs during IBI308 infusion, blood samples should be taken near the start and end of this event and around 30 days after the reaction and used for comparative analysis of immunogenicity. Tests will be conducted in the central laboratory.
12. Including tests for HCV and HIV antibodies, as well as HBsAg, HBsAb, HBcAb, HBeAg, and HBeAb. They are tested during screening. Tests will be conducted at each study site.
13. Refer to PK/PD sampling schedule (Table 6). Tests will be conducted in the central laboratory.
14. AEs and laboratory safety assessments will be performed based on NCI CTCAE V4.03. Refer to Section 7 for definitions, recording, causality determination, severity level, reporting deadlines, and treatment of AEs and SAEs.

15. Tumor evaluations are based on RECIST V1.1 and irRECIST. There is no central imaging evaluation in this study. Tumor imaging examinations usually include contrast-enhanced CT or MRI of the chest, abdomen, and pelvic cavity. The same subject should receive the same type of imaging examination during the study. Baseline evaluation is conducted within 28 days prior to enrollment. The investigators can evaluate imaging results within 28 days prior to enrollment. Tumor imaging evaluation should be carried out every 9 weeks (± 7 days) after first dose of the study drug. For subjects with initial response (CR or PR), an imaging evaluation is carried out 4 weeks (± 7 days) later to confirm the response, and the imaging evaluation is carried out every 9 weeks (± 7 days) thereafter until imaging PD is recorded. For subjects who are first recorded as imaging PD, an imaging evaluation should be carried out 4 weeks (± 7 days) later for confirmation. For subjects with first imaging PD but an unstable clinical situation or rapid progression who are deemed as not suitable for continued drug treatment, it is not necessary for them to undergo further imaging examinations to confirm PD. For subjects who discontinue the treatment for reasons other than imaging PD, an imaging evaluation should be carried out at the end of the treatment and every 9 weeks (± 7 days) after treatment discontinuation until start of a new anti-tumor therapy, PD, ICF withdrawal by subjects, or death.
16. For Cohort D, 200 mg of IBI308 is given via intravenous infusion every 3 weeks. Pemetrexed + cisplatin, intravenous infusion, administered once every 3 weeks. Up to 4 cycles of treatment with IBI308 in combination with pemetrexed + cisplatin are given before the subjects enter the maintenance treatment phase of IBI308 in combination with pemetrexed until PD, intolerable toxicity, withdrawal of ICF, a total of 24 months of treatment, or other reasons for discontinuation of the study treatment (whichever occurs first). The treatment by IBI308 lasts for up to 24 months.
17. For Cohort E, each treatment cycle contains 3 weeks. The dosing regimen is IBI308 200 mg IV D1 + gemcitabine 1250 mg/m^2 IV D1, D8 + cisplatin 75 mg/m^2 IV D1. Up to 6 cycles of triple drug combination therapy are given. Subsequently, the subjects experiencing no PD can receive a maintenance treatment with 200 mg IV Q3W of IBI308 until PD, intolerable toxicity, withdrawal of ICF, 24 months of treatment, or other reasons for discontinuation of the study treatment (whichever occurs first). The treatment by IBI308 lasts for up to 24 months.
18. For Cohort F, 200 mg of IBI308 is given via intravenous infusion every 3 weeks. Each treatment cylce contains 3 weeks. The dosing regime is capecitabine 1000 mg/m^2 PO bid D1–14 + oxaliplatin 130 mg/m^2 IV D1 (XELOX regimen). After up to 6 cycles of treatment with IBI308 in combination with XELOX, the subjects experiencing no PD can receive a maintenance treatment with 200 mg IV Q3W of IBI308 until PD, intolerable toxicity, withdrawal of ICF, 24 months of treatment, or other reasons for discontinuation of the study treatment (whichever occurs first). The treatment by IBI308 lasts for up to 24 months.
19. Subjects are required to provide archived or fresh tumor tissue samples meeting test requirements during screening.
20. For Cohort D, up to 4 cycles of triple drug combination therapy are given; for Cohorts E and F, up to 6 cycles of triple drug combination therapy are given.
21. The end-of-treatment visit is carried out within 7 days after the end of treatment is confirmed, as detailed in 6.2.3 of the protocol.
22. A safety follow-up should be carried out within 90 ± 7 days after the last dose or before the start of a new anti-tumor treatment (whichever occurs first). The study drug-related AEs need to be followed up until resolved to grade 0 or 1, stable, or withdrawal of ICF (whichever occurs first). Refer to 6.2.3 for details.
23. Survival follow-up: once every 3 months (± 7 days) after treatment discontinuation. Telephone follow-up is allowed.

Table 5. Visit schedule for Cohorts G/H in the Phase Ib study

Stage	Screening period	Treatment period (21 days per cycle)							End-of-treatment visit[16]	Safety follow-up[17]	Survival follow-up[18]
		Combination therapy						Maintenance therapy			
		Cycle 1			Cycles 2–6			Cycle 7 and beyond			
Visit	1	2			3–7			N			
Day	−28 to −1	D1	2	3	Day 1 (± 2 days)	2	3	Day 1 (± 2 days)	Within 7 days after the end of treatment is confirmed	90 days (± 7 days) after the end of treatment	Every 90 days (± 7 days)
Standard study procedures											
Written ICF[1]	X										
Inclusion/exclusion criteria	X										
Demographics/medical history/previous medications[2]	X										
Vital signs[3]	X	X			X			X	X	X	
Weight/height[4]	X	X			X			X	X	X	
Physical examination	X				X			X	X	X	
ECOG PS score	X	X			X			X	X	X	
12-Lead ECG[5]	X	X			X			X	X	X	
Routine blood test/blood chemistry/urinalysis[6]	X				X			X	X	X	
Coagulation function[7]	X								X	X	
Pregnancy test[8]	X										
Thyroid function[9]	X				X			X	X	X	
Autoantibody[10]	X										

Stage	Screening period	Treatment period (21 days per cycle)							End-of-treatment visit[16]	Safety follow-up[17]	Survival follow-up[18]
		Combination therapy						Maintenance therapy			
		Cycle 1			Cycles 2–6			Cycle 7 and beyond			
Visit	**1**	**2**			**3–7**			**N**			
Day	**−28 to −1**	**D1**	**2**	**3**	**Day 1 (± 2 days)**	**2**	**3**	**Day 1 (± 2 days)**	**Within 7 days after the end of treatment is confirmed**	**90 days (± 7 days) after the end of treatment**	**Every 90 days (± 7 days)**
HIV, HBV, and HCV[11]	X										
AE evaluation[12]	X	X			X			X	X	X	X
Concomitant medications	X	X			X			X	X	X	
Survival condition											X
Subsequent anti-tumor therapy										X	X
Efficacy evaluation											
Tumor imaging evaluation[13]	X							X		X	
Study drug administration in Cohort G [14]											
IBI308		X			X			X			
Etoposide		X	X	X	X	X	X				
Cisplatin		X			X						
Study drug administration in Cohort H [15]											
IBI308		X			X			X			
Irinotecan		X			X						
5-FU		X	X	X	X	X	X				

Note:

1. The ICF should be signed by subjects prior to any procedures outlined in the protocol.

2. Previous medications include : treatment for the initial diagnosis, including chemotherapy, radiotherapy, and surgery.
3. Vital signs include: body temperature, pulse, respiratory rate, and blood pressure.
4. Height is measured during screening period only. Weight must be measured before every planned dose during the study. If the weight fluctuation of a subject is less than 10% compared to the baseline (the day when the first dose of IBI308 is given), then the baseline weight will be used to calculate the dose. Otherwise, the actual dose will be calculated based on the weight of scheduled dosing days.
5. Time of 12-lead ECG examinations: during the screening period, within 60 min after the end of IBI308 infusion in each cycle, and during the end-of-treatment visit and safety follow-ups.
6. Routine blood test include: RBC, HGB, HCT, WBC, PLT, and white blood cell differential (LYM, ANC, MONO, EOS, BASO). Blood chemistry include: hepatic function (TBIL, ALT, AST, γ-GT, ALP, ALB, TP, LDH), renal function (BUN, Cr), blood electrolytes (Na, K, Cl, Mg, Ca, P), lipase, amylase, and FBG. Urinalysis include: PH, UALB, UPRO, URBC, and UGLU. Any subject with urine protein ≥ 2+ from urinalysis dipstick in routine urinalysis at screening needs to undergo a 24-h urine protein test. The tests will be conducted during screening, within 7 days before the first dose of the study drug, within 3 days before each administration of the study drug starting from Cycle 2, during the end-of-treatment visit, and during the safety follow-ups. Tests will be conducted at each study site.
7. Coagulation function tests include: TT, PT, APTT, and INR. They are tested within 7 days before the first dose of IBI308, during the end-of-treatment visit, and during the safety follow-ups. Tests will be conducted at each study site.
8. Women of childbearing age should undergo a urine or blood pregnancy test within 3 days before the first dose. If the urine pregnancy test is not conclusive, then blood pregnancy test should be performed. The conclusion should be based on the blood pregnancy test. Tests will be conducted at each study site.
9. They are tested during screening, within 7 days before each administration of the study drug starting from Cycle 2, during the end-of-treatment visit, and during the safety follow-ups. T3, T4, FT3, FT4, and TSH are examined during the screening period. Starting from Cycle 2, only TSH is examined. If there are abnormalities, the examination of other thyroid function parameters will be considered. Tests will be conducted at each study site.
10. Autoantibodies include: anti-nuclear antibodies, anti-dsDNA antibodies, and anti-thyroglobulin antibodies. The test is conducted during screening, and afterwards retest will be done only if deemed necessary by the investigator. Tests will be conducted at each study site.
11. Including tests for HCV and HIV antibodies, as well as HBsAg, HBsAb, HBcAb, HBeAg, and HBeAb. They are tested during screening. Tests will be conducted at each study site.
12. AEs and laboratory safety assessments will be performed based on NCI CTCAE V4.03. Refer to Section 7 for definitions, recording, causality determination, severity level, reporting deadlines, and treatment of AEs and SAEs.
13. Tumor evaluations are based on RECIST V1.1 and irRECIST. There is no central imaging evaluation in this study. Tumor imaging examinations usually include contrast-enhanced CT or MRI of the chest, abdomen, and pelvic cavity. Additional examination sites are determined based on sites involved by tumors. The same subject should receive the same type of imaging examination during the study. Baseline evaluation is conducted within 28 days prior to enrollment. The investigators can evaluate imaging results within 28 days prior to enrollment. Tumor imaging evaluation should be carried out every 9

weeks (± 7 days) after first dose of the study drug. For subjects with initial response (CR or PR), an imaging evaluation is carried out 4–6 weeks later to confirm the response and every 9 weeks (± 7 days) thereafter until imaging PD is recorded. For subjects who are first recorded as imaging PD, an imaging evaluation should be carried out 4 weeks (± 7 days) later for confirmation. For subjects with first imaging PD but an unstable clinical situation or rapid progression who are deemed as not suitable for continued drug treatment, it is not necessary for them to undergo further imaging examinations to confirm PD. For subjects who discontinue the treatment for reasons other than imaging PD, an imaging evaluation should be carried out at the end of the treatment and every 9 weeks (± 7 days) after treatment discontinuation until start of a new anti-tumor therapy, PD, ICF withdrawal by subjects, or death.

14. Combination therapy regimen for Cohort G: Each treatment cycle contains 3 weeks. The dosing regime is IBI308 200 mg IV D1 + etoposide 100 mg/m^2 IV D1–3 + cisplatin 75 mg/m^2 IV D1. Up to 6 cycles of combination therapy are given. Subsequently, the subjects experiencing no PD can receive a maintenance treatment with 200 mg IV Q3W of IBI308 until PD, intolerable toxicity, withdrawal of ICF, 24 months of treatment, or other reasons for discontinuation of the study treatment (whichever occurs first).
15. Combination therapy regimen for Cohort H: Each treatment cycle contains 3 weeks. The dosing regime is IBI308 200 mg IV D1 + irinotecan 125 mg/m^2 IV D1, D8 + 5-FU 1000 mg/m^2 IV D1–3. Up to 6 cycles of combination therapy are given. Subsequently, the subjects experiencing no PD can receive a maintenance treatment with 200 mg IV Q3W of IBI308 until PD, intolerable toxicity, withdrawal of ICF, 24 months of treatment, or other reasons for discontinuation of the study treatment (whichever occurs first).
16. The end-of-treatment visit is carried out within 7 days after the end of treatment is confirmed, as detailed in 6.2.3 of the protocol.
17. A safety follow-up should be carried out within 90 ± 7 days after the last dose or before the start of a new anti-tumor treatment (whichever occurs first). The study drug-related AEs need to be followed up until resolved to grade 0 or 1, stable, or withdrawal of ICF (whichever occurs first). Refer to 6.2.3 for details.
18. Survival follow-up: once every 3 months (± 7 days) after treatment discontinuation. Telephone follow-up is allowed.

Table 6. PK/PD sampling schedule of Cohorts A/B/C/D/E/F in the Phase Ib study

Stage	**Screening period**	**Treatment period (21 days per cycle)**												**Safety follow-up[5]**
		Cycle 1[2]									**Cycle 2 and thereafter[3,4]**			
Day	-28~-1	1					2	3	8	15	Day 1 (± 2 days)			90 days (± 7 days)
Sampling time[1]		-1h	During infusion	Immediately at the end of infusion	1 h after the end of infusion	6 h after the start of infusion	24h	48h	168h	336h	-1h [2]	During infusion	Immediately at the end of infusion	
Time window of blood sampling				+5min	±5min	±15min	±1h	±2h	±8h	±12h			+5min	
IBI308			X									X		
PK[6]		X		X	X	X	X	X	X	X	X [3]		X [3]	X [5]
PD[6]		X					X		X		X [4]			X [5]

Note:

1. Samples should be collected from the opposite arm of the infusion site.
2. If the dosing on Day 1 of Cycle 2 is delayed due to an AE or other reasons, additional sampling is required at 504 ± 24 h (Day 22) in Cycle 1.
3. Since Cycle 2, PK samples are collected every 2 cycles (Cycles 2, 4, 6, and so on).
4. Since Cycle 2, PD samples are collected every 4 cycles (Cycles 6, 10, 14, and so on).
5. Both PK and PD samples are collected during safety follow-ups, but not collected during survival follow-ups.
6. For Cohort B, after the PK/PD blood samples of 20 subjects who meet the requirements of assay and analysis are collected, subsequent subjects are not required to undergo PK/PD assays.

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List of Abbreviations and Definitions

ADA	Anti-drug antibody
AE	Adverse event
AESI	Adverse event of special interest
ALB	Albumin
ALK	Anaplastic lymphoma kinase
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
ANC	Absolute neutrophil count
APTT	Activated partial thromboplastin time
AST	Aspartate amino transferase
AUC	Area under the curve
BASO	Basophil count
BUN	Blood urea nitrogen
CCr	Clearance of creatinine
CHO	Chinese hamster ovary cell
CI	Confidence interval
C_{max}	Maximum observed concentration
Cr	Serum creatinine
CR	Complete response
CRO	Contract research organization
CSR	Clinical study report
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTLA-4	Cytotoxic T-lymphocyte antigen 4
DCR	Disease control rate
DLT	Dose-limiting toxicity
DoR	Duration of response
ECG	Electrocardiogram
ECOG PS	Eastern Cooperative Oncology Group Performance Status
eCRF	Electronic case report form
EGFR	Epidermal growth factor receptor
EOS	Eosinophil count
FAS	Full analysis set
FBG	Fasting blood glucose
FFPE	Formalin fixed paraffin-embedded
FT3	Free triiodothyronine

FT4	Free thyroxine
GCP	Good Clinical Practice
HBV	Hepatitis B virus
HCC	Hepatocellular carcinoma
HCT	Hematocrit
HCV	Hepatitis C virus
HGB	Hemoglobin
HIV	Human immunodeficiency virus
ICF	Informed consent form
ICH	International Conference for Harmonization
IgG	Immunoglobulin G
INR	International normalized ratio
irAE	Immune related adverse events
IRR	Infusion-related reaction
irRECIST	Immune-related Response Evaluation Criteria in Solid Tumors
IV	Intravenous infusion
LDH	Lactate dehydrogenase
LYM	Lymphocyte count
MedDRA	Medical Dictionary for Regulatory Activities
MONO	Monocyte count
mOS	Median overall survival
mPFS	Median progression free survival
MRI	Magnetic resonance imaging
MTD	Maximal tolerated dose
NAb	Neutralizing antibody
NEC	Neuroendocrine carcinoma
NCI	National Cancer Institute
NOAEL	No-observed-adverse-effect level
NOEL	No-observed-effect level
NSCLC	Non-small cell lung cancer
nsNSCLC	Non-squamous non-small cell lung cancer
ORR	Objective response rate
OS	Overall survival
PD	Pharmacodynamics
PD-1	Programmed cell death receptor 1
PD-L1	Programmed cell death ligand 1
PFS	Progression free survival

PH	Potential of hydrogen
PK/PD	Pharmacokinetics/pharmacodynamics
PLT	Platelet
PR	Partial response
PVC	Polyvinyl chloride
Q2W	Once every 2 weeks
Q3W	Once every 3 weeks
RBC	Red blood cell
RECIST	Response Evaluation Criteria in Solid Tumors
SAE	Serious adverse event
SAP	Statistics analysis plan
scNSCLC	Squamous-cell non-small cell lung cancer
SD	Stable disease
SS	Safety analysis set
SUSAR	Suspected unexpected serious adverse reaction
$t_{½}$	Half-life
T3	Triiodothyronine
T4	Thyroxine
TBIL	Total bilirubin
TEAE	Treatment emergent adverse event
TP	Total protein
TSH	Thyroid stimulating hormone
TT	Thrombin time
TTR	Time to response
UALB	Urinary white blood cell
UGLU	Urine glucose
ULN	Upper limit of normal
UPRO	Urine protein
URBC	Urine red blood cell
WBC	White blood cell
WHO	World Health Organization
γ-GT	γ-glutamyltransferase

1. BACKGROUND

1.1. Introduction

Due to prolonged life expectancy and lifestyle changes of humans, malignant tumors have become an important serious health threat and also the most life-threatening disease for humans. As estimated, there were 14.1 million new cancer cases and 8.2 million new cancer deaths worldwide in 2012[1]. In 2009, the total cancer incidence in China was 285.9/100,000 and the total mortality was 180.5/100,000[2]. Among all cancer deaths, the leading cause of death is lung cancer (25.2%), successively followed by liver cancer (14.4%), stomach cancer (14.3%), and esophageal cancer (9.3%). These 4 cancers have poor prognosis and cause 63.2% of all cancer deaths[2]. The incidence of melanoma in Chinese population is about 20,000 new cases per year, but the incidence has increased quickly in recent years. In China, the 5-year survival is less than 5% due to poor treatment effects of advanced melanoma. Great medical needs related to advanced melanoma and esophageal, stomach, liver, and lung cancers have not been met in China.

In recent years, tumor treatment via immune checkpoints has gradually become a research hotspot, and tremendous breakthroughs have been made in this field. Unlike cytotoxic drugs, monoclonal antibodies or small molecule tyrosine kinase inhibitors that target oncogenes, immune checkpoint therapy of tumors does not directly target tumor cells, but rather improve the function of T cells, remove the tolerance of the immune system to tumor cells, and improve the effective recognition and killing of tumor cells by T cells via blocking the inhibitory signals against T cell proliferation and activation. Currently, the immune checkpoint targets showing significant clinical efficacy in tumor treatment include cytotoxic T lymphocyte-associated antigen-4 (CTLA-4) and programmed cell death receptor 1/ligand 1 (PD-1/PD-L1)[3].

Recombinant fully human anti-PD-1 monoclonal antibody injection (Sintilimab, R&D code: IBI308) is a Category 1 new drug independently developed by Innovent Biologics (Suzhou) Co., Ltd. When the study protocol 3.0 is being revised, IBI308 has been approved for marketing by the National Medical Products Administration on Dec. 24, 2018 in China. IBI308 is an anti-IgG4 (immunoglobin G4) monoclonal antibody. It can specifically bind to PD-1 molecules on the surface of T lymphocytes, thereby blocking the PD-1/PD-L1 pathway which causes immune tolerance to tumors and reactivating the anti-tumor activity of T lymphocytes so as to treat the tumors. IBI308 shares the same target as two marketed anti-PD-1 monocolonal antibodies (nivolumab and pembrolizumab), but its amino acid sequence is different from that of the two marketed antibodies. The existing study results have showed IBI308 has a clear structure and its stability, activity, PK/PD in animals, and safety are comparable or superior to those of similar drugs from foreign countries. With reference to the approved indications and clinical study data of similar drugs developed overseas, the sponsor applies for clinical studies to explore the

PK/PD characteristics of IBI308 in humans as well as the efficacy and safety of IBI308 in the treatment of various solid tumors, especially melanoma, esophageal carcinoma, gastric cancer, hepatocellular carcinoma, and NSCLC, based on the urgent clinical needs and the epidemiological characteristics of tumors in China.

This study is the first-in-human clinical study of IBI308. The phase Ia dose escalation study is mainly designed to evaluate the safety, tolerability, and PK/PD of IBI308 in the treatment of subjects with advanced solid tumors who failed standard treatment. The objective of phase Ib study is to evaluate the safety and preliminary anti-tumor activity of the monotherapy or combination chemotherapy of IBI308 in the treatment of specific types of advanced cancers (melanoma, malignant neoplasms of the digestive system, NSCLC, and neuroendocrine neoplasms). In addition, other data planned to be evaluated include immunogenicity of IBI308 and related biomarkers.

1.2. Disease Background

1.2.1. Melanoma

In the Chinese population, the incidence of melanoma is lower (about 20,000 cases per year) than that in the European and American population, but melanoma cases have obviously increased in recent years. For Chinese patients with advanced melanoma, the current standard therapy is dacarbazine chemotherapy or high-dose interleukin-2 (IL-2) therapy, but the 5-year survival rate is less than 5% due to low response rate and limited survival benefits[4]. Breakthroughs in drug therapy for advanced melanoma have been achieved in recent years. For metastatic or unresectable BRAF-mutant melanoma, tyrosine kinase inhibitors (TKIs) targeting BRAF mutations (vemurafenib and dabrafenib) has been approved by FDA to be used alone or in combination with MEK inhibitors (trametinib and cobimetinib) as the first-line therapy; for metastatic or unresectable BRAF wild-type melanoma, two types of immune checkpoint inhibitors (anti-CTLA-4 monoclonal antibody ipilimumab and anti-PD-1 monoclonal antibody nivolumab/pembrolizumab) can be used alone or combined as the first-line therapy[5]. However, these drugs have not been marketed in China.

1.2.2. Esophageal cancer and gastric cancer

Most of the esophageal and gastric cancer cases are staged at the initial diagnosis to be advanced and have been incurable. A large proportion of patients undergoing surgery for early-stage esophageal or gastric cancer experience recurrence and distant metastasis or die of this cancer or related complications. The 5-year survival rate is less than 10% in advanced cases. Patients with advanced esophageal and gastric cancers are treated mainly with systemic therapy. Active drugs for these two cancers include chemotherapeutics and targeted agents. Such chemotherapeutics for clinical use include fluorouracil or its derivatives (capecitabine, and tegafur, gimeracil, and

oteracil porassium capsules), platinum-based drugs (cisplatin and oxaliplatin), taxanes (paclitaxel and docetaxel), and epirubicin. Some of such patients can be treated with targeted agents. For examples, trastuzumab can be combined with the first-line chemotherapy in patients with HER2-positive gastroesophageal junction adenocarcinoma and gastric adenocarcinoma, and apatinib, an anti-vascular tyrosine kinase inhibitor, can be used in gastric cancer patients who have failed second-line chemotherapy. Overall, systemic therapy delivers limited efficacy against advanced esophageal and gastric cancers, and the median survival for patients with esophageal and gastric cancers is demonstrated in multiple large-scale clinical studies to be about 1 year[6, 7].

1.2.3. Liver cancer

Hepatocellular carcinoma (HCC) is the main pathological type (more than 90%) of primary liver cancer. In China, HCC is mainly caused by chronic hepatitis B infection and often complicated with chronic hepatitis or cirrhosis, resulting in poor tolerance of some patients to liver cancer therapy. Most of HCC cases are staged at the initial diagnosis to be in the middle or advanced stage due to insidious onset and rapid progression. A large proportion of patients undergoing surgery for early-stage HCC still experience a relapse, indicating extremely poor prognosis. Effective systemic drugs for advanced HCC are limited. The common ones used in China include fluorouracil, oxaliplatin, and sorafenib. Generally, the mean survival is only about six months for patients with advanced HCC[8].

1.2.4. Neuroendocrine neoplasm

Neuroendocrine neoplasms are malignant solid neoplasms that arise from diffuse neuroendocrine cells. These cells are distributed across the body, so these neoplasms may occur at any site of the body. The most common ones are neuroendocrine neoplasms of the digestive system (stomach, intestine, pancreas), about 2/3 of all of this type of neoplasms. According to the WHO 2010 nomenclature for neuroendocrine neoplasms, "neuroendocrine neoplasm (NEN)" refers to all tumors arising from neuroendocrine cells, and moderately- and highly- differentiated ones are named "neuroendocrine tumor (NET)" while poorly-differentiated ones are named "neuroendocrine carcinoma (NEC)".

Drugs for neuroendocrine neoplasms are used to control symptoms resulting from excessive secretion of functional neuroendocrine neoplasm hormones as well as tumor growth. Biologic and targeted therapies are the main drug therapies for highly-differentiated neuroendocrine neoplasms. The existing biotherapeutic agents for neuroendocrine neoplasms are somatostatin analogs including octreotide and lanreotide; targeted drugs include everolimus (a mammalian target of rapamycin protein inhibitor) and sunitinib (a tyrosine kinase inhibitor). Conventional cytotoxic chemotherapeutics still serve as the first-line therapy for poorly differentiated neuroendocrine carcinoma, but the OS is about 10 months due to rapid PD.

1.2.5. Lung cancer

About 80–85% of lung cancer cases are NSCLC ones. Approximately 70% of NSCLC patients are judged at the initial diagnosis to be locally advanced or metastatic and unsuitable for surgical resection. Besides, a large proportion of NSCLC patients undergoing surgery for early-stage NSCLC experience recurrence or distant metastasis, or even die due to progression. About 60% of Chinese NSCLC cases are nsNSCLC. Patients with advanced nsNSCLC are treated mainly with chemotherapy, and some of them are suitable for targeted therapy. The EGFR mutation rate is about 40% in Chinese nsNSCLC cases. EGFR inhibitors (gefitinib, erlotinib, or icotinib) are recommended as the first-line therapy for patients with EGFR-mutated advanced NSCLC. The incidence of ALK rearrangement is about 3% in China. The first-line therapy with crizotinib (an ALK inhibitor) is recommended for patients with ALK-rearranged advanced NSCLC. For nsNSCLC and scNSCLC patients without EGFR mutation and ALK rearrangement, the platinum-based doublet chemotherapy is the first-line standard therapy, and the survival following failed first-line chemotherapy is 6–9 months only[9].

1.3. Immune Checkpoint Therapy

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[10-11].

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[12-15]. PD-L1 expression is upregulated in a variety of solid tumors. The expression of PD-L1 is closely related to the shortened survival and poor prognosis of various tumors[16-23] such as lung caner, hepatic cancer, gastric cancer, esophageal carcinoma, urothelial carcinoma, renal carcinoma, pancreatic cancer, and ovarian cancer. 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[24].

A total of 6 PD-1/PD-L1 products have been approved by US FDA for marketing. They are nivolumab (anti-PD-1 mAb, trade name: OPDIVO) by BMS, pembrolizumab (anti-PD-1 mAb, trade name: KEYTRUDA) by Merck, atezolizumab (anti-PD-1 mAb, trade name: Tecentriq) by Roche, avelumab (anti-PD-L1 mAb, trade name: Bavencio) by Pfizer/Merck Drugs & Biotechnology, durvalumab (anti-PD-L1 mAb, trade name: Imfinzi) by AstraZeneca, and cemiplimab (anti-PD-1 mAb, trade name: Libtayo) by Regeneron/Sanofi. These products are indicated for advanced melanoma, advanced NSCLC, advanced small cell lung cancer (SCLC), advanced head and neck squamous cell carcinoma, advanced classical Hodgkin's lymphoma, primary mediastinal large B-cell lymphoma, advanced renal cell carcinoma, advanced urothelial carcinoma, microsatellite instability-high tumors, advanced gastric cancer, advanced cervical cancer, advanced HCC, metastatic or locally advanced cutaneous squamous cell carcinoma (CSCC), etc.[25-27] In addition, many indications have been under phase III clinical studies or have been submitted for approval. The approval of these drugs confirms the important role of PD-1/PD-L1 immune checkpoint inhibitors in cancer immunotherapy. It is of great significance to actively develop such inhibitors to provide better treatment options for domestic patients with advanced cancers.

1.4. Study Drug (IBI308)

IBI308 is a recombinant fully human IgG4 monoclonal antibody consisting of 1,322 amino acids, including two light chains (LCs) and two heavy chains (HCs), which are connected by 4 pairs of inter-chain disulfide bonds and 12 pairs of intra-chain ones to a "Y" structure. Each LC consists of 214 amino acids, while each HC consists of 447 amino acids. The intact molecular weight of IBI308 is about 146.4 kDa. For IBI308 containing no oligosaccharide, the theoretical molecular weight of the light chain is 143,788.4 Da, and the measured molecular weight is 143,502 Da. The theoretical molecular weight of HC containing no oligosaccharide is 48,811.4 Da, and the measured molecular weight is 48,668.2 Da. The theoretical molecular weight of the light chain is 23,098.9 Da, and the measured molecular weight is 23,099.5 Da.

The completed nonclinical studies on PD, PK in animals, and toxicology have shown IBI308 is characterized by clear targets, reliable source of cell lines, and good stability and activity. IBI308-related study conclusions are briefly described below. Refer to "Investigator's Brochure" for detailed study results.

1.4.1. Nonclinical pharmacodynamic studies of IBI308

The completed *in vitro* PD studies showed IBI308 has marked species specificity and target specificity.

IBI308 has very high affinity to recombinant human PD-1 and cynomolgus monkey PD-1, weak affinity to recombinant rabbit PD-1, and no affinity to recombinant rat PD-1 and mouse PD-1 as

well as recombinant human CTLA-4 and CD28. The affinity specificity of IBI308 is consistent with that of nivolumab, but IBI308's affinity to recombinant human PD-1 and cynomolgus monkey PD-1 is higher than that of nivolumab.

The in vitro cytological study demonstrated that, IBI308 has very high affinity to Chinese hamster ovary (CHO) cells expressing human PD-1 while competitively inhibiting binding of human PD-L1 or human PD-L2 to human PD-1-expressing CHO cells. The above effects of IBI308 are basically the same as those of nivolumab.

The *in vitro* studies have also found that IBI308 can dose-dependently promote the release of interleukin-2 (IL-2) and interferon-γ (IFN-γ) by T cells, and this effect is similar to that of nivolumab. In addition, the direct action of IBI308 and nivolumab on human peripheral blood mononuclear cells (PBMCs) does not affect the release of cytokines, and the effects of IBI308 and nivolumab are similar.

The in vivo PD study on drug antitumor efficacy demonstrated that the murine substitute (11430) of IBI308 is able to significantly inhibit tumor growth in MC38 tumor-bearing C57bl/6 mouse models, with a tumor growth inhibition (TGI) of more than 60%, and is more efficacious than the positive reference standard RMP1-14.

In the NSG mouse model (SCID-Winn model) inoculated with a mixture of NCI-H292 and human PBMCs, IBI308 was able to significantly inhibit tumor cell growth in an evident dose-dependent manner, and did not influence body weights of mice. IBI308 is more efficacious than the positive reference standard nivolumab.

The above results suggest that IBI308 has clear target, clear mechanism of action, and significant immunity-enhancing and anti-tumor effects.

1.4.2. Nonclinical pharmacokinetic studies of IBI308

IBI308 binds specifically to the surface antigens in normal human lymph nodes, spleen, and tonsil membrane. It can specifically bind to the surface antigens in normal intestinal mucosa-related lymphoid tissues, mesenteric lymph nodes, spleen and tonsil membrane in cynomolgus monkeys, and has no specific binding to other tissues. The tissue cross-reactivity characteristics of IBI308 are basically the same as those of commercially available analogous drug nivolumab. These suggest IBI308 has specific binding to major immune tissues or organs where immune cell distribution density is high.

Cynomolgus monkeys received a single IV infusion of 1 mg/kg, 6 mg/kg and 30 mg/kg IBI308 and 6 mg/kg nivolumab. For female and male animals, the concentration-time curves obtained were quite similar without gender difference and indicated a linear PK profile. The metabolic characteristics of nivolumab were basically the same as those of IBI308 at the same dose.

After intravenous infusion of IBI308 at 6 mg/kg once a week for 4 consecutive times in cynomolgus monkeys, the drug concentration-time curves at Week 4 in male ones were similar to those at Week 1, but those in female ones showed a certain difference from those at Week 1 possibly due to the presence of anti-drug antibodies (ADAs). There was no drug accumulation. This suggested IBI308 has a good linear PK profile and a low risk of accumulation following multiple doses.

The single-dose pharmacodynamic study was performed in parallel with single-dose PK study. At 24 h after a single intravenous infusion of different doses of IBI308 (1 mg/kg, 6 mg/kg, and 30 mg/kg) in cynomolgus monkeys, the results of CD3 + T cells in the body showed that the ratio of PD-1 not binding to IBI308 dropped to zero in all groups. In the 1 mg/kg dose group, the ratio of the PD-1 not binding to IBI308 increased again on Day 14 after administration. Almost no PD-1 did bind to IBI308 on Day 42 after administration. In the 6 mg/kg and 30 mg/kg groups, the PD-1 not binding to IBI308 started to appear again in the animals at Day 28 after administration, and the ratio of such PD-1 in the 6 mg/kg group was higher than that in the 30 mg/kg group. On Day 42 after administration, the ratio of non-binding PD-1 in the 6 mg/kg group was 74.06%, higher than that (62.55%) in the 30 mg/kg group. The results showed that, after a single intravenous infusion of IBI308 in cynomolgus monkeys, the changes over time in the ratio of the PD-1 not binding to IBI308 correlate with the changes in serum drug concentration, which can accurately reflect the occupancy of PD-1 by IBI308 on the surface of CD3 + T cells. However, the changes over time in the ratio of IBI308-bound PD-1 showed poor correlation with the changes in serum drug concentration, which may be due to the interference generated by the assay and serum drug concentration. These suggested that, after a single intravenous infusion of IBI308, the changes over time in the ratio of the PD-1 not binding to IBI308 highly correlate with those in the serum drug concentration, so PD-1 can be used as a pharmacodynamic biomarker.

IBI308 (6 mg/kg, 40 mg/kg, and 200 mg/kg) was intravenously infused to cynomolgus monkeys once a week for 5 consecutive doses, C_{max} and AUC_{0-t} increased proportionally with the increasing dose after the first administration, but did not change significantly after dose normalization. The values of C_{max} and AUC_{0-t} increased with the increasing dose after the fourth dose. At the dose of 6 mg/kg, dose-normalized C_{max} and AUC_{0-t} were slightly lower than those obtained at 40 mg/kg and 200 mg/kg. Such differences may be due to the higher incidence and titer of ADAs. There were no gender differences between male and female animals, and no significant drug accumulation after multiple administrations. These suggested IBI308 has no accumulation following multiple doses but is immunogenic to some extent, to which attention should be paid.

After a single intravenous infusion of 125I-IBI308 in cynomolgus monkeys, the AUC ranking of the total radioactive drug equivalent was similar to the radioactivity ranking of precipitated fraction of trichloroacetic acid (TCA), and the recovery of radioactivity from the precipitated fraction of TCA was high in most tissues. The drug in its original form, was mainly distributed in the blood circulation system, followed by organs having high blood supply, such as lungs, gonads, liver, heart and spleen (an immune-related organ). A certain distribution was also found in excretory organs and body fluids such as bladder, kidneys, and urine. The drug was less distributed in tissues such as eyeballs, fat, pancreas, bone marrow, muscle, and brain. In most tissues and organs, the trend of changes over time in the radioactive drug equivalent was consistent with the trend in the serum drug concentration-time curves after intravenous infusion of the drug. The drug was mainly excreted into the urine of cynomolgus monkeys, while a very small amount was excreted in the feces. The cumulative excretion rate exceeded 80% at 408 h after a single dose, indicating that the drug clearance was basically completed. As suggested above, IBI308 is distributed, mainly in its original form, in circulation systems; its distribution in tissues is affected by local blood flow and target antigen distribution; it is metabolized into small molecules and excreted in urine.

1.4.3. Nonclinical toxicological studies of IBI308

Cynomolgus monkeys were divided into IBI308 6, 40, and 200 mg/kg groups. Corresponding doses were given through intravenous infusion. There was no significant effect on CNS, cardiovascular system, and respiratory system. A single intravenous injection of up to 400 mg/kg IBI308 was given to cynomolgus monkeys. No reactions associated with IBI308 were observed in the animals within 14 days after administration. After IBI308 was intravenously injected to cynomolgus monkeys at doses of 6 mg/kg, 40 mg/kg and 200 mg/kg once weekly for 5 consecutive doses, followed by 4-week observation after the drug was discontinued, no adverse change was observed in animals in clinical observation, administration site observation, body weight, food intake, body temperature, blood pressure, ECG, respiration, ophthalmologic examination, hematology, coagulation, blood chemistry, urinalysis, organ weight, gross anatomical observation, and histopathological observation. A few animals in the 40 mg/kg group and the animals in the 200 mg/kg group showed an increase in globulin (immunoglobulin IgG), which may be caused by the fact that IBI308 itself is an IgG monoclonal antibody. The abnormal globulin results basically returned to normal at the end of the recovery period. In addition, at the above doses, IBI308 showed no effect on the numbers of CD3 + CD4 + cells and CD3 + CD8 + cells, or on the ratio between these two types of cells. The NOAEL of IBI308 was 200 mg/kg in multi-dose cases.

As shown by the immunogenicity study results, in the single-/multi-dose PK and toxicokinetic studies of IBI308 intravenously infused in cynomolgus monkeys, the production of ADAs was

initiated at all doses of IBI308, and some ADAs were NAbs. The result of in vitro hemolysis experiment showed that IBI308 did not cause hemolysis at the intended clinical concentrations. As suggested above, IBI308 has good safety and tolerability and is suitable for multiple intravenous infusions, but it is immunogenic to some extent, to which attention should be paid.

1.5. Risk and Benefit Assessment

Risks/benefits were assessed based on nonclinical study results of PK, PD, and toxicology. The dose range for this study is proposed to be 1–10 mg/kg. 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) vary. Therefore, investigators must closely monitor early signs and symptoms of irAEs during the trial, make correct judgments timely, adjust the dose according to Section 5.4.1 in the protocol, and provide effective treatment measures to reduce risks to subjects. Besides, subjects with autoimmune diseases shall be excluded from the trial to avoid exacerbation of the original disease due to the activation of immune system.

The in vivo PD study on drug antitumor efficacy demonstrated that the murine substitute (11430) of IBI308 is able to significantly inhibit tumor growth in MC38 tumor-bearing C57bl/6 mouse models. In the NSG mouse model (SCID-Winn model) inoculated with a mixture of NCI-H292 and human PBMCs, IBI308 was able to significantly inhibit tumor cell growth in a evident dose-dependent manner, and did not influence body weights of mice. The commercially available anti-PD-1/PD-L1 monoclonal antibodies have been widely applied and shown significant efficacy in the treatment of advanced melanoma, advanced NSCLC, advanced SCLC, advanced head and neck squamous cell carcinoma, advanced classical Hodgkin's lymphoma, primary mediastinal diffuse large B-cell lymphoma, advanced renal cell carcinoma, advanced urothelial carcinoma, microsatellite instability-high tumors, advanced gastric cancer, advanced cervical cancer, advanced HCC, metastatic or locally advanced CSCC. The above data indicate anti-PD-1 monoclonal antibodies have controllable safety and anti-tumor activity against multiple advanced solid tumors, supporting clinical studies in patients with advanced solid tumors.

2. STUDY OBJECTIVES

2.1. Primary Study Endpoints

- To assess the safety and tolerability of IBI308 alone or in combination with chemotherapy in subjects with advanced solid tumors;
- To evaluate the anti-tumor activity of the monotherapy or combination chemotherapy of IBI308 Treatment in subjects with advanced solid tumors.

2.2. Secondary Study Endpoints

- To evaluate the PK characteristics of single-dose or multi-dose IBI308 in subjects with advanced solid tumors;
- To evaluate the immunogenicity of IBI308 in subjects with advanced solid tumors;
- To evaluate the PD parameters of IBI308 in subjects with advanced solid tumors.

2.3. Exploratory Objectives

- To explore the use of irRECIST in evaluating the efficacy of IBI308 in subjects with advanced solid tumors;
- To explore the potential biomarkers in tumor tissues that can predict the efficacy of IBI308: including but not limited to immunohistochemistry assay of PD-L1 expression in tumor samples, whole exome sequencing to detect tumor mutation burden (TMB), multicolor immunohistochemistry, and PD-L1 and CD8 double staining assay.

3. Overall Study Design

This is a multicenter, open-label, phase Ia/Ib study of monotherapy or combination chemotherapy of IBI308 in the treatment of advanced malignant tumors in China.

Phase Ia study: This is designed to investigate tolerability, safety, and PK of IBI308. Around 12–24 patients with advanced solid tumors that failed standard treatment will be enrolled. The dose escalation strategy is established using the standard "3 + 3" design. Four dose levels (1 mg/kg, 3 mg/kg, 200 mg, and 10 mg/kg) will be evaluated in this section. After the completion of 1 mg/kg dose administration, subjects are randomized in a 1:1 ratio to either 3 mg/kg or 200 mg dose group for independent evaluations. DLT is observed for 28 days after the first dose for each dose group. After completion of DLT observation, subjects are treated with IBI308 Q2W (1 mg/kg, 3 mg/kg, or 10 mg/kg) or Q3W (200 mg) until PD, intolerable toxicity, withdrawal of ICF, or other reasons requiring treatment discontinuation (whichever occurs first). The specific study visit arrangement is shown in Table 1 and Table 2.

Phase Ib study: This is designed to preliminarily assess the safety and anti-tumor activity of IBI308 in the following cohorts.

- Cohort A: Melanoma study, enrolling approximately 10–20 subjects with advanced melanoma. They will receive 200 mg IV Q3W of IBI308 until PD, intolerable toxicity, withdrawal of informed consent, 24 months of treatment, or other reasons for discontinuation of the study treatment (whichever occurs first). After enrollment of up to 20 subjects, the sponsor can decide whether to expand the enrollment based on PK, preliminary efficacy, and safety data. The specific study visit arrangement is shown in **Table 3** and **Table 6**.
- Cohort B: Study on malignant tumors of the digestive system or neuroendocrine tumors, enrolling approximately 50–100 subjects with such tumors who failed or became intolerable to first-line systemic standard treatment. They will receive 200 mg IV Q3W of IBI308 until PD, intolerable toxicity, withdrawal of informed consent, 24 months of treatment, or other reasons for discontinuation of the study treatment (whichever occurs first). After enrollment of 50 subjects, the sponsor will terminate the enrollment of subjects based on the progress of clinical development and preliminary efficacy and safety data of IBI308. The specific study visit arrangement is shown in **Table 3** and **Table 6**.
- Cohort C: Lung cancer study, enrolling approximately 10–20 subjects of advanced NSCLC who failed or became intolerant to first-line systemic standard treatment. They will receive 200 mg IV Q3W of IBI308 until PD, intolerable toxicity, withdrawal of informed consent, 24 months of treatment, or other reasons for discontinuation of the study treatment (whichever occurs first). The specific study visit arrangement is shown in **Table 3** and **Table 6**.
- Cohort D: Study on the safety and preliminary efficacy evaluation of first-line treatment of advanced nsNSCLC using IBI308 in combination with chemotherapy, enrolling approximately 20 subjects. Each treatment cycle contains 3 weeks. And 200 mg IV of IBI308, 500 mg/m^2 IV of pemetrexed, and 75 mg^2 IV of cisplatin are given on D1 of each cycle. Up to 4 cycles of triple drug combination therapy are given. Subsequently, the subjects experiencing no PD can receive a maintenance treatment of 200 mg IV Q3W of IBI308 and 500 mg/m^2 IV Q3W of pemetrexed until PD, intolerable toxicity, withdrawal of informed consent, 24 months of treatment, or other reasons for discontinuation of the study treatment (whichever occurs first). The specific study visit arrangement is shown in **Table 4** and **Table 6**.

- Cohort E: Study on the safety and preliminary efficacy evaluation of first-line treatment of scNSCLC using IBI308 in combination with chemotherapy, enrolling approximately 20 subjects. Each treatment cycle contains 3 weeks. The dosing regimen is IBI308 200 mg IV D1 + gemcitabine 1250 mg/m^2 IV D1, D8 + cisplatin 75 mg/m^2 IV D1. Up to 6 cycles of triple drug combination therapy are given. Subsequently, the subjects experiencing no PD can receive a maintenance treatment of 200 mg IV Q3W of IBI308 until PD, intolerable toxicity, withdrawal of informed consent, 24 months of treatment, or other reasons for discontinuation of the study treatment (whichever occurs first). The specific study visit arrangement is shown in **Table 4** and **Table 6**.
- Cohort F: Study on the safety and preliminary efficacy evaluation of first-line treatment of inoperable locally progressing, recurrent/metastatic gastric or gastroesophageal junction adenocarcinoma using IBI308 in combination with oxaliplatin/capecitabine (XELOX), enrolling approximately 20 subjects. Each treatment cycle contains 3 weeks. And 200 mg IV of IBI308 and 130 mg/m^2 IV of oxaliplatin are given on D1, while 1000 mg/m^2 of capecitabine is given orally bid on D1–14. Up to 6 cycles of triple drug combination therapy are given. Subsequently, the subjects experiencing no PD can receive a maintenance treatment of 200 mg IV Q3W of IBI308 until PD, intolerable toxicity, withdrawal of informed consent, 24 months of treatment, or other reasons for discontinuation of the study treatment (whichever occurs first). The specific study visit arrangement is shown in **Table 4** and **Table 6**.
- Cohort G: Study on the safety and efficacy evaluation of first-line treatment of inoperable locally progressing, recurrent/metastatic high-grade (G3) neuroendocrine tumors using IBI308 in combination with chemotherapy, enrolling approximately 15 subjects. Each treatment cycle contains 3 weeks. The dosing regimen is IBI308 200 mg IV D1 + etoposide 100 mg/m^2 IV D1–3 + cisplatin 75 mg/m^2 IV D1. Up to 6 cycles of triple drug combination therapy are given. Subsequently, the subjects experiencing no PD can receive a maintenance treatment of 200 mg IV Q3W of IBI308 until PD, intolerable toxicity, withdrawal of informed consent, 24 months of treatment, or other reasons for discontinuation of the study treatment (whichever occurs first). The specific study visit arrangement is shown in **Table 5**.
- Cohort H: Study on the safety and efficacy of IBI308 in combination with chemotherapy in the treatment of subjects with advanced high-grade (G3) neuroendocrine tumors who failed first-line systemic standard treatment, enrolling approximately 15 subjects. Each treatment cycle contains 3 weeks. The dosing regimen is IBI308 200 mg IV D1 + irinotecan 125 mg/m^2 IV D1, D8 + 5-FU 1000 mg/m^2 IV D1–3. Up to 6 cycles of triple drug combination therapy are given. Subsequently, the

subjects experiencing no PD can receive a maintenance treatment of 200 mg IV Q3W of IBI308 until PD, intolerable toxicity, withdrawal of informed consent, 24 months of treatment, or other reasons for discontinuation of the study treatment (whichever occurs first). The specific study visit arrangement is shown in **Table 5**.

During the treatment with IBI308 in phase Ia and Ib studies, the subjects in Cohorts A, B, and C are allowed to continue receiving IBI308 after they are judged to have PD for the first time according to the RECIST V1.1 criteria. For the detailed criteria, refer to Section 5.1.2 of the protocol.

After the study treatment is terminated, an end-of-treatment visit is required within 7 days after the termination of the study treatment is confirmed and before the subject receive a new anti-tumor treatment. A safety follow-up should be carried out within 90 days ± 7 days after the last dose or before the start of a new anti-tumor treatment (whichever occurs first). The survival follow-up is carried out every 3 months (± 7 days) after the safety follow-up (telephone follow-up is acceptable).

Cohorts G and H of the phase Ib study are newly added for the protocol 3.0. Study sites who don't participate in studies in these two cohorts will be closed after the end of clinical studies in cohorts A–F.

Figure 1. Schematic of phase Ia study design and dosing regimen

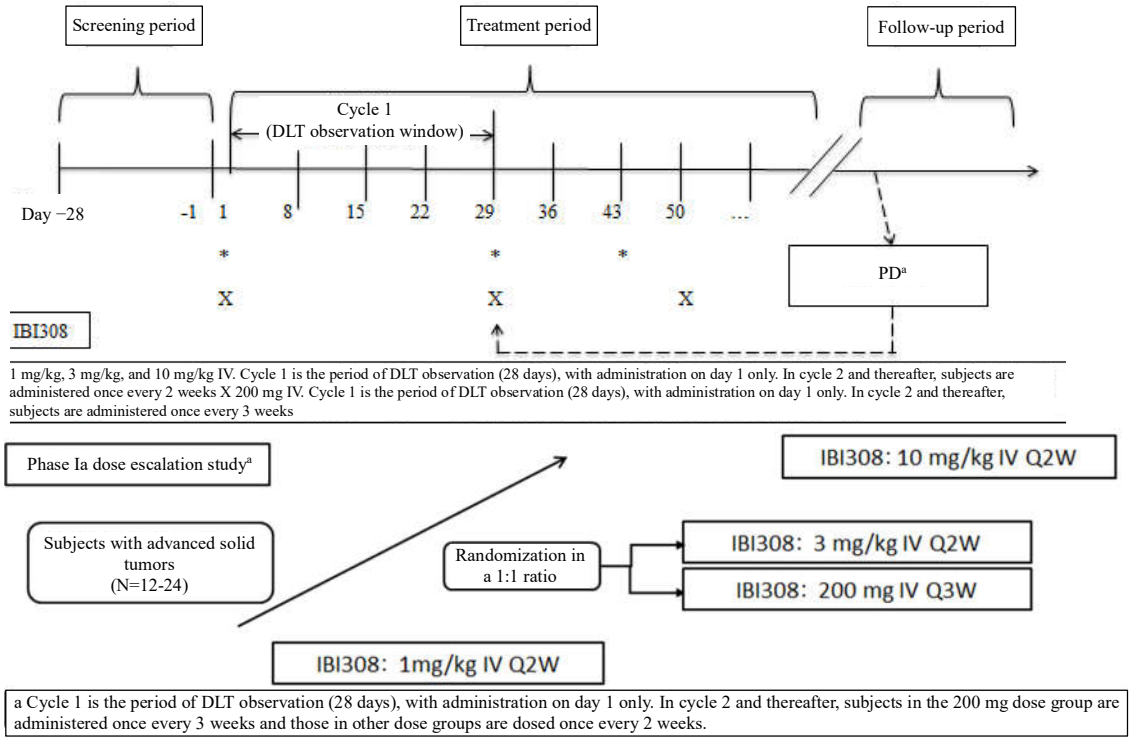
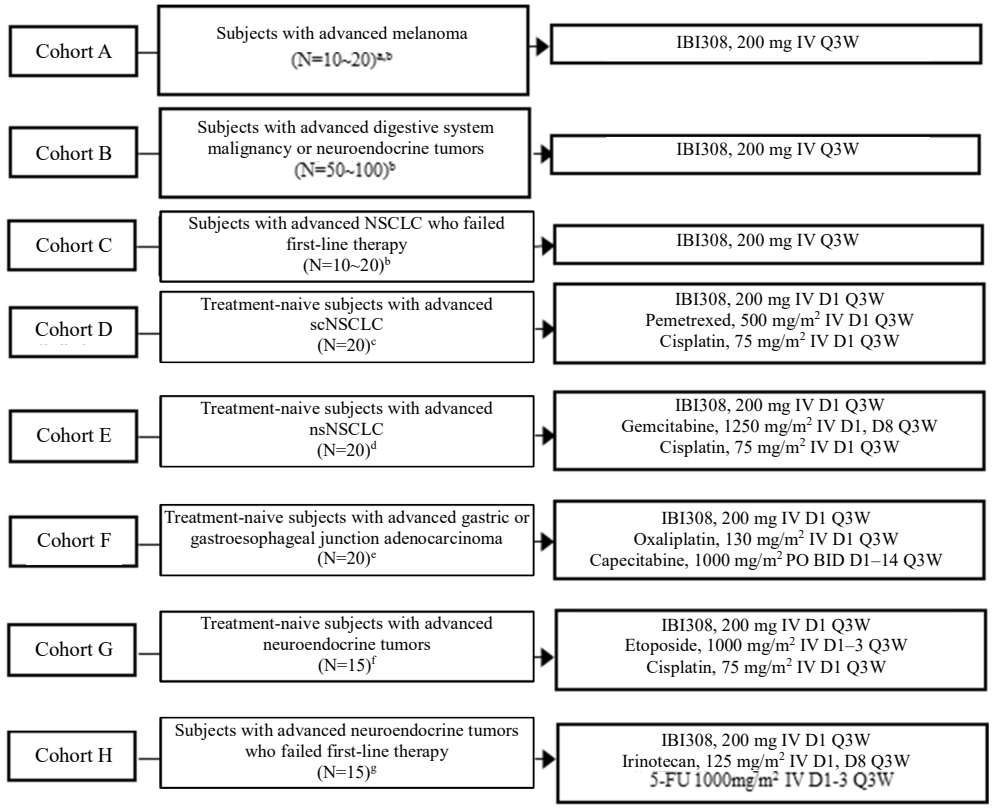


Figure 2. Schematic of phase Ib study design



a. After the completion of enrollment in the melanoma cohort, whether to expand the enrollment will be decided based on PK, preliminary efficacy, and safety

b. During the treatment with IBI308 alone, subjects meeting protocol requirements and achieving PD can continue receiving IBI308.

c. IBI308 in combination with pemetrexed and cisplatin is given for up to 4 cycles, followed by maintenance treatment with IBI308 in combination with pemetrexed.

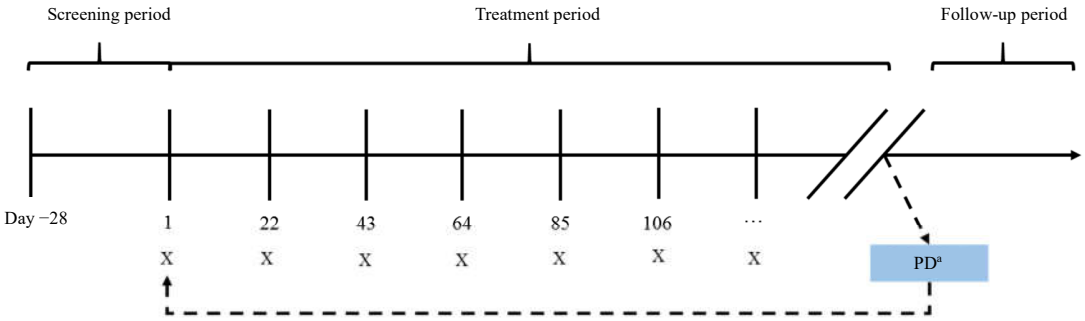
d. IBI308 in combination with gemcitabine and cisplatin is given for up to 6 cycles, followed by maintenance treatment with IBI308.

e. IBI308 in combination with oxaliplatin and capecitabine is given for up to 6 cycles, followed by maintenance treatment with IBI308.

f. IBI308 in combination with etoposide and cisplatin is given for up to 6 cycles, followed by maintenance treatment with IBI308.

g. IBI308 in combination with irinotecan and 5-FU is given for up to 6 cycles, followed by maintenance treatment with IBI308.

Figure 3. Schematic of dosing regimen for cohorts A/B/C in the phase Ib study



X IBI308, 200 mg IV D1 Q3W

a Some subjects judged to be eligible by the investigator can continue to use the drug after treatment for PD

Figure 4. Schematic of dosing regimen for cohort D in the phase Ib study

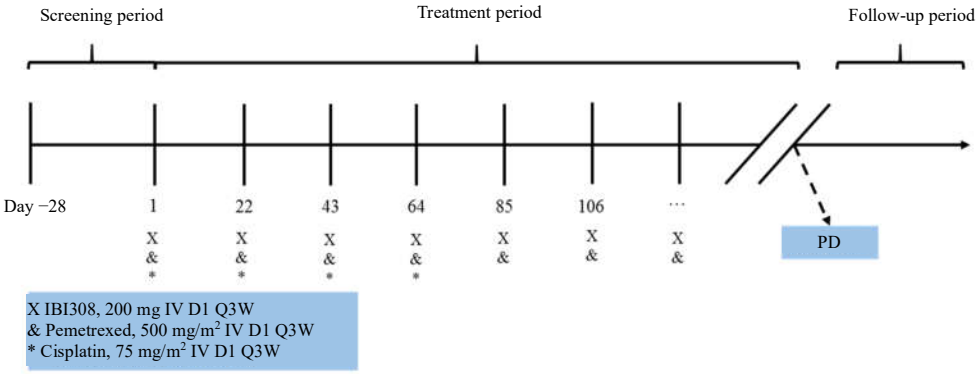


Figure 5. Schematic of dosing regimen for cohort E in the phase Ib study

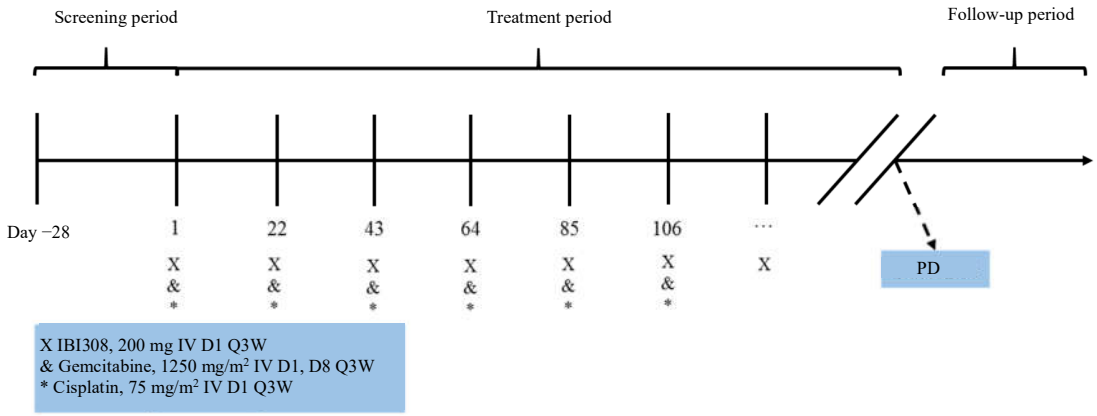


Figure 6. Schematic of dosing regimen for cohort F in the phase Ib study

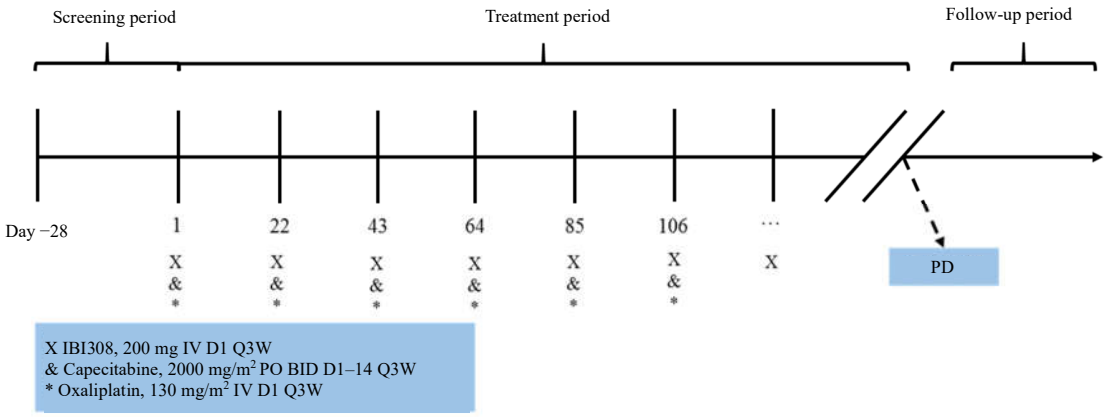


Figure 7. Schematic of dosing regimen for cohort G in the phase Ib study

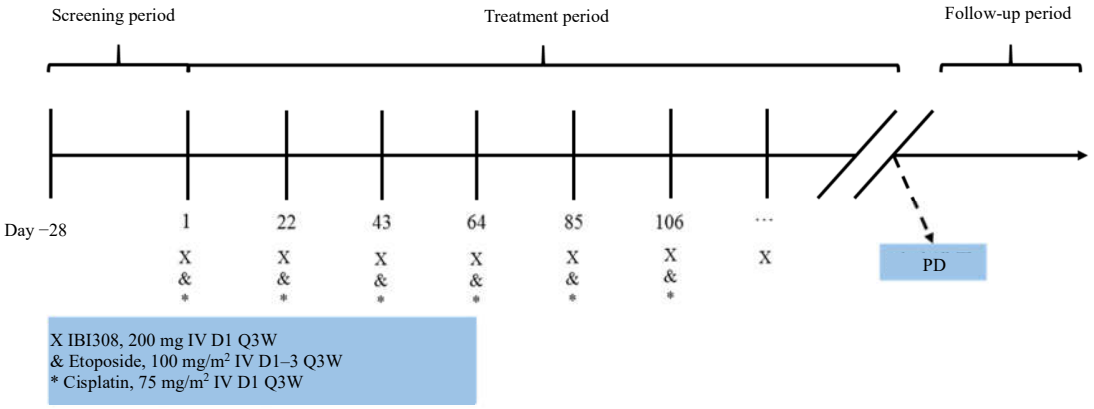
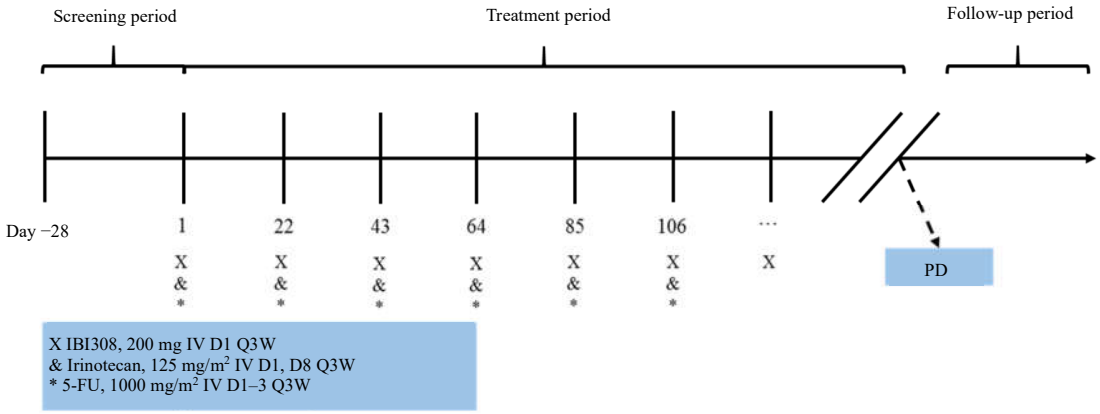


Figure 8. Schematic of dosing regimen for cohort H in the phase Ib study



3.1. Design Principles

3.1.1. IBI308 dose selection principles

In the first-in-human study of IBI308, the recommended starting dose is 1 mg/kg.

The starting dose of 1 mg/kg is designed based on multiple evidence data from in vitro activity studies, nonclinical PK/PD studies, nonclinical efficacy studies in disease models, and comparability studies of IBI308 vs. marketed drugs with the same mechanism of action. This recommended starting dose of 1 mg/kg is expected to (a) obtain the PK and immunogenicity characteristics of IBI308 in the target population for the first time and (b) to determine the IBI308 exposure (about 10 μg/mL, determined based on nonclinical data and clinical data of drugs of the same class) delivering the maximum anti-tumor activity in animal models, while ensuring the safety of subjects.

The dose range of this study is proposed, based on PK/PD data and toxicology data from completed studies, to be 1–10 mg/kg. The proposed maximum dose of 10 mg/kg is approximately 1/6 of NOAEL in cynomolgus monkeys and 1/13 of NOEL in cynomolgus monkeys.

Based on the above analyses and PK/PD characteristics, the dose is proposed to be escalated via semi-logarithmic increment including 1 mg/kg, 3 mg/kg, 200 mg, and 10 mg/kg.

3.1.2. Rationale for selecting melanoma, gastrointestinal tumors, neuroendocrine neoplasms, and lung cancer for the phase Ib study

Lung cancer and malignant gastrointestinal tumors (mainly including esophageal carcinoma, gastric cancer, and hepatic cancer) rank the top four causes of cancer-related deaths in China, and there is a large unmet medical demand. Although the incidence of melanoma and neuroendocrine neoplasms among Chinese is low, it has increased rapidly in recent years. Currently, nivolumab and pembrolizumab have been approved for the treatment of advanced melanoma and lung cancer. At present, anti-PD-1/PD-L1 treatment has shown some positive clinical study results in the treatment of esophageal carcinoma, gastric cancer, and hepatic cancer, but the current standard treatment for neuroendocrine neoplasms is poorly efficacious, especially in the treatment of G3 type neuroendocrine tumors. Therefore, the efficacy of anti-PD-1 monoclonal antibody in neuroendocrine tumors is worth further exploration.

In a phase Ib clinical study (KEYNOTE-028) of pembrolizumab in advanced esophageal carcinoma that failed or became intolerant to at least first-line systemic treatment[28], the ORR was 30% (95% CI: 13–53). In a phase Ib study of averumab monotherapy in treating unresectable advanced gastric and gastroesophageal junction carcinoma, the patients who failed first-line treatment or received a maintenance treatment after first-line chemotherapy were

enrolled, and their ORR was 9.7% and 9.0%, respectively, while their DCR was 29.0% and 57.3%, respectively. In the PD-L1 positive (≥ 1%) population, the ORR was 18.2% (95% CI: 2.3–51.8) and 10.0% (95% CI: 1.2–31.7), respectively[29]. The CheckMate-032 study was a Phase I/II study evaluating the use of nivolumab alone or in combination with anti-CTLA-4 antibody ipilimumab in the treatment of patients with malignant tumors of the stomach, esophagus, and gastroesophageal junction who failed standard chemotherapy, and the ORR judged by the investigator was 12% (nivolumab 3 mg/kg), 24% (nivolumab 1 mg/kg in combination with ipilimumab 3 mg/kg), and 8% (nivolumab 3 mg/kg in combination with ipilimumab 1 mg/kg), respectively, while the ORR in the PD-L1 positive (≥ 1%) population was 19%, 40%, and 23%, respectively[30]. Currently, a number of clinical studies for registration are ongoing to test anti-PD-1/PD-L1 monoclonal antibody products in the treatment of advanced esophageal carcinoma and gastric cancer.

In a phase I/II clinical study (CheckMate-040) evaluating the efficacy of nivolumab in subjects with advanced hepatic cancer[31], the ORR in the dose-escalation stage and dose-expansion stage was 15% (95% CI: 6–28) and 20% (95% CI: 15–26), respectively, and the 9-month OS rates were 66% (95% CI: 51–78) and 74% (95% CI: 67–79), respectively. Currently, a phase III clinical study comparing the efficacy of nivolumab and sorafenib in the first-line treatment of advanced hepatic cancer is ongoing (CheckMate-459)[32].

Nivolumab and pembrolizumab have good efficacy and safety in the second-line treatment of NSCLC, and both have been approved by the US FDA[25,26]. Compared with docetaxel, nivolumab prolonged the survival of unselected nsNSCLC and scNSCLC without EGFR mutation or ALK rearrangement by 3.2 months and 2.8 months, respectively, with significant statistical differences[25]. Compared with docetaxel, pembrolizumab shows significant survival benefits in NSCLC of weakly positive PD-L1 expression that has failed first-line treatments[26].

3.1.3. The principle of giving combined treatment of IBI308 and chemotherapy to patients with lung cancer

Nivolumab and pembrolizumab have good efficacy and safety in the second-line treatment of NSCLC, and both have been approved by the US FDA. However, the ORR of their monotherapy is only about 20%[25,26], and most subjects cannot benefit from the drugs. Currently, many clinical studies evaluating the efficacy of anti-PD-1/PD-L1 monoclonal antibody products in combination with chemotherapy, anti-vascular therapy, targeted therapy, and other immunomodulatory target drugs in lung cancer treatment are ongoing. In the KEYNOTE-021 study, the efficacy of pembrolizumab in combination with platinum-based chemotherapy as the first-line treatment of advanced NSCLC without EGFR mutation or ALK rearrangement was evaluated. The ORR reached 48% (pembrolizumab in combination with carboplatin and paclitaxel, for all histological types), 56% (pembrolizumab in combination with carboplatin,

paclitaxel, and bevacizumab for nsNSCLC), and 75% (pembrolizumab in combination with carboplatin and pemetrexed for nsNSCLC), respectively, while the median PFS reached 10.3 months (95% CI: 6.1–14.6), 7.1 months (95% CI: 4.2–14.3), and 10.2 months (95% CI: 6.5–13.9), respectively[33]. In a phase I clinical trial evaluating the safety and efficacy of nivolumab in combination with different platinum-based doublet chemotherapies as the first-line dual-drug treatment of NSCLC, the combination therapy was well tolerated. The ORR of nivolumab in combination with pemetrexed + cisplatin was 47%, while the ORR of nivolumab in combination with cisplatin + gemcitabine was 33%. The PFS rates after 24 weeks of treatment were 51% and 71%, respectively, while the 2-year survival rates were 25% and 33%, respectively[34]. The KEYNOTE-189 study was a phase III, randomized, and double-blind study comparing pembrolizumab or placebo in combination with pemetrexed and platinum-based chemotherapy for the first-line treatment of metastatic nsNSCLC without EGFR mutation or ALK rearrangement. The 12-month OS rates of pembrolizumab vs. placebo were 69.2% and 49.4% (HR 0.49; 95% CI, 0.38–0.64; $P < 0.001$), respectively, and the benefit in OS was present in all subgroups with various levels of PD-L1 expression. The ORR of the two groups was 47.6% (95% CI: 42.6–52.5) and 18.9% (95% CI: 13.8–25.0) ($P < 0.001$), respectively[35].

3.1.4. The principle of giving combined treatment of IBI308 and chemotherapy to patients with previously untreated gastric or gastroesophageal junction adenocarcinoma

For advanced gastric cancer, several studies have shown that compared with the best supportive care, chemotherapy can give subjects a significant survival benefit. Based on the ML17032 study, 5-FU in combination with cisplatin or capecitabine is one of the recognized first-line treatment options for advanced gastric cancer[36]. The REAL-2 study further proved that capecitabine was not inferior to 5-fluorouracil, and oxaliplatin was not inferior to cisplatin[37]. In the TOGA study, the combination of trastuzumab with chemotherapy can significantly prolong the survival of patients of gastric or gastroesophageal junction adenocarcinoma with HER2 gene amplification or high HER2 protein expression[38]. The KEYNOTE-012 study enrolled PD-L1 positive patients with recurrent or metastatic gastric or gastroesophageal junction adenocarcinoma. The ORR of pembrolizumab monotherapy (judged by central imaging) was 22.2% (95% CI, 10–39); the median DOR was 40 weeks; and the median OS was 11.4 months (95% CI, 5.7–NR)[39]. In a phase Ib study of averumab monotherapy in treating unresectable advanced gastric and gastroesophageal junction carcinoma, the patients who failed first-line treatment or received a maintenance treatment after first-line chemotherapy had ORR of 9.7% and 9.0%, respectively, while their DCR was 29.0% and 57.3%, respectively. In the PD-L1 positive (≥ 1%) population, the ORR was 18.2% (95% CI, 2.3–51.8) and 10.0% (95% CI, 1.2–31.7), respectively[29]. However, in a phase III randomized and open-label study (JAVELIN Gastric 300) of avelumab versus chemotherapy for third-line treatment of advanced gastric or gastroesophageal junction

carcinoma, the primary endpoint OS and secondary endpoints PFS and ORR were not reached[40].

Based on the preliminary study results of anti-PD-1/PD-L1 antibody in advanced gastric cancer, a number of phase II/III clinical studies are underway to evaluate the survival benefit of immune checkpoint drugs in the first-line treatment of gastric or gastroesophageal junction carcinoma, including CheckMate-649[41] (comparing nivolumab in combination with ipilimumab vs. nivolumab in combination with chemotherapy vs. chemotherapy alone, NCT02872116), ATTRACTION-4 (comparing nivolumab in combination with chemotherapy vs. placebo in combination with chemotherapy, NCT02746796), KEYNOTE-062[42] (comparing pembrolizumab alone or in combination with chemotherapy vs. chemotherapy alone for the treatment of PD-L1 positive patients, NCT02494583), and JAVELIN Gastric 100 (comparing avelumab monotherapy or maintenance chemotherapy for the treatment of patients achieving SD after first-line treatment with platinum-based chemotherapy, NCT02625610). Among them, the interim analysis of part 1 of the ATTRACTION-4 study[43] obtained an ORR of 68.4% and a DCR of 86.6%.

3.1.5. Rationale for exploring PD-L1 as a biomarker

PD-L1 expression is upregulated in a variety of solid tumors. The expression of PD-L1 is closely related to the shortened survival and poor prognosis of various tumors[16-23] such as lung caner, hepatic cancer, gastric cancer, esophageal carcinoma, urothelial carcinoma, renal carcinoma, pancreatic cancer, and ovarian cancer. In in vitro studies, tumor cells expressing PD-L1 could promote the apoptosis of activated tumor-specific T cells, while tumor cells could avoid being killed by effector T cells[44,45]. The PD-L1 expression level in tumor tissue was shown in multiple clinical studies of nivolumab and pembrolizumab to be positively correlated with the efficacy[46,47]. Based on the above evidence, the PD-L1 expression level in tumor tissue may be associated with the efficacy of IBI308, so preliminary biomarker exploration is necessary.

3.1.6. Rationale for treatment after progressive disease

Clinical data from approved products showed that a small number of subjects receiving immunotherapy may benefit clinically despite of preliminary evidence of PD (based on routine response criteria) prior to achieving objective response and/or SD. This phenomenon may be explained by two reasons. First, aggravated inflammation in tumors may lead to increase of tumor volume, manifested as an increased measurable lesion size and emergence of new, visible, non-measurable lesions. Over time, the malignant and inflammatory parts of the mass may shrink, resulting in significant imaging response and improvement in clinical signs. Second, in some patients, the initiation of anti-tumor immune response is slow, and tumor inhibition in the early stages is less than the tumor growth. Over time, anti-tumor activity will dominate, giving rise to imaging response and improvement in clinical signs. Therefore, study treatment continued

for subjects treated with IBI308 if they benefited clinically from and were tolerant to the study drug despite of preliminary evidence of PD defined by RECIST V1.1, as assessed by the investigators (see Section 5.1.2). Subjects must discontinue the study treatment if there is further evidence of PD.

3.2. Phase Ia Study

3.2.1. Dose-limiting toxicity (DLT)

Based on the toxicity evaluation criteria from NCI CTCAE V4.03, DLT refers to any of the following IBI308-related AE that is observed during the Cycle 1 (Days 1–28) in the phase Ia dose-escalation study:

1. Hematological toxicity:
    - Grade 4 hematological toxicity lasting > 7 days.
    - Grade 3 thrombocytopenia with bleeding tendency or requiring platelet transfusion.
    - Grade 3 neutropenic fever with bacteremia or sepsis.
2. Non-hematological toxicity:
    - Any grade 4 irAE.
    - Grade 3 pneumonia.
    - Grade 2 pneumonia that does not recover to ≤ grade 1 within 14 days after intervention.
    - Other grade 3 irAEs that do not recover to ≤ grade 2 within 3 days after intervention or ≤ grade 1 within 14 days after intervention (except for asymptomatic grade 3 thyroid, adrenal gland, or pituitary insufficiency, and grade 3 inflammatory responses at the tumor site).
    - Other grade 3 or 4 non-hematological toxicity (excluding: grade 3 electrolyte abnormalities, grade 3 or 4 IRRs, manageable grade 3 hypertension, grade 3 infusion site extravasation, grade 3 arthralgia/myalgia, grade 3 asthenia/fatigue, manageable grade 3 vomiting, grade 3 or 4 liver transaminase elevation lasting < 7 days).
3. Any grade 5 AE.

Note: Grade 3 or 4 IRR is not a DLT. However, if a grade 3 or 4 IRR occurs, subject needs to discontinue treatment and be replaced by a new subject. If ≥ 2 subjects experience a grade 3 or 4 IRR in any treatment group, then enrollment must be suspended. The sponsor needs to review the safety data to determine whether to continue enrolling subjects.

3.2.2. Maximal tolerated dose (MTD)

MTD often refers to the highest dose that causes DLT in ≤ 1/6 of subjects in Cycle 1 of treatment (Days 1–28). If DLT is observed in > 1/6 of subjects in one dose group, the previous lower dose level will be regarded as the MTD.

3.2.3. Dose escalation method

The dose escalation in this study is based on the standard "3 + 3" design.

The initial daily dose is 1 mg/kg and is proposed to escalated to 3 mg/kg and 200 mg (randomized at 1:1 and studied simultaneously) and then to 10 mg/kg. The Safety Assessment Committee will determine, based on the safety of the previous dose, whether the next dose will be studied. If no DLT is observed in the first three subjects enrolled in one dose group, the trial will be initiated in the next dose group. If DLT is observed in one (1/3) of the first three subjects enrolled in one dose group, three new subjects will be enrolled in this dose group (thus 6 in total in this dose group). The trial will be carried out in the next dose group if no DLT is observed in the three new subjects. If DLT is observed in one or more of the three new subjects or in 2 or more of all 6 subjects, the dose escalation won't be allowed. Meanwhile, another 3 subjects need to be enrolled into the previous dose group (and so on) until determination of MTD. Therefore, the MTD dose group requires at least 6 subject for confirmation. The dose escalation is detailed in **Table 7**.

Table 7. Dose escalation method

Dose group	Dose	Route of administration	Number of subjects
1	1 mg/kg	IV, Day 1 of Cycle 1	3–6
2	3 mg/kg or 200 mg (randomized at 1:1 and studied simultaneously)	IV, Day 1 of Cycle 1	3–6 per group
3	10 mg/kg	IV, Day 1 of Cycle 1	3–6

3.2.4. Subjects evaluable for DLT

Subjects evaluable for DLT need to meet any of the following criteria:

1. DLT is observed in the DLT observation window (Cycle 1, Days 1–28).
2. DLT observation is completed within the specified time window.

When one subject does not meet one of the above criteria, a new subject will be enrolled.

3.3. Phase Ib Study

3.3.1. Treatment regimen selection for the phase Ib study

Based on animal experimental results and published data of products of the same class, the 200 mg IV Q3W is selected as the primary treatment regime for the phase Ib study.

4. STUDY POPULATION

4.1. Inclusion Criteria

1. Subjects with advanced solid tumors, including:

1) Phase Ia: Patients with locally advanced, recurrent, or metastatic solid tumors that failed standard treatment;

2) Phase Ib:

Cohort A:

- Patients with locally advanced, recurrent or metastatic melanoma confirmed by cytology or histology.

Cohort B:

- Patients with locally advanced, recurrent or metastatic esophageal squamous cell carcinoma confirmed by cytology or histology who failed or became intolerant to first-line systemic standard treatment;
- Patients with locally advanced, recurrent or metastatic gastric adenocarcinoma (including gastroesophageal junction adenocarcinoma) confirmed by cytology or histology who failed or became intolerant to first-line systemic standard treatment;
- Patients with locally advanced, recurrent or metastatic HCC confirmed by cytology or histology who were not suitable for locoregional treatment or failed locoregional treatment and failed or became intolerant to first-line systemic standard treatment;
- Patients with other advanced malignant tumors of the digestive system who failed or became intolerant to standard therapy;
- Patients with advanced neuroendocrine neoplasms who failed, became intolerant, or refused to receive standard therapy:
  - Metastatic neuroendocrine neoplasms confirmed by histopathology, including well differentiated neuroendocrine tumors and poorly differentiated neuroendocrine carcinomas;
  - With imaging-confirmed tumor PD within 12 months before the first dose;

- For poorly differentiated neuroendocrine carcinoma, they should show progression after being treated with platinum-based regimens; for well-differentiated neuroendocrine tumors, they should have received at least one systemic treatment, including somatostatin analogs, mTOR inhibitors, anti-angiogenic drugs, and chemotherapy;
- Patients with neuroendocrine tumors or neuroendocrine carcinomas who cannot tolerate or refuse to receive the above treatment can also be enrolled;

Cohort C:

- Patients with locally advanced, recurrent or metastatic NSCLC confirmed by cytology or histology who failed or became intolerant to first-line systemic standard treatment;
- Excluding patients with EGFR mutations and ALK rearrangements.

Cohort D:

- Patients with inoperable locally advanced (stage IIIB), recurrent or metastatic (stage IV) nsNSCLC (staged according to the 7th edition of "Staging Manual in Thoracic Oncology" published by the International Association for the Study of Lung Cancer) confirmed by histology or cytology who previously not received first-line treatment;
- Excluding patients with EGFR mutations and ALK rearrangements;
- For patients with stage IIIB nsNSCLC who previously received platinum-based adjuvant, neoadjuvant, or radical chemoradiotherapy, if local recurrence or distant metastasis occurred within 6 months after the treatment was completed, the previous platinum-based treatment will be considered to be a first-line treatment and hence the patients cannot be enrolled into the cohort.

Cohort E:

- Patients with inoperable locally advanced (stage IIIB), recurrent or metastatic (stage IV) scNSCLC (staged according to the 7th edition of "Staging Manual in Thoracic Oncology" published by the International Association for the Study of Lung Cancer) confirmed by histology or cytology who previously not received first-line treatment;
- Excluding patients with EGFR mutations and ALK rearrangements.
- For patients with stage IIIB scNSCLC who previously received platinum-based adjuvant or neoadjuvant chemotherapy or radical chemoradiotherapy, if local recurrence or distant metastasis occurred within 6 months after the treatment was completed, the previous platinum-based treatment will be considered to be a first-line treatment and hence the patients cannot be enrolled into the cohort.

Cohort F:

- Patients with inoperable locally advanced, recurrent or metastatic gastric or gastroesophageal junction adenocarcinoma confirmed by histopathology;
- Excluding patients with known HER2 gene amplification or overexpression.
- Not previously treated by chemotherapy for advanced diseases, or with progression occurring more than 6 months after the end of systemic adjuvant therapy;

Cohort G:

- Previously untreated patients with inoperable locally progressive, recurrent or metastatic high-grade (G3) neuroendocrine tumors confirmed by histology or cytology.
- Patients must have high-grade (G3) neuroendocrine tumors with a Ki-67 index of > 20%.
- Not previously treated by chemotherapy for advanced diseases, or with progression occurring more than 6 months after the end of systemic adjuvant therapy.

Cohort H:

- Patients with advanced high-grade (G3) neuroendocrine neoplasms confirmed by histology or cytology who failed first-line systemic standard treatment.
- Patients must have high-grade (G3) neuroendocrine tumors with a Ki-67 index of > 20%.
- For patients who received adjuvant or neoadjuvant chemotherapy for neuroendocrine tumors, if local recurrence or distant metastasis occurred within 6 months after this treatment was completed, this treatment will be considered to be a first-line treatment and hence the patients can be enrolled into the cohort.

2. Patients who have signed ICF, and are able to complete follow-up visits and relevant procedures required in the protocol.
3. Ages ≥ 18 and ≤ 70 years.
4. Estimated survival ≥ 12 weeks.
5. Patients with at least one measurable or evaluable lesion according to "Response Evaluation Criteria in Solid Tumors" version 1.1 (RECIST V1.1).
6. An Eastern Cooperative Oncology Group Performance Status (ECOG PS score) score of 0 or 1.

7. Patients (female patients of childbearing age or male patients whose sexual partners are of childbearing age) must take effective contraceptive measures during the entire course of the trial and 6 months after the treatment (see Table 22 in Section 5.7.2)
8. Sufficient organ and bone marrow functions, as defined below:

1) Routine blood test: ANC ≥ 1.5 × 10^9/L, PLT ≥ 100 × 10^9/L, HGB ≥ 9.0 g/dL.
2) Hepatic function: TBIL ≤ 1.5 × ULN; for patients with HCC, liver metastases, or suspected/history of Gilbert syndrome (persistent or recurrent hyperbilirubinemia, mainly unconjugated bilirubin, no evidence of hemolysis or liver disease), TBIL≤ 3 × ULN; for patients without HCC or liver metastases, ALT and AST ≤ 2.5 × ULN; for patients with HCC or liver metastases, ALT and AST ≤ 5 × ULN.
3) Renal function: Cr ≤ 1.5 × ULN or CCr ≥ 50 mL/min; urinalysis results showing urine protein < 2+; for patients whose baseline urinalysis results showed urine protein ≥ 2+, 24-h urine collection should be required and the protein content in the collected urine should be < 1 g.
4) Coagulation: APTT and INR ≤ 1.5 × ULN.
5) TSH or FT4 is within the normal range.

4.2. Exclusion Criteria

1. Previous exposure to any anti-PD-1 or anti-PD-L1 antibody.
2. Experienced any ≥ grade 3 irAE (based on NCI CTCAE V4.03) while receiving any immunotherapy drugs in the past. Patients who were treated with ipilimumab are not enrolled unless all of the following criteria are met:
   - The ipilimumab-related irAE has completely recovered, and the treatment of irAE have ended 4 weeks before the first dose of IBI308;
   - There was at least a 12-week interval between the first dose of ipilimumab and the first dose of IBI308 and a 6-week interval between the last dose of ipilimumab and the first dose of IBI308;
   - The use of ipilimumab did not result in grade 4 irAEs or grade 3 irAEs requiring > 4 weeks of treatment;
   - A clear PD was observed after the last dose of ipilimumab.
3. 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.
4. Received any investigational drug within 4 weeks prior to the first dose of IBI308.

5. Received the last dose of anti-tumor therapy (chemotherapy, endocrine therapy, targeted therapy, immunotherapy, tumor embolization) within 3 weeks before the first dose of IBI308; received the last dose of biologics, nitrosourea or mitomycin C within 6 weeks before the first dose of IBI308 (if the biological product received was for antitumor endocrine therapy, refer to the requirement of "received the last dose within 3 weeks before the first dose of IBI308").
6. Received immunosuppressants within 4 weeks before the first dose of IBI308, excluding locoregional glucocorticoids administered by nasal, inhaled, or other routes, or systemic glucocorticoids of physiological doses (no more than 10 mg/day of prednisone or equivalents). Glucocorticoid administration for pretreatment or special examinations is allowed.
7. Received a live attenuated vaccine within 4 weeks prior to the first dose of IBI308, or plan to receive this vaccine during the study period.
8. Received major surgery (craniotomy, thoracotomy, or laparotomy) within 4 weeks prior to the first dose of IBI308, or has unhealed wounds, ulcers, or fractures.
9. Antitumor therapy-induced toxicity (excluding alopecia) that has not yet resolved to NCI CTCAE V4.03 grade 0 or 1 prior to the first dose of IBI308.
10. Previously received whole pelvic radiotherapy.
11. Subjects with known leptomeningeal metastasis; subjects with untreated or treated but uncontrolled CNS metastasis, excluding those who were treated, are now stable, and stopped glucocorticoids and anticonvulsants ≥ 4 weeks prior to receiving the first dose of IBI308.
12. Known active autoimmune disease (see Appendix 5) or a history of such disease within the past 2 years (subjects with vitiligo, psoriasis, alopecia, or Graves' disease not requiring systemic treatment within the next 2 years, or those with hypothyroidism only requiring thyroid hormone replacement, or those with type I diabetes only requiring insulin replacement may be enrolled). For patients with positive autoimmune antibodies only, they should be evaluated by the investigator to determine whether they have an autoimmune disease.
13. Known history of primary immunodeficiency diseases.
14. Known history of pulmonary tuberculosis.
15. Known history of allotransplantation or allogeneic hematopoietic stem cell transplantation.

16. Known allergy to any ingredients in IBI308; or previous severe allergic reactions to other monoclonal antibodies; for Cohort D of the phase Ib study, patients who were previously allergic to pemetrexed or cisplatin, or patients who were unable or unwilling to receive folic acid and/or vitamin B12 treatment; for Cohort E of the phase Ib study, patients who were previously allergic to cisplatin or gemcitabine. For Cohort F of the phase Ib study, patients who were previously allergic to capecitabine or oxaliplatin; for Cohort G of the phase Ib study, patients who were previously allergic to etoposide or cisplatin; for Cohort H of the phase Ib study, patients who were previously allergic to irinotecan or 5-FU.
17. Uncontrolled concurrent diseases including but not limited to:
    - Those infected with HIV (positive for HIV1/2 antibody).
    - Active or poorly clinically controlled serious infections.
    - Symptomatic congestive cardiac failure (New York Heart Association (NYHA) Class II–IV) or symptomatic or poorly controlled arrhythmia.
    - Uncontrolled hypertension (systolic blood pressure ≥ 160 mmHg or diastolic blood pressure ≥ 100 mmHg) despite of standard treatment.
    - Any arterial thromboembolic events occurred within 6 months prior to enrollment, including myocardial infarction, unstable angina, cerebrovascular accident, or transient cerebral ischemic attack.
    - Patients with esophageal or gastric varices requiring immediate intervention (such as variceal ligation or sclerotherapy) or those considered to have a high bleeding risk by the investigator, gastroenterologist, or hepatologist. Patients with signs of portal hypertension (including splenomegaly confirmed by medical imaging) or a history of variceal bleeding are required to undergo endoscopy within 3 months prior to enrollment.
    - Life-threatening hemorrhagic events or grade 3 or 4 gastrointestinal/variceal hemorrhage requiring blood transfusion, endoscopy, or surgical treatment within 3 months prior to enrollment.
    - 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).
    - Uncontrolled metabolic disorders, non-malignant organ or systemic diseases, or cancer-related secondary diseases that may lead to high medical risks and/or uncertainty in survival evaluation.

- Hepatic encephalopathy, hepatorenal syndrome, or cirrhosis with Child-Pugh Class B or C (see Appendix 7 for Child-Pugh grading).
- Bowel obstruction 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, ulcerative colitis, or chronic diarrhea.
- 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 investigators.

18. Patients with acute or chronic active hepatitis B or hepatitis C infection (for patients treated with IBI308 monotherapy, they will be enrolled if their HBsAg is positive but their HBV DNA copy number is $\leq 1 \times 10^4$/mL; for patients treated with IBI308 in combination with chemotherapy, they will be enrolled only if their HBsAg is positive and their HBV DNA copy number is below the LLD. For the prevention and treatment requirements, refer to "The Guideline of Prevention and Treatment for Chronic Hepatitis B: A 2015 Update"; patients with inactive Hepatitis C are allowed for enrollment).
19. History of GI perforation and/or fistula within 6 months prior to the enrollment.
20. Interstitial lung diseases (including previous and current history, refer to Appendix 6).
21. Clinically uncontrollable third space effusion, such as pleural effusion and ascites that cannot be controlled by drainage or other methods prior to enrollment.
22. History of other primary malignant tumors, excluding:
    - History of radical treatment for malignant tumors with no evidence of tumor recurrence for more than 5 years prior to enrollment and with a very low risk of recurrence;
    - Adequately treated nonmelanoma skin cancer or lentigo maligna with no signs of disease recurrence;
    - Adequately treated carcinoma in situ with no signs of disease recurrence.
23. Pregnant or breastfeeding female patients.

4.3. Restrictions During the Study

- Subjects should not donate blood during the study or within 12 weeks after the end of the last dose.

- See Section 5.7 for medications in pregnant or lactating females and females of childbearing age.

4.4. Study Discontinuation/Withdrawal of Subjects

Subjects should discontinue/withdraw from the study in any of the following circumstances:

1. Subjects do not meet the inclusion/exclusion criteria, and are deemed unsuitable to continue participating in this study by the sponsor and investigator;
2. Subjects are enrolled in any other clinical trial of study drugs or in another clinical trial that is considered scientifically or medically incompatible with this study.
3. Subjects seriously violate the study protocol, and are deemed unsuitable to continue this study by the sponsor and investigator.
4. Subjects are lost to follow-up (study site personnel shall regain contact with the subjects to determine the cause of loss to follow-up and reschedule study visits if possible. The date and method of contact shall be documented in the study documents).
5. Decided by the investigator
   - Based on the safety and benefits of the subjects, the investigator believes that the subjects should terminate the treatment and withdraw from the study.
   - If the subjects require treatment with another drug for any reason, and the drug has been demonstrated to be effective for the indication of this study, then the subject shall withdraw from this study prior to starting the new drug.
   - Subjects receiving IBI308 monotherapy develop PD, and the investigator believes it is inappropriate for them to continue the study treatment (IBI308 therapy can be continued after PD in the circumstances specified in "Section 5.1.2" of the study protocol).
   - Grade 3–4 IRRs occur and cannot be attributed to one study drug in the opinion of the investigator (considered to be likely related to at least one study drug).
   - Any treatment-related event that is considered to be life-threatening occurs, regardless of the severity level of the event.
   - The study drug shall be discontinued due to toxicities (see Section 5.4.1 and 5.4.2).
   - The investigator believes that the concurrent disease during the treatment or any change in the subject's condition renders the subject unsuitable for subsequent treatment.

6. Subjects or their representatives (such as parents or legal guardians) request withdrawal from the study or discontinuation of the study drug (subjects may be eligible for long-term follow-up if they withdraw ICF for treatment but not for follow-up).
7. The sponsor may discontinue the study or discontinue subject participation in the study due to medical, safety, regulatory, or other reasons related to the applicable laws, regulations, and "Good Clinical Practice" (GCP).

The reasons and dates of discontinuation for all the subjects shall be documented. Subjects who have been randomized but have discontinued the treatment shall undergo related study procedures as specified in the study visit schedule regardless of whether they have received the study drugs.

5. STUDY DRUGS AND OTHER TREATMENTS

5.1. Treatment Regimen

5.1.1. Treatment regimen for the phase Ia/Ib study

In phase Ia an Ib studies, the study drug of Cohorts A, B, and C is IBI308. In the phase Ib study, the study drugs of Cohort D are IBI308, pemetrexed, and cisplatin; those of Cohort E are IBI308, gemcitabine, and cisplatin; those of Cohort F are IBI308, oxaliplatin, and capecitabine; those of Cohort G are IBI308, etoposide, and cisplatin; those of Cohort H are IBI308, irinotecan, and 5-FU. Other drugs used in the study are non-study drugs. The treatment regimen is shown in **Table 8**. Refer to Section 5.3 of the protocol for chemotherapy pretreatment. Subjects in Cohorts D, E, and F are given chemotherapy after 1 h of observation following the end of the administration of IBI308 in the first 2 cycles; if there are no infusion related adverse reactions, this observation can be omitted in Cycle 3 and subsequent cycles.

Table 8. Dose and treatment protocol

Study phase	Drug	Dose, route of administration, and cycle	Duration of administration
Phase Ia	IBI308	1 mg/kg, 3 mg/kg, and 10 mg/kg IV Q2W, 200 mg IV Q3W	Until PD (refer to Section 5.1.2 in the protocol for continued treatment after PD), intolerable toxicity, withdrawal of informed consent, up to 24 months of treatment, or other reasons for discontinuation of the study treatment (whichever occurs first).
Cohorts A–C of the phase Ib study	IBI308	200 mg IV Q3W	
Cohort D of the phase Ib study	IBI308	200 mg IV D1 Q3W	Up to 4 cycles of triple drug combination therapy are given. Subsequently, the subjects receive the maintenance treatment with IBI308 in combination with pemetrexed until PD, intolerable toxicity, withdrawal of informed consent, 24 months of treatment, or other reasons for discontinuation of the study
	Pemetrexed[a]	500 mg/m^2 IV D1 Q3W	
	Cisplatin[a]	75 mg/m^2 IV D1 Q3W	

Study phase	Drug	Dose, route of administration, and cycle	Duration of administration
			treatment (whichever occurs first).
Cohort E of the phase Ib study	IBI308	200 mg IV D1 Q3W	Up to 6 cycles of triple drug combination therapy are given. Subsequently, the subjects experiencing no PD can receive a maintenance treatment with IBI308 until PD, intolerable toxicity, withdrawal of informed consent, 24 months of treatment, or other reasons for discontinuation of the study treatment (whichever occurs first).
	Gemcitabine[a]	1250 mg/m^2 IV D1,D8 Q3W	
	Cisplatin[a]	75 mg/m^2 IV D1 Q3W	
Cohort F of the phase Ib study	IBI308	200 mg IV Q3W	Up to 6 cycles of triple drug combination therapy are given. Subsequently, the subjects experiencing no PD can receive a maintenance treatment of 200 mg IV Q3W of IBI308 until PD, intolerable toxicity, withdrawal of informed consent, 24 months of treatment, or other reasons for discontinuation of the study treatment (whichever occurs first).
	Capecitabine[a]	2000 mg/m^2/day PO BID D1–14, Q3W	
	Oxaliplatin[a]	130 mg/m^2 IV Q3W	
Cohort G of the phase Ib study	IBI308	200 mg IV D1 Q3W	Up to 6 cycles of triple drug combination therapy are given. Subsequently, the subjects experiencing no PD can receive a maintenance treatment of 200 mg IV Q3W of IBI308 until PD, intolerable toxicity, withdrawal of informed consent, 24 months of treatment, or other reasons for discontinuation of the study treatment (whichever occurs first).
	Etoposide[a]	100 mg/m^2 IV D1-3 Q3W	
	Cisplatin[a]	75 mg/m^2 IV D1 Q3W	
Cohort H of the phase Ib study	IBI308	200 mg IV D1 Q3W	Up to 6 cycles of triple drug combination therapy are given. Subsequently, the subjects experiencing no PD can receive a maintenance treatment of 200 mg IV Q3W of IBI308 until PD, intolerable toxicity, withdrawal of informed consent, 24 months of treatment, or other reasons for discontinuation of the study treatment (whichever occurs first).
	Irinotecan[a]	125 mg/m^2 IV D1,D8 Q3W	
	5-FU[a]	1000 mg/m^2 IV D1-3 Q3W	

a The study site determines the actual dose that one subject should receive by calculating his/her body surface area on the scheduled administration day in each cycle (the body surface area is calculated in accordance with routine method of the study site). The maximum body surface area adopted by the protocol is 2.0 m^2. For subjects with a body surface area of > 2.0 m^2, the staff of the study site will calculate the dose based on a body surface area of 2.0 m^2. For convenience, the protocol allows for a deviation of ± 5% of the total infusion dose each time.

5.1.2. Continued treatment after progressive disease

During the treatment with IBI308 alone (Cohorts A–C in both phase Ia and Ib studies), subjects are allowed to continue receiving IBI308 after they are judged to experience PD for the first time (first PD) according to the RECIST V1.1 criteria. The IBI308 treatment can be continued if all the following criteria are met:

1. The investigator believes that the subject may enjoy clinical benefits from continued study treatment, and the disease does not show rapid progression (rapid progression is defined as the occurrence of PD during the first imaging evaluation);
2. The subject can tolerate the study drug (no ≥ grade 2 adverse reactions or serious adverse reactions related to the study drug);
3. No clinically significant symptoms and signs suggesting PD (including worsenin laboratory test values);
4. An ECOG PS score of 0–1;
5. Will not delay the treatment of serious complications requiring urgent intervention (such as metastasis in the CNS or spinal cord compression);
6. Before continuing treatment with IBI308, subjects must be fully informed and the investigator must elucidate the foreseeable risks or discomforts and alternative treatments.

If the above criteria are met, the investigator and sponsor's medical manager will decide whether the subjects shall continue the treatment after PD, and record it in the study records.

Data from subjects who continue IBI308 treatment after initial PD shall be collected. Refer to Table 1 or 3 for collection of data variables.

For subjects who are first recorded to have imaging PD that is confirmed related to immunity by the imaging evaluation carried out 4 weeks later, if they can continue receiving the treatment with the study drug, an imaging evaluation should be carried out every 9 weeks (± 7 days) until the recurrence of PD. The second PD is defined as an increase of more than 10% in the sum of the longest diameter of tumor target lesions and/or the presence of a new measurable lesion. Subjects with the recurrent PD will terminate the IBI308 treatment. The main criteria for the judgment of "deterioration of clinical symptoms" are:

- Clinically significant signs and symptoms suggesting PD (including worsening laboratory test values);
- Continued increase in ECOG PS or > 2 ;
- The appearance of serious complications requiring urgent intervention (such as metastasis in the CNS or spinal cord compression)

In this case, the investigator shall continue imaging evaluation as described in the "Section 6.3" of the study protocol.

For Cohorts D–H of the phase Ib study, the IBI308 therapy is not allowed to be continued after PD is confirmed.

5.2. IBI308

5.2.1. Description

The study drug is a recombinant fully human anti-PD-1 monoclonal antibody injection (hereinafter referred to as IBI308).

The main active ingredient of IBI308 is the recombinant fully human anti-PD-1 monoclonal antibody. The strength of IBI308 drug product is 10 mL: 100 mg. IBI308 does not contain any preservatives. The concentration is 10 mg/mL, with excipients including 140 mmol/L mannitol, 25 mmol/L histidine, 20 mmol/L sodium citrate (dihydrate), 50 mmol/L sodium chloride, 0.02 mmol/L disodium edetate, 0.2 mg/mL polysorbate 80, citric acid (monohydrate), and water for injection, at a pH of 6.0.

This product is a clear to slightly opalescent, colorless to light yellow liquid, free of flocs and precipitation.

IBI308 is manufactured by Innovent Biologics (Suzhou) Co., Ltd.

5.2.2. Labels

The smallest packaging unit is one box. Each box contains one vial of IBI308 injection. The IBI308's package contains the drug name, drug number, dosage form, strengths, drug code, batch number, shelf life, storage conditions, dosage and administration, precautions, and sponsor's information. The label on the vial contains the same information as the outer package except for dosage form and precautions. Both package and vial shall be labeled "use for clinical study only".

5.2.3. Storage

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.

5.2.4. Preparation and infusion

5.2.4.1 Preparation before infusion

Eligible subjects selected during screening will be approved to be admitted to the study site's wards 24 h before dosing. All baseline safety evaluation results must be obtained pre-dose.

On dosing days, vital signs are observed, and dosing is initiated after blood sampling as per visit requirements.

5.2.4.2 Preparation and infusion

The preparation and infusion of IBI308 are as follows:

1. The volume of IBI308 to be extracted should be calculated using the formula in **Table 9**.

Table 9. Calculation formulas for volume of IBI308 required

Group	Volume of IBI308 added into the IV infusion bag (mL)
1 mg/kg group	1 mg/kg × weight (kg)[a] ÷ IBI308 concentration (rated: 10 mg/mL)
3 mg/kg group	3 mg/kg × weight (kg)[a] ÷ IBI308 concentration (rated: 10 mg/mL)
10 mg/kg group	10 mg/kg × weight (kg)[a] ÷ IBI308 concentration (rated: 10 mg/mL)
200 mg group	200 mg ÷ IBI308 concentration (rated: 10 mg/mL)

a The dose is calculated based on baseline weight, but if a change from baseline weight by ≥ 10% is found, the actual dose will be calculated based on the weight of scheduled dosing days.

2. An appropriate volume of IBI308 is taken and added into 100 mL of sterile normal saline containing 0.9% (w/v) sodium chloride. The start time of preparation is documented.
3. The IV bag is gently inverted to mix the solution, ensuring the uniformity of the contents. No vigorous shaking is allowed to avoid foam.
4. IBI308 is administered with an IV infusion pump equipped with a 0.2–1.2 μm in-line filter (suggested infusion time is 30–60 min). The start and end time of infusion are documented.

Note: IBI308 should be infused before dosing of chemotherapeutics. Different batches of IBI308 cannot be mixed for a single infusion. Make sure that the IBI308 injection is clear without any quality issues 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 (storage conditions for the prepared solution is 2–8 °C in the fridge). Avoid mixing with other drugs. Do not administer as an IV push.

5.3. Chemotherapeutics

Pemetrexed, cisplatin, gemcitabine, capecitabine, oxaliplatin, etoposide, irinotecan, and 5-FU have been approved as anti-tumor drugs. They will be provided by the sponsor after re-labeling. The study site should store, prepare, and administer these drugs according to the approved prescribing information. The following information is for reference.

5.3.1. Pemetrexed

Pemetrexed for injection is provided as sterile lyophilized powder for IV injection in 100 mg or 500 mg vials. The active ingredient of lyophilized drug product is pemetrexed which is present as pemetrexed disodium. The drug product is white to pale yellow or yellow green lyophilized

solid. The actual amount of pemetrexed in each vial is more than the labeled amount to ensure extraction of the labeled amount of pemetrexed.

100 mg or 500 mg of pemetrexed is reconstituted with 0.9% sodium chloride solution to get a clear solution. The solution is colorless to yellow or yellow green (refer to the reconstitution volume requirement described in the prescribing information). The content in the vial should be visually inspected pre-dose to determine whether there are sub-visible particles and discoloration. If the content contains sub-visible particles or is dark green, dosing will not be allowed.

For clinical use, the reconstituted content will be diluted in 0.9% sodium chloride injection (refer to the reconstitution volume requirement described in the prescribing information). The dilution for infusion can keep stable for up to 24 h in a fridge or at room temperature.

Pemetrexed is compatible with dosing devices and IV infusion bags made from polyvinyl chloride and polyolefin. No antibacterial preservative is contained in both reconstituted pemetrexed and dilution for infusion. The unused pemetrexed in the open vial should be discarded. Pemetrexed is incompatible with calcium-containing diluents including sodium lactate ringer's injection and ringer's injection, so it should not be diluted with these diluents.

5.3.2. Cisplatin

Cisplatin is a solution or lyophilized powder. It is provided in 10 mg, 20 mg, or 30 mg vials and diluted with sterile normal saline. Before cisplatin therapy, hydration should be made according to clinical practice of each study site. Intravenous drip infusion of 2000 mL of isotonic glucose solution is recommended before 12 h prior to cisplatin therapy, and infusion of 3000–3500 mL of isotonic saline or glucose solution on the cisplatin dosing day. Besides, potassium chloride, mannitol, and furosemide are administered to maintain a daily urine volume of 2000–3000 mL. During treatment, attention is paid to changes in blood potassium and blood magnesium. Low levels of potassium and magnesium will be corrected if necessary.

5.3.3. Gemcitabine

Gemcitabine hydrochloride for injection is provided as lyophilized powder for injection in 200 mg or 1 g vial. The preservative-free 0.9% sodium chloride solution is recommended as the only solvent to dissolve lyophilized gemcitabine hydrochloride powder for injection. For dilution, at least 5 mL of 0.9% sodium chloride solution should be added into a 200 mg vial; at least 25 mL of this solution should be added into a 1000 mg vial. The vial is shaken for complete dissolution, followed by dilution with 0.9% sodium chloride solution. The post-dilution concentration should not be higher than 40 mg/mL, avoiding incomplete dilution due to a too high concentration. The prepared gemcitabine solution keeps stable for 24 h at room temperature.

5.3.4. Capecitabine

Capecitabine is provided as a 500 mg tablet. The starting dose is 1000 mg/^{2} bid PO for 14 consecutive days every 3 weeks. Capecitabine is orally taken, with 200 mL of water (not juice) , within 30 minutes after a meal (breakfast or dinner) twice (12-h interval) a day.

Each capecitabine dose will be based on the subject's body surface area (mg/m^2, calculated based on height and weight) at baseline. Subjects are recommended to receive a standard therapy of capecitabine 1500 mg (morning) + 2000 mg (evening). The dose to each subject can be adjusted by the investigator based on the actual body surface area of the subject, but the total dose should not be more than 4000 mg/day.

5.3.5. Oxaliplatin

Oxaliplatin is lyophilized powder in a 100 mg or 50 mg vial. The preparation is completed with 5% glucose solution (do not prepare or dilute the product with saline solution). One 50 g vial of oxaliplatin is prepared with 10 mL of 5% glucose solution to 5.0 mg/mL; one 100 mg vial of oxaliplatin is prepared with 20 mL of 5% glucose solution to 5.0 mg/mL. The prepared solution is taken out of the vial and immediately diluted with 250–500 mL of 5% glucose solution to more than 0.2 mg/mL (normally, the physicochemical properties of solution remain stable at 2–8 °C for 24 h). 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% glucose 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.

5.3.6. Etoposide

Preparation is completed with 0.9% sodium chloride solution. Etoposide should be administered, after administration of cisplatin, via IV drip for no less than 60 minutes. Rapid IV push is not allowed. The prophylactic use of antiemetic drugs is recommended, and such drugs are used according to the routine practice of each study site.

5.3.7. Irinotecan

Preparation is completed with 0.9% sodium chloride solution. Irinotecan should be administered via IV drip for about 90 minutes. The prophylactic use of antiemetic drugs is recommended, and such drugs are used according to the routine practice of each study site. If subjects develop early diarrhea (any grade) or other cholinergic syndromes, prophylactic administration of atropine (0.25–1 mg) in the subsequent treatment cycles will be considered unless this is clinically contraindicated. In case of delayed diarrhea (any grade), loperamide will be considered for treatment.

5.3.8. 5-FU

Preparation is completed with 0.9% sodium chloride solution. 5-FU is intravenously infused with a micro infusion pump for 72 h. The prophylactic use of antiemetic drugs is recommended, and such drugs are used according to the routine practice of each study site.

5.4. Dose Adjustments

5.4.1. General principles

- On the first dosing day of study drug, the subject's hematologic, hepatic, and renal function pre-dose must meet the requirements (ANC $\geq 1.5 \times 10^9$/L, PLT $\geq 75 \times 10^9$/L, Hb ≥ 80 g/L, and hepatic and renal function: CTCAE V4.03 grade 0–1 or baseline level). All other toxicities must resolve to NCI CTCAE V4.03 grade 0–1 or baseline levels (excluding alopecia, fatigue, and other cases which are judged by the investigator to be of no clinical significance).
- The dose of chemotherapeutics in each subsequent cycle will be adjusted based on the lowest platelet and neutrophil counts in the previous cycle.
- Dose adjustments for chemotherapeutics are permanent. Once the dose is reduced, the reduced dose will be maintained or reduced in subsequent cycles. A dose increase is not permitted in the study.
- During treatment suspension due to hematologic toxicity, routine blood parameters should be followed up until recovery to the lowest level at which the treatment can be received.

- Prior to the start of any chemotherapy, growth factor support (e.g., GM-CSF) can be adopted to prevent hematologic toxicity induced by chemotherapeutics, but routine prophylactic medications are prohibited.
- All the dose adjustments should be documented, including the reasons and actions taken.
- For Cohorts D, E, F, G, and H in the phase Ib study, IBI308 therapy may be continued if the chemotherapy is terminated due to toxicity. The chemotherapy may be continued if IBI308 therapy is discontinued due to irAEs.
- If chemotherapy is delayed in a 3-week treatment cycle, all the subsequent administration days should be delayed to ensure a dosing interval of 21 ± 2 days between two chemotherapy cycles. If the administration of irinotecan on day 8 is delayed for more than 7 days due to toxicity, skip the administration on day 8 and resume the treatment in the next cycle.
- The chemotherapy cycle and the IBI308 cycle should be kept in synchronization as far as possible by adjusting the permitted window period.

5.4.2. IBI308 administration adjustments

Dose adjustments of IBI308 are not permitted throughout the trial. Refer to **Table 10** for principles for interruption and permanent discontinuation of IBI308 therapy.

Table 10. Dose adjustments of IBI308

IBI308-related AE	Severity level	Dose adjustment
Pneumonia	Grade 2 pneumonia	Interruption[a]
	Grade 3 or 4 pneumonia, or recurrent grade 2 pneumonia	Permanent discontinuation
Diarrhea/enterocolitis	Grade 2 or 3 diarrhea or enterocolitis	Interruption[a]
	Grade 4 diarrhea or enterocolitis	Permanent discontinuation
Dermatitis	Grade 3 dermatitis	Interruption[a]
	Grade 4 dermatitis	Permanent discontinuation
Hepatitis	Grade 2 AST, ALT, or TBIL elevation for subjects with normal AST, ALT, or TBIL at baseline; AST, ALT, or TBIL elevation by ≥ 50% for < 7 days for subjects with AST, ALT, or TBIL > ULN at baseline	Interruption[a]
	Grade 3 or 4 AST, ALT, or TBIL elevation for subjects with normal AST, ALT, or TBIL at baseline; AST, ALT, or TBIL elevation by ≥ 50% for ≥ 7 days for subjects with AST, ALT, or TBIL > ULN at baseline	Permanent discontinuation
Hypophysitis	Grade 2 hypophysitis	Interruption[b]
	Grade 3 or 4 hypophysitis	Permanent discontinuation

IBI308-related AE	Severity level	Dose adjustment
Adrenocortical insufficiency	Grade 2 adrenocortical insufficiency	Interruption[b]
	Grade 3 or 4 adrenocortical insufficiency	Permanent discontinuation
Hyperthyroidism	Grade 3 or 4 hyperthyroidism	Permanent discontinuation
Type I diabetes	Grade 3 hyperglycemia	Interruption[b]
	Grade 4 hyperglycemia	Permanent discontinuation
Renal insufficiency	Grade 2 or 3 Cr elevation	Interruption[a]
	Grade 4 Cr elevation	Permanent discontinuation
Neurotoxicity	Grade 2 neurotoxicity	Interruption[a]
	Grade 3 or 4 neurotoxicity	Permanent discontinuation
Infusion reactions	Grade 3 or 4 infusion reaction	Permanent discontinuation
Other AEs	First occurrence of other grade 3 AEs	Interruption[a]
	Second occurrence of the same grade 3 AE	Permanent discontinuation
	Grade 3 AE that cannot resolve to grade 0–2/baseline levels within 7 days or grade 0–1/baseline levels within 14 days	Permanent discontinuation
	Grade 4 AE	Permanent discontinuation[c]

a: Resume administration of the investigational drug after symptoms improve to grade 0–1 or baseline levels.

b: Resume administration of the investigational drug if hypophysitis, adrenocortical insufficiency, or type I diabetes is adequately controlled and require only physiological hormone replacement.

c: For grade 4 laboratory abnormalities, whether to terminate the treatment shall be determined based on clinical signs/symptoms and the clinical judgment of the investigator.

Investigational drug is allowed to be interrupted for up to 6 weeks. If the symptoms do not resolve to the level, at which the treatment can be resumed, within 6 weeks, the subject must permanently discontinue IBI308 treatment and enter the follow-up phase of the study, except for the following two cases:

- IBI308 interruption > 6 weeks due to dose reduction of glucocorticoid that is used to treat irAEs. Consult the sponsor's medical manager prior to resuming IBI308. Tumor imaging for evaluation efficacy should not be affected by treatment interruption and should be performed as scheduled.
- IBI308 interruption > 6 weeks due to the treatment of AEs possibly related or unrelated to IBI308. Consult the sponsor's medical manager prior to resuming IBI308. Tumor imaging for evaluation efficacy should not be affected by treatment interruption and should be performed as scheduled.
- The IBI308 therapy is resumed when related AEs resolve to grade 0–1 or baseline level and a ECOG PS score of 0–1.

5.4.3. Dose adjustments of pemetrexed and cisplatin

One drug whose dose has been reduced twice must be discontinued permanently if the 3rd dose reduction is required due to toxicity (or the dose following the 3rd reduction is lower than that after the second one). Pemetrexed and/or cisplatin therapy must be permanently discontinued if it has been interrupted for over 6 weeks. But the necessity for continuation of pemetrexed and/or cisplatin therapy will be discussed with the sponsor's medical manager if this therapy is interrupted for over 6 weeks due to an AE that is possibly-unrelated or unrelated to this therapy (since day 1 after the last dose). Tumor imaging for evaluation efficacy should not be affected by treatment interruption and should be performed as scheduled.

5.4.3.1 Hematological toxicity

Growth factor support can be adopted, but routine prophylactic medications are prohibited. The dose adjustment at the start of each subsequent cycle will be based on the lowest ANC and PLT counts in the previous cycle. The guidelines for dose adjustments due to hematological toxicity are shown in **Table 11**.

Table 11. Dose adjustments of pemetrexed and cisplatin due to hematological toxicity

Toxicity	Dose adjustments
PLT ≥ 50 × 10^9/L and ANC ≥ 0.5 × 10^9/L	100% of the previous dose
PLT ≥ 50 × 10^9/L and ANC < 0.5 × 10^9/L	75% of the previous dose
PLT < 50 ×10^9/L, any ANC level	75% of the previous dose
PLT < 50 × 10^9/L with bleeding of grade 3 or greater, any ANC level	50% of the previous dose
Febrile agranulocytosis, any PLT level	75% of the previous dose

5.4.3.2 Nephrotoxicity

The same CCr calculation as that at baseline should be used throughout the study. CCr must be ≥ 45 mL/min before each cycle of chemotherapy. If CCr is < 45 mL/min, the pemetrexed and/or cisplatin therapy should be delayed until subjects recover from the toxicity.

5.4.3.3 Other non-hematological toxicity

The guidelines for dose adjustments due to other non-hematological toxicity are shown in **Table 12**.

Table 12. Dose adjustments of pemetrexed and cisplatin due to other non-hematological toxicity

Toxicity	**Grade**	**Dose adjustment of pemetrexed**	**Dose adjustment of cisplatin**
Mucositis	Grade 1 or 2	100% of the previous dose	100% of the previous dose
	Grade 3 or 4	50% of the previous dose	100% of the previous dose

Toxicity	Grade	Dose adjustment of pemetrexed	Dose adjustment of cisplatin
Diarrhea	Grade 3 or 4	75% of the previous dose	100% of the previous dose
Sensory neurotoxicity	Grade 1	100% of the previous dose	100% of the previous dose
	Grade 2	50% of the previous dose	100% of the previous dose
	Grade 3 or 4	Permanent discontinuation	Permanent discontinuation
Folic acid or vitamin B12 deficiency	-	Pemetrexed therapy is interrupted. In Cycle 1, the subject must receive vitamin B12 injection and at least 5 days of oral folic acid within 7 days before the first dose of pemetrexed. In Cycle 2 and thereafter, the subject must receive at least 14 days of oral folic acid within 21 days before dosing of pemetrexed in this cycle.	
Other toxicities	Grade 3 or 4	The chemotherapeutics are interrupted until the AE resolves to grade 0–1 or baseline level, and then resuming the pemetrexed and cisplatin therapy at 75% of the previous dose can be considered based on the investigator's judgment. In case of other laboratory test abnormalities, the necessity for permanent discontinuation of the pemetrexed and cisplatin therapy should be determined based on accompanying clinical symptoms and signs as well as clinical judgments of the investigator.	

5.4.4. Dose adjustments of gemcitabine and cisplatin

The dose adjustment method for gemcitabine and cisplatin is shown in **Table 13**. The dose levels of these two drugs are unrelated and can be adjusted independently.

For any patient, one drug whose dose has been reduced twice must be discontinued permanently if the 3rd dose reduction is required due to toxicity (or the dose following the 3rd reduction is lower than that after the second one). The gemcitabine and/or cisplatin therapy must be discontinued permanently if this therapy is interrupted for over 6 weeks (since day 1 after the last dose) due to toxicity (the necessity for continuation of gemcitabine and/or cisplatin therapy will be discussed with the sponsor's medical manager if this therapy is interrupted for over 6 weeks due to an AE that is possibly-unrelated or unrelated to this therapy. Tumor imaging for evaluation efficacy should not be affected by treatment interruption and should be performed as scheduled). If the use of one chemotherapeutic agent must be interrupted, the treatment with other drugs can be continued once it is deemed reasonable by the investigator.

Table 13. Dose adjustments of gemcitabine and cisplatin

Dose	Gemcitabine	Cisplatin
Starting dose	1250mg/m^2	75mg/m^2
1st dose reduction	950mg/m^2	56 mg/m^2
2rd dose reduction	625mg/m^2	38mg/m^2

5.4.4.3 Hematological toxicity

The guidelines for dose adjustments due to hematological toxicity are shown in **Table 14**.

Table 14. Dose adjustments of gemcitabine and cisplatin due to hematological toxicity

Toxicity	Dose adjustment of gemcitabine	Dose adjustment of cisplatin
ANC < 0.5×10^9/L and PLT ≥ 50×10^9/L	Reduction by 1 dose level	Reduction by 1 dose level
PLT < 50×10^9/L without bleeding manifestation, any ANC level	Reduction by 1 dose level	Reduction by 1 dose level
PLT < 50×10^9/L with bleeding manifestations, any ANC level	Reduction by 2 dose levels	Reduction by 2 dose levels
ANC < 1×10^9/L with fever > 38.5 °C, any PLT level	Reduction by 1 dose level	Reduction by 1 dose level

Note: If the above criteria are not met, the investigator will make dose adjustments based on clinical practice and benefits to subjects after communication with and approval by the sponsor's medical manager. The level and frequency of dose adjustments are the same as above.

5.4.4.4 Non-hematological toxicity

The dose adjustment method in case of non-hematological toxicity is shown in **Table 15**. In the event of grade ≥ 3 non-hematological toxicity, the treatment must be delayed until this event resolves to grade 2 or below or baseline level. The treatment with the dose reduced by one dose level can be allowed if deemed suitable by the investigator, but it is necessary to determine whether the toxicity causes the loss of an opportunity to receive the best treatment or prodrug(s).

When SCr > 1.2 × ULN or CCr < 50 mL/min, it is allowed not to reduce the dose of cisplatin, but the treatment must be delayed or interrupted.

Table 15. Dose adjustments of gemcitabine and cisplatin due to non-hematological toxicity

Toxicity	Grade	Dose adjustment of gemcitabine	Dose adjustment of cisplatin
Diarrhea	Grade 3 or 4	Reduction by 1 dose level	No dose adjustment
Mucositis/stomatitis	Grade 3 or 4	Reduction by 1 dose level	No dose adjustment
Neurotoxicity	Grade 1	No dose adjustment	No dose adjustment
	Grade 2	No dose adjustment	Reduction by 2 dose levels
	Grade 3 or 4	Permanent discontinuation	Permanent discontinuation
Ototoxicity	Grade 2, 3, or 4	No dose adjustment	Permanent discontinuation considered
Others	Grade 3 or 4[a]	Reduction by 1 dose level[b]	Reduction by 1 dose level[b]

a Grade 3 emesis/nausea and grade 3 paronychia are excluded.

b Permanent discontinuation can be considered, at the discretion of the investigator.

5.4.5. Dose adjustments for oxaliplatin and capecitabine

Oxaliplatin and capecitabine should be administered at the original dose instead of being interrupted in case of toxicity that is considered by the investigator to impossibly cause serious or life-threatening events and delay or discontinuation of treatment (e.g., asthenia, alopecia, and taste alterations).

In case of an AE that is judged by the investigator to be related to both oxaliplatin and capecitabine, a comprehensive evaluation should be conducted to determine which drug is more closely associated with this AE and leads to worse outcomes, and then the dose of this drug is adjusted first, minimizing the need for a simultaneous dose adjustment of both drugs.

The oxaliplatin/capecitabine therapy must be discontinued permanently if this therapy is interrupted for over 6 weeks. But the necessity for continuation of oxaliplatin and capecitabine therapy will be discussed with the sponsor's medical manager if this therapy is interrupted for over 6 weeks due to an AE that is possibly-unrelated or unrelated to this therapy (since day 1 after the last dose). Tumor imaging for evaluation efficacy should not be affected by treatment interruption and should be performed as scheduled).

5.4.5.1 Hematological toxicity

The dose adjustment at the start of each subsequent cycle will be based on the lowest PLT and ANC counts in the previous cycle. Growth factor support can be adopted, but routine prophylactic medications are prohibited. After recovery, the dose of oxaliplatin and/or capecitabine should be adjusted according to **Table 16**. When the dose of capecitabine is reduced to 75% of the starting dose, the routine daily administration of 1000 mg (2 tablets) in the morning and 1500 mg (3 tablets) at night is recommended. When the dose is reduced to 50% of the starting dose, the routine daily administration of 1000 mg (2 tablets) in the morning and 1000 mg (2 tablets) at night is recommended. The dose to each subject can be adjusted by the investigator based on the actual body surface area of the subject. Discontinuation of oxaliplatin and capecitabine is recommended in case of the third occurrence of the following hematological toxicity following standard dose adjustments.

Table 16. Dose adjustments of oxaliplatin and capecitabine

Toxicity	First occurrence		Second occurrence	
	Capecitabine	Oxaliplatin	Capecitabine	Oxaliplatin
Grade 4 neutropenia for over 5 days	75% of the starting dose	75% of the starting dose	50% of the starting dose	50% of the starting dose
Grade 4 thrombocytopenia	Maintain initial dose	75% of the starting dose	75% of the starting dose	50% of the starting dose

Toxicity	First occurrence		Second occurrence	
	Capecitabine	Oxaliplatin	Capecitabine	Oxaliplatin
Grade 3 neutropenic fever (ANC < 1.0×10^9/L and fever ≥ 38.5 °C)	75% of the starting dose	75% of the starting dose	50% of the starting dose	50% of the starting dose
Grade 4 neutropenic fever (ANC < 1.0×10^9/L with fever ≥ 38.5 °C and life-threatening sepsis)	As guided by the investigator, the treatment with 50% of the starting dose is continued when toxicity recovers to grade 0–1	As guided by the investigator, the treatment with 50% of the starting dose is continued when toxicity recovers to grade 0–1	Discontinue the treatment	Discontinue the treatment

5.4.5.2 Hematological toxicity

The dose adjustment method in case of non-hematological toxicity is shown in **Table 17**.

Table 17. Dose adjustments of capecitabine and oxaliplatin due to non-hematological toxicity

Toxicity	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 75% of the starting dose, provide prophylactic treatment if possible	Discontinue, unless the investigator determines that it is for the best interest of the subjects to resume at 50% of the starting dose when 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 75% of the starting dose	Interrupt until resolve to grade 0–1, then resume at 50% of the starting dose	-
Third occurrence	Interrupt until resolve to grade 0–1, then resume at 50% of the starting dose	Permanently discontinue	-
Fourth occurrence	Permanently discontinue	-	-

Management of common capecitabine toxicities

- Grade 2 or 3 hand-foot syndrome

Provide symptomatic treatment (emollients are recommended). Refer to **Table 16** for dose adjustments of capecitabine.

- Grade 2 or 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 16. Capecitabine can be resumed after diarrhea resolves to grade 0–1 and until 24 h has 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 16**.

- 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. Then, administer capecitabine at the dose listed in **Table 16**.

- Cardiotoxicity

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

Management of common oxaliplatin toxicities

- 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 original dose for subsequent treatment cycles.

- Neurotoxicity

In case of a nervous system symptom (sensory disturbance and spasm), the following oxaliplatin dose adjustment methods are recommended based on duration and severity level of the symptom.

The dose of oxaliplatin should be reduced by 25% if this symptom lasts for over 7 days and is serious.

The dose of oxaliplatin will be reduced by 25% if sensory disturbance without functional impairment lasts until the next cycle.

Oxaliplatin should be discontinued if sensory disturbance with insufficiency lasts until the next cycle.

Continuation of oxaliplatin can be considered if this symptom has improved after interruption.

5.4.6. Dose adjustments of etoposide

Toxicity-induced dose adjustments of etoposide are allowed. The initial dose should not be adopted once it is reduced. Etoposide should be permanently discontinued in the following cases.

- Occurrence of toxicity requiring a dose reduction after two reductions.

- Toxicity-induced etoposide interruption for over 6 weeks (since day 1 after the last dose). But the necessity for continuation of etoposide therapy will be discussed with the sponsor's medical manager if this therapy is interrupted for over 6 weeks due to an AE that is possibly-unrelated or unrelated to this therapy (since day 1 after the last dose). Tumor imaging for evaluation efficacy should not be affected by treatment interruption and should be performed as scheduled).

5.4.6.1 Hematological toxicity

Growth factor support can be adopted, but routine prophylactic medications are prohibited. The dose adjustment methods in case of hematological toxicity are shown in **Table 18**. No dose adjustment is recommended for anemia patients.

Table 18. Dose adjustments of etoposide due to hematological toxicity

Toxicity	Dose adjustments
ANC < 0.5 × 10^9/L and PLT ≥ 50 × 10^9/L	75% of the previous dose
PLT < 50 ×10^9/L, any ANC level	75% of the previous dose
ANC < 1.0 × 10^9/L with body temperature ≥ 38.5 °C	75% of the previous dose
PLT < 50 × 10^9/L with bleeding of grade 3 or greater, any ANC level	50% of the previous dose

5.4.6.2 Nephrotoxicity

The dose adjustment methods in case of nephrotoxicity are shown in **Table 19**.

Table 19. Dose adjustments of etoposide due to nephrotoxicity

CCr (mL/min)	Dose adjustments
> 50	100% of the previous dose
15–50	75% of the previous dose

5.4.6.3 Other non-hematological toxicity

The dose adjustment methods in case of other non-hematological toxicities are shown in **Table 20**.

Table 20. Dose adjustments of etoposide due to other non-hematological toxicity

Toxicity	Grade	Dose adjustments
Diarrhea	Grade 3 or 4[a], or diarrhea of any grade requiring hospitalization	75% of the previous dose
Nausea/emesis	Grade 3 or 4[b]	75% of the previous dose
Neurotoxicity	Grade 2	75% of the previous dose
	Grade 3 or 4	50% of the previous dose or permanent discontinuation

Toxicity	Grade	Dose adjustments
Transaminase increased	Grade 3	75% of the previous dose
	grade 4	Permanent discontinuation
Other toxicities	Grade 3 or 4	75% of the previous dose

a Grade 3 or 4 diarrhea that still persists after adequate antidiarrheal therapy.

b Grade 3 or 4 nausea/emesis that still persists after antiemetic therapy.

5.4.7. Dose adjustments of irinotecan

Toxicity-induced dose adjustments of irinotecan are allowed. The initial dose should not be adopted once it is reduced. The next cycle of irinotecan therapy cannot be initiated unless the treatment-related diarrhea is eliminated completely and no anti-diarrheal drug is required at least 24 h before this cycle. Irinotecan should be discontinued permanently if it is interrupted for over 6 weeks (since day 1 of the previous cycle) due to toxicity. But the necessity for continuation of irinotecan therapy will be discussed with the sponsor's medical manager if this therapy is interrupted for over 6 weeks due to an AE that is possibly-unrelated or unrelated to this therapy (since day 1 after the last dose). Tumor imaging for evaluation efficacy should not be affected by treatment interruption and should be performed as scheduled.

In case of toxicities listed in **Table 21**, the dose of irinotecan will be reduced by one or more dose levels (one dose level is 25 mg/m^2) in the next cycle.

Table 21. Dose adjustments of irinotecan

Toxicity	Grade	Dose adjustments
Neutropenia	Grade 1–3	Dose maintenance
	grade 4	Reduction by 1 dose level
Neutropenic fever	-	Reduction by 1 dose level
Diarrhea	Grade 1 or 2	Dose maintenance
	Grade 3	Reduction by 1 dose level
	grade 4	Reduction by 2 dose levels
Allergic reaction	Any grade	Permanent discontinuation

5.4.8. Dose adjustments of 5-FU

Toxicity-induced dose adjustments of 5-FU are allowed. The initial dose should not be adopted once it is reduced. 5-FU whose dose has been reduced twice must be discontinued permanently if the 3rd dose reduction is required due to toxicity. The 5-FU therapy must be discontinued permanently if this therapy is interrupted for over 6 weeks (since the start of dosing on day 1 of the previous cycle) due to toxicity (the necessity for continuation of 5-FU therapy will be discussed with the sponsor's medical manager if this therapy is interrupted for over 6 weeks due

to an AE that is possibly-unrelated or unrelated to this therapy. Tumor imaging for evaluation efficacy should not be affected by treatment interruption and should be performed as scheduled).

5.4.8.1 Hematological toxicity

Growth factor support can be adopted, but routine prophylactic medications are prohibited. The dose adjustment methods in case of hematological toxicity are shown in **Table 22**.

Table 22. Dose adjustments of 5-FU due to hematological toxicity

Toxicity	Dose adjustment of 5-FU
ANC < 0.5×10^9/L and PLT ≥ 50×10^9/L	75% of the previous dose
PLT < 50×10^9/L, any ANC level	75% of the previous dose
ANC < 1.0×10^9/L with body temperature ≥ 38.5 °C	75% of the previous dose
PLT < 50×10^9/L with bleeding of grade 3 or greater, any ANC level	50% of the previous dose

5.4.8.2 Non-hematological toxicity

The dose adjustment methods in case of non-hematological toxicities are shown in **Table 23**.

Table 23. Dose adjustments of 5-FU due to non-hematological toxicity

Toxicity		Dose adjustment of 5-FU
Grade 3 or 4 hand-foot syndrome		75% of the previous dose
Angina or myocardial infarction		Permanent discontinuation
Grade 3 or 4 diarrhea or Diarrhea complicated with fever or grade 3 or 4 neutropenia	First occurrence	75% of the previous dose
	Second occurrence	50% of the previous dose or permanent discontinuation

5.5. Principles of Managing Immune Checkpoint Inhibitor Toxicities

AEs related to IBI308 exposure may be etiologically associated with immunity. These irAEs may occur within a short period after the first dose or within months after the last dose. They may influence more than one systems simultaneously. Therefore, early diagnosis and treatment are critical to reduce complications. Based on the existing clinical trial data, most irAEs are reversible, and can be managed through discontinuation of IBI308, administration of glucocorticoids, and/or other supportive therapies. For suspected irAEs, an appropriate evaluation should be ensured to confirm pathogenesis or rule out other reasons. Other procedures or examinations, such as bronchoscopy, endoscopy, or skin biopsy, may be included into this evaluation. Temporary or permanent discontinuation of IBI308 and administration of glucocorticoids are adopted depending on the severity level of irAEs.

See Appendix 7 for dose adjustments and toxicity management of potential irAEs, potential non-irAEs, and infusion reactions.

5.6. Concomitant Treatment

5.6.1. Prohibited treatments

- Other chemotherapy, immunotherapy, targeted therapy, and hormonal therapy used for systemic anti-tumor treatment, as well as traditional Chinese medicines, proprietary Chinese medicines, and replacement therapy with anti-tumor indications.
- Immunosuppressive agents and high-dose glucocorticoids (except for the treatment of AEs or pretreatment for special examinations; high-dose glucocorticoids are defined as 10 mg/d of prednisone or an equivalent dose of other glucocorticoids).
- Blood products such as albumin, immunoglobulin, gamma globulin, whole blood or component blood, and cytapheresis blood cells (except for the treatment of AEs).
- Receiving live attenuated vaccine.

5.6.2. Permitted treatments

- Medications judged by the investigator to meet the protocol requirements and specification in Section 5.6.1 (for example, concomitant medications for the treatment of disease-related symptoms and various 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 (the radiotherapy field does not cover lungs) used for isolated lesions (excluding target lesions) during the study treatment.
- 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.

5.6.3. Drug-drug interactions

5.6.3.1 IBI308

There are no data on drug interactions with IBI308 at present.

5.6.3.2 Pemetrexed

For subjects with mild to moderate renal insufficiency, non-steroidal anti-inflammatory drugs (NSAIDs) with short half-lives are not recommended at least 2 days before, on the day when, and at least 2 days after pemetrexed is administered, and those with long half-lives are not recommended at least 5 days before, on the day when, and at least 2 days after pemetrexed is administered.

5.6.3.3 Cisplatin

Cisplatin in combination with aminoglycoside antibiotics, amphotericin B, or cefalotin may aggravate renal toxicity; cisplatin in combination with probenecid may induce hyperuricemia; chloramphenicol, furosemide, or ethacrynate sodium can worsen the ototoxicity of cisplatin; antihistamine may cover up tinnitus, vertigo, and other symptoms caused by cisplatin.

5.6.3.4 Gemcitabine

Cumulative myelosuppression should be considered when combining gemcitabine with other anti-tumor drugs or sequentially using gemcitabine and chemotherapy. Gemcitabine cannot be administered in parallel with radiotherapy (because of the risk of radiosensitization and serious pulmonary and esophageal fibrinoid degeneration). The combination of gemcitabine and cisplatin is prohibited in subjects with severe renal insufficiency.

5.6.3.5 Capecitabine

- Coumarin anticoagulants: Altered coagulation parameters and/or hemorrhage have been reported in subjects receiving capecitabine concomitant 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 20 mg dose of warfarin followed by capecitabine, the mean AUC of S-warfarin increased by 57% and INR 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 substrates: No formal drug-drug interaction studies between capecitabine and other medications known to be metabolized by P-450 2C9 have been conducted. Care should be exercised when capecitabine is 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 capecitabine and phenytoin.

- Drug-food interactions: In all clinical trials, subjects were 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 concentrations of capecitabine and one of its metabolites (5-capecitabine) increased slightly. No effect was observed on the other three 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 at least a 4-week waiting period from the treatment end of sorivudine and its analogues (such as brivudine) to capecitabine.

5.6.3.6 Etoposide

When warfarin is combined with etoposide, the international normalized ratio (INR) may be extended, and the INR needs to be monitored at a higher frequency.

5.6.3.7 Irinotecan

- Neuromuscular blockers: The interaction between irinotecan hydrochloride and neuromuscular blockers can not be ruled out. Because irinotecan hydrochloride has the activity of a cholinesterase inhibitor, drugs with cholinesterase inhibitory activity can prolong the neuromuscular blockade of chlorosuccinylcholine and can fight neuromuscular blockade of non-depolarizing drugs effect.
- Anticonvulsants: Combined use of CYP3A-induced anticonvulsants (such as carbamazepine, phenobarbital, or phenytoin) can cause reduced exposure to SN-38. For patients requiring anticonvulsant therapy, consideration should be given to starting or switching to a non-enzyme-induced anticonvulsant at least one week prior to the initial treatment with irinotecan hydrochloride.

- Ketoconazole: Simultaneous treatment with ketoconazole can cause a significant reduction in the clearance of irinotecan hydrochloride, leading to increased exposure of its active metabolite SN-38. Ketoconazole should be stopped at least one week before starting irinotecan hydrochloride treatment. Of course, it can not be co-administered with irinotecan hydrochloride.
- St. John's wort: In patients receiving St. John's wort at the same time, the exposure of active metabolite SN-38 is reduced. St. John's wort should be discontinued at least one week before the first use of irinotecan hydrochloride, and the drug cannot be used simultaneously with irinotecan hydrochloride.
- Atazanavir: Simultaneous use of atazanavir, an inhibitor of CYP3A4 and UGT1A1, may increase SN-38 exposure. Physicians should consider this when using these drugs at the same time.
- Dexamethasone: Lymphopenia has been reported in patients receiving irinotecan hydrochloride, which may be exacerbated when dexamethasone is used as an antiemetic drug. However, neither serious opportunistic infections were found, nor any complications due to lymphopenia. Patients receiving this product have reported with increased blood glucose. Usually this happens in patients who have a history of diabetes or have impaired glucose tolerance before treatment with this product. The increase in blood sugar in some patients may be caused by receiving dexamethasone.
- Prochlorperazine: In a clinical study of a single-dose weekly dosing regimen, patients who were given prochlorperazine on the same day as irinotecan hydrochloride had a higher incidence of akathisia (8.5%, 4/47 patients), when these two drugs are not given on the same day, the incidence is relatively low (1.3%, 1/80 patients). However, the incidence of 8.5% of akathisia is still within the range of reports of akathisia as a pre-chemotherapy with prochlorperazine.
- The combination of laxatives with this product may increase the severity level or incidence of diarrhea, but no research in this area has been conducted.
- Diuretics: Because of the potential risk of secondary dehydration after vomiting and/or diarrhea, physicians should avoid the use of diuretics during irinotecan hydrochloride treatment, and of course they should not use diuretics during diarrhea or vomiting.

5.6.3.8 5-FU

- Tinidazole: Tinidazole will affect liver metabolism, increase the accumulation of 5-FU, and thus the combination of the two should be avoided.

- Warfarin and heparin: 5-FU will increase the anticoagulant effect of warfarin and heparin and may increase the risk of bleeding in the latter.
- Allopurinol: Allopurinol may affect the efficacy of 5-FU, and thus the combination of the two should be avoided.
- Pavlimin: Pavlimin increases the toxicity of 5-FU, and thus the infusion of pavlimin should be avoided 24 h before and after the infusion of 5-FU.
- Iron chelating dose (deferiprone): A synergistic effect was observed when using with 5-FU, and thus the combination will increase toxicity and the combination of the two should be avoided.

5.7. Dosing During Pregnancy, Childbearing Age and Lactation

5.7.1. Pregnancy

So far, human IgG4 is known to be able to penetrate the placental barrier and is not recommended for use during pregnancy. Therefore, pregnant women should not be enrolled into this study.

5.7.2. Childbearing age

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, the subjects and their partners must use one of the acceptable methods of contraception listed in **Table 24** from screening to 6 months after the last dose of study treatment, 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 24. 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 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.

5.7.3. During Lactation

IBI308 is unknown for secretion from breast milk. Considering that many drugs are present in breast milk, IBI308 may be potentially toxic to infants. Therefore, lactating women should not be enrolled into this study.

5.8. Treatment Compliance

Study treatment will be given at the study sites. Treatment compliance will be monitored by medication dispensing and return records, medical records, and electronic case report forms (eCRFs).

5.9. Drug Return and Destruction

The containers, vials, infusion bags, and syringes of used and partially used study drugs 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 study drugs were made by the clinical research associate (CRA) designated by the sponsor.

5.10. Study Drug-related Records

The designee of the study sites should make timely records of receiving, dispensing, using, storing, returning, and destroying the study drugs in accordance with the relevant regulations and guidelines.

5.11. 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 should be used to document product complaints and relevant description completely.
- The completed product complaint form should be submitted to the sponsor or designee by fax within 24 hours.

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 EVALUATIONS AND RELEVANT PROCEDURES

6.1. Enrollment and Randomization

6.1.1. Subject enrollment

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.

The sponsor will monitor the enrollment for each cohort to ensure the sample size in each cohort meets study requirements.

Subjects who fail 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 with the study is appropriate medically, which is not agreed with by the sponsor's medical manager, then the subject shall not continue participating in the study (regardless of

receiving the study drug or not). The investigator must not allow the subject to continue with the study until receive the written approval from the sponsor.

6.1.3. Randomization and blinding

To avoid bias in the selection of subjects, the investigator will randomize subjects at 1:1 as per the random number table provided by the sponsor when the dose level is escalated to 3 mg/kg IV Q2W and 200 mg IV Q3W in the phase Ia dose-escalation study.

Blinding is not adopted in this study.

6.2. Study Plan and Schedule

6.2.1. Screening period

The following procedures must be completed during the screening (Days -28 to -1) period of phase Ia and Ib studies to ensure subject eligibility:

- Signing of informed consent form
- Confirming the inclusion/exclusion criteria
- Recording the demographics, medical history, and previous medications
- Recording the vital signs, height, and weight (for cohort D of phase Ib, the body surface area needs to be calculated)
- Physical examination
- ECOG PS score
- 12-lead electrocardiogram (ECG)
- Routine blood test/blood chemistry/routine urinalysis (within 7 days prior to the first dose)
- Coagulation function (within 7 days prior to the first dose)
- Pregnancy test (within 3 days prior to the first dose)
- Thyroid function (within 7 days prior to the first dose)
- Autoantibody
- HIV, HBV, and HCV
- AE evaluation
- Concomitant medications
- Tumor imaging evaluation

- Archived or fresh tumor tissue sample (not for patients in cohorts G and H in phase Ib)

  Refer to Sections 6.3 and 6.4 for details regarding tumor imaging evaluation and safety evaluation.

6.2.2. Treatment visits

- Recording of vital signs and body weight; If the weight fluctuation is less than 10% compared to baseline (the day of the first dose), the baseline weight will be used to calculate the chemotherapeutic dose. Otherwise, the actual dose will be calculated based on the weight of scheduled dosing days.
- Physical examination
- ECOG PS score
- The examination of 12-lead ECG, performed within 60 min after the infusion of IBI308
- Routine blood test/blood chemistry/routine urinalysis
- Thyroid function
- Immunogenicity
- PK/PD
- AE evaluation
- Concomitant medication
- Tumor imaging evaluation
- Administration: of study drug:
  - Phase Ia study: The cycle 1 for every dose group is the period of DLT observation (28 days) and the drug is only administered on Day 1. Since cycle 2, IBI308 is intravenously infused once every 2 weeks in the 1 mg/kg, 3 g/kg, and 10 mg/kg groups and once every 3 weeks in the 200 mg group. All reatment will be carried out until PD, intolerable toxicity, withdrawal of informed consent, or other reasons requiring treatment discontinuation (whichever occurs first). Some subjects could continue to use the investigational drug if they met certain conditions after PD (Protocol 5.1.2).
  - A-C cohorts in the phase Ib study: Subjects receive 200 mg IV Q3W of IBI308 until PD is found for the first time, intolerable toxicity, withdrawal of informed consent, 24 months of treatment, or other reasons for discontinuation of the study treatment (whichever occurred first). Some subjects could continue to use the investigational drug if they met certain conditions after PD (Protocol 5.1.2).

- Cohort D in the phase Ib study: Each treatment cycle contained 3 weeks. And 200 mg IV of IBI308, 500 mg/m^2 IV of pemetrexed, and 75 mg/m^2 IV of cisplatin are given on D1 of each cycle. Up to 4 cycles of triple drug combination therapy are given. Subsequently, the subjects experiencing no PD can receive a maintenance treatment of 200 mg IV Q3W of IBI308 and 500 mg/m^2 IV Q3W of pemetrexed until PD, intolerable toxicity, withdrawal of informed consent, 24 months of treatment, or other reasons for discontinuation of the study treatment (whichever occurs first).
- Cohort E in the phase Ib study: Each treatment cycle contains 3 weeks. The dosing regimen is IBI308 200 mg IV D1 + gemcitabine 1250 mg/m^2 IV D1, D8 + cisplatin 75 mg/m^2 IV D1. Up to 6 cycles of triple drug combination therapy are given. Subsequently, the subjects experiencing no PD can receive a maintenance treatment of 200 mg IV Q3W of IBI308 until PD, intolerable toxicity, withdrawal of informed consent, 24 months of treatment, or other reasons for discontinuation of the study treatment (whichever occurs first).
- Cohort F in the phase Ib study: 200 mg of IBI308 are given via intravenous infusion every 3 weeks. Capecitabine 1000 mg/m^2 PO BID D1-14+ oxaliplatin 130 mg/m^2 IV D1, with 3 weeks in a cycle (XELOX regimen). After up to 6 cycles of treatment of IBI308 in combination with XELOX, the subjects showing no PD could subsequently receive a maintenance treatment of 200 mg IV Q3W of IBI308 until PD, intolerable toxicity, withdrawal of ICF, 24 months of total treatment, or other reasons for discontinuation of the study treatment (whichever occurred first).
- Cohort G in the phase Ib study: Each treatment cycle contains 3 weeks. The dosing regimen is IBI308 200 mg IV D1, etoposide100 mg/m^2 IV D1-3, and cisplatin 75 mg/m^2 IV D1. After up to 6 cycles of treatment of IBI308 in combination with chemotherapy, the subjects showing no PD could subsequently receive a maintenance treatment of 200 mg IV Q3W of IBI308 until PD, intolerable toxicity, withdrawal of ICF, 24 months of total treatment, or other reasons for discontinuation of the study treatment (whichever occurred first).
- Cohort H in the phase Ib study: Each treatment cycle contains 3 weeks. The dosing regimen is IBI308 200 mg IV D1, irinotecan 125 mg/m^2 IV D1, and D8+5-FU 1000 mg/m^2 IV D1-3. After up to 6 cycles of treatment of IBI308 in combination with chemotherapy, the subjects showing no PD could subsequently receive a maintenance treatment of 200 mg IV Q3W of IBI308 until PD, intolerable toxicity, withdrawal of ICF, 24 months of total treatment, or other reasons for discontinuation of the study treatment (whichever occurred first).

- Tumor tissue samples from an exploratory study (optional, biopsy again after receiving the first dose of study medication until PD or termination of study treatment).

See Table 1 and Table 2 for the flow chart of the visit during the treatment period of phase Ia; see Table 3 and Table 6 for the flow chart of the visit during the A-C treatment period of the phase Ib study cohort; see the flow chart of the visit during the D/E/F treatment period of the phase Ib study cohort in Table 4 and Table 6; see Table 5 for the flow chart of the I/B study cohort during the G/H treatment period.

Refer to Sections 6.3, 6.4, 6.5, 6.6, and 6.7 for details regarding tumor imaging evaluation, safety evaluation, blood sampling for PK, PD, and immunogenicity.

6.2.3. End-of-treatment visit/safety follow-up

If the treatment ends or the study drug is discontinued prematurely for any reasons, an end-of-treatment visit shall be carried out as soon as possible the study drug within 7 days after the end of treatment and before the subject receives new anti-tumor therapy. The visit shall include the followings:

- Vital signs and body weight
- Physical examination
- ECOG score
- 12-lead electrocardiogram (ECG)
- Routine blood test/blood chemistry/routine urinalysis
- Coagulation function
- Thyroid function
- AE evaluation
- Concomitant medication
- Tumor imaging examination

A safety follow-up should be carried out within 90 days ± 7 days after the last dose or before the start of a new anti-tumor treatment (whichever occurred first). Subjects of treatment discontinuation due to drug-related AE should be followed up until the AE is resolved to grades 0–1, with stable symptoms or withdrawal of ICF (whichever occurs first). The visit shall include the followings:

- Vital signs and body weight
- Physical examination

- ECOG score
- 12-lead electrocardiogram (ECG)
- Routine blood test/blood chemistry/routine urinalysis
- Coagulation function
- Thyroid function
- Autoantibody
- Immunogenicity
- PK/PD
- AE evaluation
- Concomitant medication
- Subsequent anti-tumor therapy (if applicable)
- Tumor imaging examination (if applicable)

6.2.4. Survival follow-up

After the last dose of the study treatment, the subject shall be contacted every 90 (± 7) days (telephone visits are acceptable) to obtain the survival information, any subsequent systemic anti-tumor therapy, and PD information (for subjects with no imaging PD). Long-term follow-up should be continued until death or end of study.

6.3. Efficacy Evaluation

There is no central imaging evaluation in this study. The methods used for the evaluation of tumor burden in the baseline period should be the same as the methods used for each subsequent follow-up evaluation (contrast-enhanced CT/MRI were usually used), and the sites of imaging examination included the chest, abdomen, and pelvic cavity. 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.

Tumor imaging evaluation should be carried out every 9 weeks (± 7 days) after first dose of the study drug. For patients who recorded disease remission (CR or PR) for the first time in the phase Ia study, an imaging evaluation will be performed after 4 weeks (±7 days) to confirm the remission, and thereafter every 12 weeks (±7 days) until the time of imaging PD is recorded; for patients with disease remission (CR or PR) recorded in the phase Ib study, an imaging evaluation will be performed after 4 weeks (±7 days) to confirm the remission, and thereafter every 9 weeks (±7) until the time of imaging PD was recorded. For cohorts A–C in phase Ia and Ib studies, the

patients who are first recorded as progressive disease (PD) in cohorts A–C during the imaging evaluation and then confirmed as irPD by the imaging evaluation carried out 4 weeks later, if they could continue to receive the treatment of the study drug, imaging evaluations should be carried out every 9 weeks (± 7 days) until the recurrence of PD. The recurrence of PD is defined as the increase in the sum of the longest diameter of the tumor target lesion by > 10% on the basis of the initial imaging-based PD or the appearance of a new measurable lesion. Cohorts D-H in the phase Ib study: Imaging studies confirm the tumor progression and need to stop the treatment with the study drug. For subjects with first imaging PD but an unstable clinical situation or rapid progression who are deemed as not suitable for continued drug treatment, it is not necessary for them to undergo further imaging examinations to confirm PD.

For subjects who discontinue the treatment for reasons other than PD, an imaging evaluation should be carried out at the end of the treatment, and another imaging evaluation should be carried out every 9 weeks (± 7 days) after the drug treatment is discontinued until one of the following events occurred: start of a new anti-tumor therapy, PD, withdrawal of ICF, and death.

Subjects who are known or suspected of having brain metastases at the time of screening should undergo a CT/MRI examination of the brain before the start of study treatment. During the study, such subjects should be followed up, and the CT/MRI assessment should be repeated at the same frequency as required by the RECIST V1.1 assessment. Brain metastases are evaluated as non-target lesions.

The subject may continue the treatment if PD cannot be confirmed, especially for non-target lesions and new lesions, until clinically indicated disease or the next scheduled evaluation time point. The subject's disease status will then be re-evaluated. If repeated scans confirm PD, then the PD should be recorded using the date of the initial scan.

In this study, the tumor evaluations are performed based on RECIST V1.1 at the study site. Refer to Appendix 3 for the evaluation methods.

6.3.1. RECISIT 1.1 efficacy evaluation

The efficacy evaluation is based on RECIST V1.1. For more information, see Appendix 3. The ORR, TTR, DOR, PFS, 6-month and 1-year PFS rates, DCR, OS, and 6-month and 1-year survival rates after medication are evaluated.

6.3.2. Efficacy evaluation by immune-related remission standard (irRECIST)

Immune-related RECIST (irRECIST) is a revised RECIST V1.1, which takes into account the unique tumor remission pattern seen in immunotherapy and is first proposed by Nishino et al. Immunotherapy drugs (such as IBI308) can exhibit an anti-tumor effect by strengthening the endogenous tumor-specific immune response. The remission patterns that are observed this

therapy can not only extend the typical remission time course shown in cytotoxic drug therapy, but also lead to clinical remission after the initial increase in tumor burden or even after the findings of new lesions. Therefore, RECIST V1.1 may not provide an accurate response assessment protocol for immunotherapy drugs such as IBI308. The evaluation standard for one-dimensional target lesions based on irRECIST is generally the same as RECIST V1.1. The main difference between this standard and RECIST V1.1 is that when the first imaging examination is evaluated as PD, the irRECIST evaluation is initiated 4 weeks (±7 days) later, and the evaluation results are defined as follows:

- irPD: The total tumor diameter (if there is a measurable new lesion, the diameter of the new lesion should be added to the total diameter of the target lesion according to the RECIST V1.1 standard) increases by ≥ 20% from the minimum value, or the absolute value increases by at least 5 mm; If irPD is not confirmed, the tumor evaluation will be continued by the previous imaging evaluation time point according to the RECIST standard until the next imaging PD is confirmed as irPD.
- irCR: The evaluation standard is the same as RECIST V1.1, which occurs after irPD is confirmed;
- irPR: The evaluation standard is the same as RECIST V1.1, which occurs after irPD is confirmed;
- irSD: The evaluation standard is the same as RECIST V1.1, which occurs after irPD is confirmed;

The irRECIST is explored as a methodology to evaluate the clinical benefits of IBI308, and evaluate irORR, irDCR, irPFS, and irDOR according to the immune-related remission standard.

6.4. Safety Evaluation

6.4.1. Routine laboratory safety evaluation

Table 25. Routine laboratory safety evaluation

Routine blood test	RBC, HGB, HCT, WBC, PLT, LYM, ANC, MONO, EOS, and BASO
Coagulation function	TT, PT, APTT, and INR
Blood chemistry	TBIL[a], ALT, AST, γ-GT, ALP, ALB, TP, LDH, Urea, Cr, Na, K, Cl, Mg, Ca, P, amylase, and FBG
Urinalysis	PH, UWBC, UPRO[b], URBC, and UGLU

a. If TBIL is ≥ 2 × ULN (and no evidence of Gilbert syndrome), direct and indirect bilirubin will be measured separately.

b. Any subject with urine protein ≥ 2+ from urinalysis blood cells undergo a 24-hour urine protein test.

6.4.2. Physical examination

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, and nervous system.

Refer to the schedule of visits in Tables 1, 3, 4, and 5 for examination time. Refer to Appendix 2 for ECOG PS score.

6.4.3. 12-lead electrocardiogram (ECG)

A resting 12-lead ECG is performed at the local laboratory in accordance with the schedule of visits in Tables 1, 3, 4, and 5.

All resting 12-lead ECGs are performed while the subjects are resting in the supine position. Further ECG will be performed if clinically indicated, such as a cardiac AE. The investigators review the ECG on the day it is performd, and documented the results on the ECG. The same method of evaluation is used throughout the trial.

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

6.4.4. Vital signs

Vital signs are examined in accordance with the schedule of visits in Tables 1, 3, and 4. Vital signs include body temperature, pulse, respiratory rate, and blood pressure.

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.

6.4.4.1 Pulse and blood pressure

The subject's blood pressure and pulse in the supine position are measured after a rest for at least 5 minutes. The time and date of collection and measurement should be documented in the appropriate section of the eCRF.

In the phase Ia study, the blood pressure and pulse are collected at the following time points before, during and after each infusion of IBI308 (based on a 60-minute infusion):

- At the start of infusion (minute 0)

- Every 15 minutes during infusion (minute 15, 30, and 45) (all ± 5 minutes)
- At the end of infusion (minute 60, ± 5 minutes)
- During the observation period 1 hour after infusion: 30 and 60 minutes after infusion (i.e., 90 and 120 minutes from the start of the infusion) (± 5 minutes).

In the event that the infusion is longer than 60 minutes, the blood pressure and pulse are measured following the above principles or at a higher frequency when clinically indicate.

For the Phase Ib study, pulse and blood pressure are only measured before the infusion of IBI308.

6.4.4.2 Body temperature and respiratory rate

The body temperature and respiratory rate should be collected prior to the infusion on the scheduled administration day.

6.4.5. Weight and height

Height is measured only during screening.

Weight must be measured before every planned dose during the study. If the weight fluctuation is less than 10% compared to baseline (date of chemotherapy: first dose), then use the baseline weight to calculate the chemotherapeutic dose. Otherwise, the actual dose will be calculated based on the weight of scheduled dosing days.

6.4.6. Pregnancy test

Urine or serum human chorionic gonadotropin (hCG) pregnancy test is performed in women of childbearing age (for the definition, see Section 5.6.2) within 3 days prior to the first dose of the study treatment. 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. For the serum β-hCG result of positive, the subject is not eligible or discontinued participating in the study. A repeated test is performed for the suspected pregnancy during the study.

6.4.7. Autoantibody

The testing items during the screening period include ANA, anti-dsDNA antibodies, and anti-thyroglobulin antibodies, and then the investigators will judge whether to check the relevant autoimmune antibody parameters based on clinical indications.

6.4.8. Other safety inspections include the followings:

- HBV-related tests, including five items for hepatitis B: HBsAg, HBsAb, HBcAb, HBeAg, and HBeAb. HBV-DNA should be further tested for subjects positive to HBsAg and/or HBcAb;

- HIV 1/2 antibody and HCV antibody tests;
- Thyroid function: T3, T4, TSH, FT3, and FT4.

6.4.9. Safety Review Committee

The Safety Review Committee is composed of the sponsor and the investigators. After completing the DLT observation of the previous dose group in the phase Ia dose escalation, the Safety Review Committee will evaluate and decide whether the group can enter the next dose group for treatment. The discussion in the Safety Review Committee can also be triggered by a sudden safety event during the phase Ib trial.

6.5. Pharmacokinetics:

6.5.1. Collection of specimens

6.5.1.1 Phase Ia study

A total of 9 PK sampling time points are designed for cycle 1: within 1 h before IBI308 infusion, at 0 h (+ 5 min) and 1 h ± 5 min after the end of infusion, and at 6 h ± 15 min, 24 ± 1 h, 48 ± 2 h, 168 ± 8 h (day 8), 336 ± 12 h (day 15), and 504 ± 24 h (day 22) after the start of infusion.

From cycle 2, blood collection for PK testing is performed every 2 cycles (i.e., cycles 2, 4, 6...). Except for cycle 4, the blood collection times are all within 1 h before the start of the infusion and immediately after the end of the infusion (+ 5 min).

In Cycle 4 (dense sampling), for the 200 mg cohort, blood is sampled within 1 h before the start of infusion, at 0 h (+ 5 min) and 1 h ± 5 min after the end of infusion, and at 6 h ± 15 min, 24 ± 1 h, 48 ± 2 h, 168 ± 8 h (Day 8), 336 ± 12 h (Day 15), and 504 ± 24 h (Day 22) after the start of infusion; and for 1 mg/kg, 3 mg/kg, and 10 mg/kg cohorts, blood is sampled within 1 h before the start of infusion, at 0 h (+ 5 min) and 1 h ± 5 min after the end of infusion, and at 6 h ± 15 min, 24 ± 1 h, 48 ± 2 h, 168 ± 8 h (Day 8), and 336 ± 12 h (Day 15) after the start of infusion.

6.5.1.2 Phase Ib study

The same PK collection method is used in cohorts A–F in the phase Ib study. No PK sampling will be performed for cohorts G and H in the phase Ib study.

There are a total of 8 PK blood sampling points in Cycle 1: within 1 h before the start of IBI308 infusion, immediately after the end of infusion (+ 5 min), 1 h ± 5 min after the end of infusion, and 6 h ± 15 min, 24 h ± 1 h, 48 h ± 2 h, 168 h ± 8 h (D8), and 336 h ± 12 h (D15) after the start of infusion.

From cycle 2, samples are collected every 2 cycles (i.e., cycles 2, 4, 6...), with 2 blood sampling points per cycle: within 1 h before the start of infusion, and immediately after the end of infusion (+ 5 min).If the dosing on Day 1 of Cycle 2 is delayed due to an AE or other reasons, additional sampling is required at 504 ± 24 h (Day 22) in Cycle 1.

In the phases Ia and Ib studies, one PK sampling was required in each safety follow-up of cohorts A–F.

A vacutainer with coagulant will be used to collect 2 mL of whole blood. Then, the serum will be separated from the whole blood sample and frozen in aliquots for the PK analysis. Refer to the Laboratory Manual provided by the sponsor-designated central laboratory for sampling methods, sample storage, transport, and analysis.

6.5.2. Measurement of drug concentration

The concentration of IBI308 in the serum is measured by ELISA, and tested by the central laboratory designated by the sponsor. The plasma drug concentration needs to be determined in all subjects at the sampling time points specified in the study protocol.

6.6. Pharmacodynamics

6.6.1. Phase Ia study

There are a total of three PD blood collection points in cycle 1: within 1 h before the start of IBI308 infusion, and 24 h ± 1 h, and 168 h ± 8 h (day 8) after the start of the infusion. From Cycle 2, sample collection will be performed every four cycles (Cycles 6, 10, 14…), with blood sampling points within 1 h before the start of infusion. One blood sample must be collected during safety follow-ups.

6.6.2. Phase Ib study

There are a total of three PD blood collection points in cycle 1: within 1 h before the start of IBI308 infusion, and 24 h ± 1 h, and 168 h ± 8 h (day 8) after the start of the infusion. From cycle 2, blood collection is performed every 4 cycles (i.e., cycles 6, 10, 14...). Blood collection time point: within 1 h before the start of the infusion. Blood samples must be collected during safety follow-ups.

A vacutainer with anticoagulant will be used to collect 1 mL of whole blood for the analysis of PD-1 receptor occupancy. Refer to the Laboratory Manual provided by the sponsor-designated central laboratory for sampling methods, sample storage, transport, and analysis.

No PD sampling will be performed for cohorts G and H in the phase Ib study.

6.7. Immunogenicity

Immunogenicity assays are performed within 1 h prior to IBI308 infusion in cycles 1, 2, and then every 2 cycles thereafter (cycles 4, 6, 8...) and during the safety follow-up visits. If an IBI308 infusion-related reaction occurs, 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.

ADA titer should be tested for each subject. ADA-positive samples should be further tested for neutralizing antibodies (NAbs).

For ADA and NAb assays, 4 mL of whole blood will be collected using vacutainers with coagulant. Then, the serum will be 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.

No immunogenicity assay will be performed for cohorts G and H in the phase Ib study.

6.8. Biomarker Analysis

When permitted by the IEC, subjects who met the inclusion criteria are required to provide diagnosed tumor tissues at baseline (except for cohorts G and H in the phase Ib study). For the acceptable tumor tissues, including the archived tumor tissues or those newly collected and prepared during the screening period, at least 5 unstained sections of 4 micron will be required.

With the subject's informed consent, a biopsy is performed again after the use of the study drug and before the PD or termination of the treatment. The tumor tissues are submitted to the central laboratory for testing, and the relationship between the changes in PD-L1 expression before and after treatment and the efficacy is compared. The samples could also be used for exploratory biomarker analysis, including but not limited to PD-L1 expression, tumor mutation burden (TMB) test, multicolor immunohistochemistry, and PD-L1 and CD8 double staining assay.

For the study sites participating in cohorts D/E/F studies, after the protocol V2.0 takes effect, tumor tissues and peripheral blood (as a reference standard) that meet the following requirements must also be provided at the baseline, in order to analyze biomarkers (such as TMB) based on the whole exome sequencing.

For the study sites participating in cohorts A/B/C studies, the TMB test must be optional.

Tumor tissues: (any samples meeting one of the following requirements for sources)

Sample type	Sample collection	Storage temperature	Transportation method	Notes
Formalin-fixed and parrffin-embedded tissues (FFPE)	10–15 (at least 5) pieces of surgical tissue sections; Puncture tissues > 15 pieces; Paraffin block of 50 mg (with bean size)	<37°C	Transportation at ambient temperature	Paraffin samples within half a year should be submitted for tests in sections without staining
Puncture tissues	2 needles, at least 1, with a sample diameter of 1–2 mm and a length of more than 0.5 m	With tissue storage buffer: < 25 °C Without tissue storage buffer: < -20 °C	Mail with dry ice	Formalin immersion should be possibly avoided
Fresh tissues	No less than 60 mg for submission (with bean size)	With tissue storage buffer: < 25 °C Without tissue storage buffer: < -20 °C	Mail with dry ice	In case of using the tissue storage buffer, the tissues must be completely immersed into the buffer

Normal reference standard:

Sample type	Sample collection	Storage temperature	Transportation method	Notes
Peripheral blood	A collection of ≥ 2 mL, with sodium citrate or EDTA as an anticoagulant	<-20°C	Mail with dry ice	Using heparin as an anticoagulant is not recommended

Refer to Laboratory Manual for details regarding sample processing, handling, and transport.

6.9. 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 CSR.

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.

7. SAFETY REPORTS AND AE MANAGEMENT

7.1. Definition of AEs

An adverse event (AE) is defined as any adverse medical event that is observed in the period from the signing of the ICF to 90 days after the last dose of the study drug, regardless of whether or not considered as related to the study 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 conditions (including symptoms, signs, and newly diagnosed diseases);
- Clinically significant laboratory test abnormalities.

7.2. Definition of SAEs

A 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, 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
  - ✓ Day surgery (e.g. outpatient/same-day/ambulatory surgery)
  - ✓ Hospitalizations or prolonged hospitalizations due 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 starts); 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: defined as events that may jeopardize the subjects and require medical or surgical interventions to prevent one of the other outcomes listed in the definition above.

7.3. 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 4.03 are graded in accordance with the following CTCAE grading principles:

- Grade 1 Mild; asymptomatic or mild sings; 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, etc.).
- Grade 3 Severe or medically 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.

7.4. Correlation Between AEs and Study Drug

The relationship between the study drugs and AEs can be determined by the classification and the criteria in **Table 26**.

Table 26. Correlation determination between AEs and study drug

Correlation	Criteria
Definitely related	• The AE occurrence has a reasonable time relationship with administration time; • The investigational drug can more reasonably explain the AE than the other causes (such as concurrent disease, environment, toxicity, or other treatment received); • The AE resolves or is alleviated after treatment interruption or dose reduction; • The event meets the recognized pharmacological AE type; • The AE is observed again after re-administration.

Correlation	Criteria
Possibly related	• The AE occurrence has a reasonable time relationship with administration time; • The investigational drug provides same reasonable explanations on the AE as the other causes (such as concurrent disease, environment, toxicity, or other treatment received); • The AE resolves or is alleviated after treatment interruption or dose reduction (if applicable);
Possibly not related	• Other causes provide more reasonable explanations on the AE than the investigational drug (such as concurrent disease, environment, toxicity, or other treatment received); • The AE does not resolve or be alleviated after treatment interruption or dose reduction (if applicable), or the situation is unclear; • The AE is not observed again after re-administration or the situation is unclear.
Definitely not related	• The AE occurrence has no reasonable time relationship with administration time, or • Other causes provide evident explanations (such as concurrent disease, environmental, toxicity, or other treatment received by the subject).
Cannot be determined	• The above information is unclear and cannot be determined based on the available information. Further follow-up information is not accessible to the investigator.

7.5. Documentation of AEs

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

7.5.1. Collection and Time of AEs

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

All the AEs, including SAEs, that occurr 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 the subject initiates other anti-tumor therapies within 90 days after the last dose of the study drug, then only AEs considered related to the drug are required to be collected.

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

7.5.2. AE follow-up

The AE should be followed until the events return to the baseline values or grade 0–1, or until the investigator believes that no further follow-up is required for reasonable reasons (if the event cannot 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 study drugs.

7.5.3. Contents of AE documentation

The investigator must document all the AEs, including the diagnosis (document signs and symptoms including the laboratory abnormalities if there is no diagnosis), time and date of occurrence (if applicable), CTCAE grade of severity and changes in severity (events ≥ grade 3), whether it is an SAE, whether it is an adverse event of special interest (AESI), measures taken for the study drugs, treatment for the AE and outcome of the event, and relationship between the event and study drugs.

For an SAE, the investigator shall also provide the date when the AE meets the criteria for an SAE, the date when the investigator is informed of the SAE, the reason of being an 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 shall provide the rationales of the causality and a description of the SAE. In the SAE description, the followings shall also be included: the subject number, age, gender, height, and weight; indication for receiving the investigational drug, cancer staging, and overall condition; SAE occurrence, development, outcome, and result; laboratory results related to the SAE (the time of the examination, units, and normal ranges must be provided); medical history, onset and duration of concurrent diseases related to the SAE; medication history and initiation, duration, and dosage of concomitant medications related to the SAE; initiation, duration, and dosage of the study drug.

Descriptions of the AE are as follows:

Diagnosis, signs, and symptoms

Document the definite diagnosis, if there is one, rather than just listing the independent signs and symptoms (e.g. hepatic failure rather than jaundice, elevated transaminase, and asterixis). Signs and symptoms should be reported as separate AEs/SAEs if 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, included the signs and symptoms. The record of signs and symptoms shall then be deleted. A follow-up SAE report shall 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 an 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 assessment 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.

Recurring AEs refer to AE that have resolved between the two time points of assessment 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 investigators has responsibilities to review all the laboratory test abnormalities and determine whether the abnormalities should be reported as AEs.

Death

During the entire course of the study, all the deaths that occurr within 90 days after the last dose are documented in the Death Report Form in the eCRFs and reported to the sponsor timely, regardless of the causality with the study 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 submitt an SAE report; for a death with an unknown cause, the AE is recorded as "unknown cause of death" in the AE form, and submitted an SAE report. Further investigation is performed for the exact cause of the death.

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.

Progressive disease

A PD 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. Expected PD should 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 should not be reported as an SAE.

7.6. Expedited Reporting of SAEs and Pregnancy

SAE reporting:

SAEs that occur from the signing of ICF within 90 days (inclusive) since the last dose must be reported. The investigator must fill out the "CFDA (now NMPA) SAE Report Form", regardless of whether it is the initial report or a follow-up report, and sign and date the form. The investigator must report the SAE to the sponsor, CFDA (now NMPA), and EC within 24 hours of noticing the event. Refer to the table below for contact details.

For SAEs occurring outside of the above-mentioned period, those considered related to the study drug should also be reported to the sponsor.

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 event to the CFDA (now NMPA), health administration departments, and ECs in accordance with the regulations.

Table 27. SAE report contacts

Unit	Contact	Fax/Telephone/Address
Hospital Name	Ethics committee	Hospital Fax/Telephone
Innovent Biologics (Suzhou) Co., Ltd.	Clinical Study Department PV	Fax: 021-31652800 Email: drugsafety@innoventbio.com
National Medical Products Administration		Address: No. 1, Lu Yuan, North Zhanlan Road, Xicheng District, Beijing, China Postal code: 100037 Switchboard: 010-68313344
Medical Administrative Department, Health Administration		Address: No. 38, Lishi Road, Xicheng District, Beijing Tel.: 010-68792001 Fax: 010-68792734
Province, Autonomous Region, Municipality Food and Drug Administration	Based on the requirements of the food and drug administration department of each province, autonomous region or municipality	

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 study drugs becomes pregnant, she must be excluded in the study. The investigator must report to the sponsor within 24 hours of noticing the event and submit the Innovent Clinical Study Pregnancy Report/Follow-Up Form.

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

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

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

If the subject also experiences a SAE during the pregnancy, the "CFDA (now NMPA) SAE Report Form" should also be filled out and reported according to SAE's procedures.

7.7. 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 conditions in **Table 28** are met without other possible causes. Such cases should always be considered as important medical events.

Table 28. Liver injuries required to be reported as SAEs

Baseline	Normal (AST/ALT and TBIL)	Abnormal (AST/ALT and TBIL)
Treatment period	ALT or AST ≥ 3 × ULN with TBIL ≥ 2 × ULN and ALP ≤ 2 × ULN and no hemolysis	ALT or AST ≥ 8 × ULN and TBIL increase ≥ 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 assessment must include the laboratory tests, detailed medical history, and physical assessment, and the possibility of hepatic tumor (primary or secondary) shall be considered.

Other than repeated AST and ALT tests, albumin, creatine kinase, TBIL, direct and indirect bilirubin, γ-GT, PT/INR, and ALP shall also be tested. Detailed medical history include 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 showed consistency with the criteria outlined in Table 28 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 injury shall be reported as SAEs, and the Appendix 4: Abnormal Hepatic Function Monitoring and Follow-Up Report shall be submitted to the sponsor.

7.8. Management of Drug-Related Toxicities

During the course of the trial, the sponsor will conduct regularly monitoring of safety. Detailed information regarding the frequency of review and type of data to be reviewed will be presented in a separate safety review plan.

7.8.1. Immune related adverse events

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 are monitored. In case of no alternative causes (e.g. infections), signs and symptoms of the subjects during the study may be related to the immune system.

Refer to Sections 5.4 and 5.5 for dose adjustments of IBI308 and principles of AE management. Refer to Appendix 8 (Tables 1 to 3) for a detailed guide on irAE management.

7.8.2. Adverse events of special interest (AESIs)

AESIs refer to events that require close monitoring in order to enhance the understanding of the safety of the investigational drug. AESIs can be non-serious events.

Examples of irAE are as follows:

- Immune-related pneumonia of grade 2 or above.
- Immune-related nervous system disorders of grade 2 or above.
- IrAE except for pneumonia and nervous system disorders of grade 3 or above.

For the AESIs specified in the clinical trial protocol, the "Innovent Clinical Study Adverse Event of Special Interest Report Form" should be completed within 24 hours of the investigator's knowledge of the event, and reported to the sponsor. If the SAE standards are met, the "CFDA (now NMPA) Serious Adverse Event Report Form" must also be completed, while reporting based on the requirements and the deadlines for SAE.

8. STATISTICS

8.1. Statistics Analysis Plan

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

8.2. Hypothesis Test

The main objectives of this study include: to evaluate the safety and tolerability of IBI308 in subjects with advanced malignant solid tumors, and to assess the anti-tumor activities of IBI308 in monotherapy or combination chemotherapy in subjects with advanced solid tumors. The main evaluation endpoints are AEs (including DLT), and efficacy evaluation endpoints (ORR, PFS, DcR, DOR, TTR, and OS based on RECIST V1.1 standard). No formal hypothesis test will be performed, while 95% CI will be provided if necessary.

Also, the endpoints related to secondary and exploratory objectives are based on descriptive statistics, without formal hypothesis test.

8.3. Statistical Populations

The analysis sets include the safety set (SS), full analysis set (FAS), and PK analysis set.

1. SS: subjects who receive at least one dose of the study drug.
2. FAS: subjects who has a measurable lesion at baseline, and who has used the study drug at least once.
3. PPS: a subset of the FAS, including subjects with good compliance and no serious protocol deviations or prohibited medications.
4. PK analysis set: subjects who has no major protocol deviation or significant PK blood sample collection missing.

Regardless of phases Ia or Ib, anti-tumor activity (clinical efficacy or PD parameters) will be evaluated using the FAS, SS for the safety analysis, and PK analysis set for the analysis of PK parameters.

The PFS and OS are analyzed simultaneously using the SS.

8.4. Statistical Analysis Methods

8.4.1. General statistical analysis

Variable data are summarized using the mean, standard deviation, median, maximum, and minimum. Attributes data are described using frequency and percentage.

No formal hypothesis testing is performed and 95% CI is calculated when necessary.

For phase Ia study, the tumor evaluation for each subject will be tabulated, with items of optimal overall response, PFS, OS, and DOR. For phase Ib study, each endpoint indicator will be analyzed by sub-cohort (tumor species) according to Sections 8.4.2 and 8.4.3.

All statistical analyses are carried out using SAS 9.2 or above.

8.4.2. Analysis of the primary endpoint

1. Safety indicators: For the analysis, see the section "8.4.4 Safety Analysis".
2. All efficacy endpoints (excluding OS) are evaluated based on the RECIST V1.1.

- ORR

$ORR = \frac{CR + \text{Number of subjects achieving PR}}{\text{Number of all subjects}} * 100\%$, 95% CI is calculated using the binomial distribution

- DCR

$DCR = \frac{CR + PR + \text{Number of subjects achieving SD}}{\text{Number of all subjects}} * 100\%$, 95% CI is calculated using the binomial distribution

The ORR and DCR are calculated based on the optimal tumor efficacy evaluation that is secondarily confirmed during the study period.

- PFS

PFS: The time from the first use of the study drug to the time of first PD (imaging). For patients died of any cause before PD, the PFS is the time from the first use of the study drug to death. Subjects who do not have PD or die will be censored on the date of their last imaging evaluation. For subjects who do not undergo imaging evaluation after baseline, the censoring date is the date when the first dose of the study drug is given.

The PFS analysis uses Kaplan-Meier to estimate mPFS, 6-month and 1-year PFS rates, and their 95% CI, and survival curves are plotted.

- OS

OS: The time from the first dose of the study drug to the death of the subject. At the end of the study, if the subject is still alive, the known "last date of subject survival" will be used as the censoring date.

The Kaplan-Meier method is used in the OS analysis to estimate mOS, 6-month and 1-year survival rates, and their 95% CI, and survival curves are plotted.

- DOR

For subjects showing a response (CR or PR), their DOR: the time from the date of first response to PD or death. For subjects without PD or death, the censoring date is the date when the last imaging evaluation is done.

The DOR of the responded subjects will be tabulated; and if the data is acceptable, a survival curve will be plotted.

- TTR

For subjects with an objective response (CR or PR), their time to objective response: the time from the first dose of the study drug to the first confirmation of objective response.

The TTR for subjects will be tabulated; and if the data is acceptable, a survival curve will be plotted.

- Maintenance response rate

For subjects with an objective response (CR or PR), the ratio of those whose response is maintained till the end of the study.

8.4.3. Analysis of secondary endpoints

- PK parameters.
- PK parameters: $AUC_{0\text{-}tlast}$, $AUC_{0\text{-}inf}$, C_{max}, T_{max}, CL, V_z, $t_{1/2}$, MRT, accumulation ratio, C_{ss_min}, C_{ss_max}, C_{ss_av}, AUCss, fluctuation coefficient, mean descriptive statistics, standard deviation, CV, maximum, and minimum.
- Immunogenicity indicators.
- The rates of ADA and NAb development will be calculated. Subjects' antibody titer will be tabulated.
- PD parameters.
- Variations of PD indicators (including but not limited to receptor saturation) will be descriptively statistically analyzed.

8.4.4. Safety analysis

Safety analysis is performed using the SS. The safety parameters include DLT, other AEs, laboratory tests, vital signs, ECG, etc. The data will be summarized by stages and by queue. AEs will be summarized (8 cohorts in phases Ia and phase Ib).

8.4.4.1 Drug exposure

The subjects will be summarized by the drug exposure, administration time (number of cycles), tumor species, and overall conditions.

8.4.4.2 Adverse events

All the AEs will be coded according to MedDRA.

According to NCI CTCAE V4.03, the distributions of incidences (frequency) and severity levels of AEs, TEAEs, ADRs, SAEs, and AESIs should be summarized by SOC and PT in the MedDRA coding.

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

The subjects with DLT will be described in a list and the incidence of DLT will be calculated.

8.4.4.3 Laboratory test

Measurements and changes before and after treatment in routine blood test and blood chemistry parameters will be described using mean ± SD, maximum, minimum, and median. Normal and abnormal changes after treatment will be described using a cross-classification table.

The proportion of subjects with "clinically significant abnormalities" will be presented. The clinical significance should be determined by the investigator. The severity level and the incidence rates of each disease will be calculated by the NCI CTCAE 4.03 (when performing the same test item, the case of the highest severity level and the incidence rate should be counted), and tabulated by the changes before and after the treatment.

Subjects with abnormal changes after treatment (whether clinically significant or not) will be listed.

8.4.4.4 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.

8.4.4.5 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 listed.

8.4.5. Compliance analysis

The frequency and proportion of subjects who violated the expecte dosing regimen will be summarized.

The proportion of subjects who are given 80–120% 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 will also be summarized.

8.4.6. Subjects' baseline characteristics

Subjects' demographic characteristics (sex and age), tumor diagnosis information (tumor types, pathological diagnosis, tumor staging, and previous therapy), 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, ECOG PS scores, laboratory tests, past/concomitant medications) will be analyzed using descriptive statistics.

8.4.7. Interim analysis

N/A.

8.4.8. Subgroup analysis

A subgroup analysis of anti-tumor activity (ORR) will be carried out on factors that are clinically considered to affect prognosis, such as gender, age, and ECOG PS score.

8.4.9. Multiple comparisons and adjustments

Multiplex adjustments are not considered.

8.4.10. 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.

8.4.11. Exploratory analysis

The parameters of the clinical benefit evaluation are based on the irRECIST criteria, including irORR, irDOR, irPFS, and irDCR (see Section 8.4.2 for the analytical procedure).

Descriptive statistics will be given for baseline PD-L1 expression, the ratio of subjects at different levels of PD-L1 expression, and their corresponding ORR and DOR;

Exploratory analysis will be carried out on the relationship between PK-PD and the relationship between AUC and anti-tumor activity (ORR, DOR).

8.5. Sample Size Determination

No formal estimation of sample size will be performed in this clinical study.

Phase Ia study: This dose escalation study uses the standard "3 + 3" design to evaluate 4 dose levels. It is planned to enroll around 12–24 patients with advanced solid tumors that have failed standard treatment.

Phase Ib study: A total of 10–20 subjects will be enrolled into cohorts A and C, 50–100 for cohort B, 20 each for cohorts D, E, and F. and 15 each cohorts G and H.

8.6. Methods for Controlling Bias

8.6.1. Randomization and blinding

To avoid bias in the selection of subjects, the investigator will randomize subjects at 1:1 as per the random number table provided by the sponsor when the dose level is escalated to 3 mg/kg IV Q2W and 200 mg IV Q3W in the phase Ia dose-escalation study.

Blinding is not adopted in this study.

8.6.2. Blinding maintenance evaluation

N/A.

8.6.3. Unblinding and emergency unblinding

N/A.

8.7. Statistical Analysis and Clinical Study Report

The first data analysis for cohorts A–F in phase Ib of this study will be performed about 6 months after the last subject in each cohort was enrolled. And the results of the first data analysis will be presented in the statistical analysis report. No clinical study report will be prepared separately for cohorts A–F. The clinical study reports for this study will be completed in two individual parts, each of which will include the corresponding cohorts and deadlines of statistical analyses, as shown in **Table 29**.

Table 29. Schedule of clinical study reports

Clinical study report	Included cohort	Deadline of statistical analysis
Report 1	Phase Ia	Completed by the finalization of study protocol V3.0
Report 2	Cohorts A–F of phase Ib	6 months after the enrollment of the last subject in cohort F of phase Ib
Report 3	Cohorts G and H of phase Ib	6 months after the enrollment of the last subject in cohort H of phase Ib

After completing the data cut-off at each time point of statistical analysis, each study site should continue to complete the treatment, follow-up, and data entry for the subjects in the study groups, until all the subjects of the site complete all follow-ups. Cohorts G and H in the phase Ib study are cohorts added for the protocol V3.0. The study sites that have not participated in the study of these two cohorts will be closed after the completion of the clinical studies on cohorts A–F.

9. QUALITY ASSURANCE AND QUALITY CONTROL

According to the GCP guidelines, the sponsor is responsible for implementing and maintaining quality assurance and quality control systems in accordance with the corresponding standard operation procedures to ensure that the implementation of the clinical trial and the collection, recording, and reporting of clinical trial data comply with the requirements in the protocol, GCP, and corresponding regulations.

9.1. Clinical Monitoring

The sponsor or its authorized contract research organization (CRO) will conduct clinical monitoring of this study. The CRA shall 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 CRA should maintain regular communication with the investigator and the sponsor.

Before the start of the study, the CRA assesses the qualifications of each study site, and reports issues related to facilities, technical equipment, or medical staff to the sponsor. During the course of the study, the CRA is responsible for the monitoring of whether the written ICF from all subjects has been obtained and whether the data records are correct and complete. Also, the CRA compares the data entered into the eCRF with the source data, and informs the investigator of any errors or omissions. The CRA shall also control the study center's adherence to the protocol, arrange for the supply of trial drugs and ensure that the drugs are preserved in the 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.

9.2. Data Management/Coding

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

Data entry into the eCRFs should be completed as soon as possible during or after visiting. The eCRFs should be updated at any time to ensure that they reflect the latest developments of the subjects. To avoid the differences in outcome evaluations by different evaluators, it is recommended that the baseline and all the subsequent efficacy and safety evaluations of a given subject shall be performed by the same individual. The investigators are required to review the data to ensure the accuracy and correctness of all the data entered into the eCRFs. 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 shall review the eCRF and assess its completeness and consistency. The CRA shall compare the eCRF with the source documents to ensure consistency of key data. Data entry, corrections, and modifications should be performed by the investigator or his/her designee. The data in the eCRFs is submitted to the data server and any modifications in the data should be recorded in the audit trail, including reasons, operator names, time, and dates of modification. The roles and permission levels of the personnel responsible for data entry in the study site will be determined in advance. The CRA or data 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 used by the investigators or hospital, including all records related to the subjects, which are able to demonstrate the presence, inclusion criteria, and participation of subjects (laboratory records, ECGs, pharmaceutical records, and subject folders etc.).

The investigators are required to maintain all source documents and to offer the documents to the CRA for review during each visit. In addition, the investigator must submit a complete eCRF for each enrolled subject, regardless of the duration of participation. The protocol number and subject numbers of all supporting documents (such as laboratory records or hospital records) submitted with the eCRFs should be carefully verified. All the personal privacy information (including the subjects' names) should be deleted or made illegible to protect the privacy of the subjects. The investigators 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 could 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 medical dictionary used for coding will be described in the Clinical Study Report (CSR).

9.3. Quality Assurance Audits

During the course of the study, the sponsor or his/her authorized representative may conduct quality assurance audits on the study site, study database and related documents. At the same time, the corresponding regulatory authority may conduct inspections on the study site, study database and related documents. The investigator must inform the sponsor immediately when an inspection notice is received from the regulatory authorities.

The sponsor's quality assurance department conducts an audit on the clinical study sites, which 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 trials and inspections conducted by the regulatory authorities. The primary purpose of an audit or a 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 study drugs have been processed, reported and pre-planned. In addition, the protocol, facility, ethical standard operation procedures, GCP and applicable regulatory requirements are consistent. The investigators should have direct access to all trial files, source records, and source data.

10. ETHICS

10.1. Ethics Committee

The sponsor or designee will prepare the relevant documents including the trial 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 in of the study site for approval. Prior to the start of the trial, written approval from the EC must be obtained and submitted to the sponsor. The written approval from the EC should specify the name, number, version number of the study protocol and other documents (such as ICF), and date of approval. The investigator is required to notify the sponsor of the EC's written comments regarding delay, interruption, and re-approval of the study.

The study site must follow the requirements of the EC in the study site. Protocol modifications, 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.

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

10.3. Subject Information and Informed Consent

Prior to undergoing 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 consent 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.

10.4. Data Protection of Subjects

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.

11. STUDY MANAGEMENT

11.1. Data Processing and Record Keeping

Records from the clinical trial (such as protocol and protocol revision, completed eCRFs, and 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.

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.

11.2. Source Data/File Access

The investigator agrees that the sponsor, CRO, and relevant authorized regulatory agencies shall have direct access to all the study-related documents, including medical records of the subjects.

11.3. Protocol Revisions

Any possible revisions to the protocol during the course of the study will be communicated between and agreed by the sponsor and the investigator. The sponsor shall ensure that the protocol revision is submitted to the regulatory authority in a timely manner.

All revisions to the protocol shall be kept as supplements to the protocol. Any changes to the protocol must be submitted to the EC for approval or filing in accordance with the EC's regulations. If necessary, it should also be submitted to regulatory authorities for approval and only implemented after being approved by the EC and regulatory authorities (if applicable).(With the exception of changes to the protocol that eliminate direct hazards to the trial subjects.)

11.4. Responsibilities of the Investigator

The investigator shall adhere to the protocol, ethical principles of the Declaration of Helsinki, Chinese GCP and requirements of the corresponding regulations for this study.

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

11.5. Publishing Policy

All the data generated in this study is the confidential information owned by the sponsor. The sponsor has the right to publish 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.

11.6. Financing and Insurance

The sponsor shall purchase insurance for participants in the study in accordance with local regulations and minimum requirements. Insurance related terms shall be saved in the study folder.

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APPENDIX

Appendix 1: Signature Page for Investigator

Protocol Title: An Open-Label, Multi-Center, and Phase Ia/Ib Study Evaluating the Monotherapy or Combination Chemotherapy of IBI308 in the Treatment of Chinese Subjects with Advanced Malignant Tumors

Protocol No.: CIBI308A101

This protocol is a trade secret owned by Innovent Biologics (Suzhou) Co., Ltd. I have read and fully understood this protocol, and agree to conduct this study in accordance with the requirements found in this protocol and the 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:

Signature of Investigator: _____ Date: _____

Name (Print): _____

Title of Investigator: _____

Name and 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 chair
5	Dead

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Appendix 3: Response Evaluation Criteria in Solid Tumors Version 1.1 (RECIST V1.1)

The following is an excerpt from the RECIST V1.1.

1. MEASURABILITY OF TUMOR AT BASELINE

1.1 Definitions

At baseline, tumor lesions/lymph nodes will be categorized measurable or non-measurable as follows:

1.1.1 Measurable lesion

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

- 10 mm by CT scanning (with a thickness of no more than 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 thickness measured by CT scanning should be no more than 5 mm). At baseline and in follow-up, only the short axis will be measured and followed.

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 of ≥ 10 mm to < 15 mm) and non-measurable lesions. Lesions considered truly non-measurable include: leptomeningeal disease, ascites, pleural or pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung, abdominal masses/abdominal organomegaly identified by physical exam that is not measurable by reproducible imaging techniques.

1.1.3 Special considerations for lesion measurement

Bone lesions, cystic lesions, and lesions with prior locoregional treatment must be specified:

Bone lesions:

- Bone scan, PET scan, or plain film 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 therapy, are usually not considered measurable unless there has been demonstrated progression in the lesion. Study protocols should detail the conditions under which such lesions would be considered measurable.

1.2 Specifications by Methods of Measurements

1.2.1 Measurement of lesions

All measurements should be recorded in metric notation, using calipers if clinically assessed. 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 methods

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging based evaluation should always be done rather than clinical examination unless the lesion(s) being followed cannot be imaged but are assessable by clinical exam.

Clinical lesions: Clinical lesions can only be considered as measurable lesions (such as skin nodules) when they are on the surface and have a measured diameter of ≥ 10 mm. For subjects with skin lesions, it is recommended to use color photos containing the size of the lesion measured by ruler as an archive. As noted above, when lesions can be evaluated by both clinical exam and imaging, imaging evaluation should be undertaken since it is more objective and may also be reviewed at the end of the study.

Chest X-ray: Chest CT is preferred over chest X-ray, particularly when progression is an important endpoint, since CT is more sensitive than X-ray, particularly in identifying new lesions. However, lesions on chest X-ray may be considered measurable if they are clearly defined and surrounded by aerated lung.

CT, MRI: CT is the best currently available and reproducible method to measure lesions selected for response assessment. 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 is not useful in assessment of lesion size and should not be used as a method of measurement. Ultrasound examinations cannot be reproduced in their entirety for independent review at a later date and, because they are operator dependent, it cannot be guaranteed that the same technique and measurements will be taken from one assessment to the next. If new lesions are identified by ultrasound in the course of the study, confirmation by CT or MRI is advised. If there is concern about radiation exposure at CT, MRI may be used instead of CT in selected instances.

Endoscopy, laparoscopy: The utilization of these techniques for objective tumor evaluation is not advised. However, they can be useful to confirm CR when biopsies are obtained or to determine relapse in trials where recurrence following CR or surgical resection is an endpoint.

Tumor markers: Tumor markers 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 TUMOR ASSESSMENT

2.1 Evaluation 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., only one or two subject[s] with accumulated organs can be selected for the measurement of at most 2 or 4 target lesions at the baseline).

Target lesions must be selected based on size (the maximum diameter), can represent all involved organs, and measurements must be well reproducible. 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, 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: a 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 short 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 be not 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 evaluation. 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 Evaluation 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): At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters.

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); except that the absolute value of the sum of the diameter must be increased by at least 5 mm (the appearance of one or more new lesions is also considered to be PD).

Stable disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.

2.3.2 Considerations for non-target lesion assessment

Lymph nodes: Even if the lymph nodes were 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 evaluations, 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 longest diameter of the entire combined lesion.

2.3.3 Evaluation 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.

Complete response (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-PD: At least 1 non-target lesion is found with/without persistent tumor marker levels that exceed normal levels.

Progressive disease (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 is stable or partially resolved, 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 required in the inclusion criteria. However, the overall evaluation 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 evaluation 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 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 was 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 was performed at baseline.

If a new lesion is not definitive due to its 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 (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 optimal overall efficacy refers to the optimal efficacy 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 optimal overall efficacy. Also in the protocol, it must be specified that how any new therapy before progression affects the optimal response. The optimal 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 optimal overall efficacy.

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 evaluation 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 optimal 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 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 CR or PR 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 nodular lesions are included in the overall target lesion assessment and the diameter of such lesions is reduced to the "normal" level (< 10 mm), a scan report of the lesion size will still be provided. 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 with CR will not be recorded as 0 on the eCRF.

If the efficacy confirmation is required during the study, the optimal overall efficacy 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 a global exacerbation 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 exacerbation 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 CRs, 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 literature. 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).

Table 1. Time point efficacy: subjects with target lesions (including or excluding non-target lesions)

Target lesion	Non-target lesion	New lesion	Overall response
CR	CR	Absent	CR
CR	Non-CR/non-PD	Absent	PR
CR	NE	Absent	PR
PR	Non-progressive or not completely evaluable	Absent	PR

Target lesion	Non-target lesion	New lesion	Overall response
SD	Non-progressive or not completely evaluable	Absent	SD
Not completely evaluable	Non-progressive	Absent	NE
PD	Any	Present or absent	PD
Any	PD	Present or absent	PD
Any	Any	Present	PD

CR = complete response; PR = partial response; SD = stable disease; PD = progressive disease; NE = non-evaluable

Table 2. Time point efficacy: subjects with non-target lesions only

Non-target lesion	New lesion	Overall response
CR	Absent	CR
Non-CR/non-PD	Absent	Non-CR/non-PD
Not completely evaluable	Absent	NE
PD that cannot be determined	Present or absent	PD
Any	Absent	PD

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

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.

Table 3. ptimal overall responses required to be confirmed for efficacy by CR and PR

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

Overall response at the first time point	Overall response at the subsequent time points	Optimal overall response
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 unbalanced 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 is 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 ones) 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 import in preventing deviations, especially for non-blind experimental 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 SD 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 relativity 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 using 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 a persistent, poor condition), 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: Abnormal Hepatic Function Monitoring and Follow-Up Report

Please submit the report to Innovent PV:

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

Contact information of reporter (please provide the followings in order to receive a timely response):

Reporter's Email: Reporter's Telephone:

Reporter's Signature: Date of Report:

Abnormal Hepatic Function Follow-Up Information:

Trial No.: Subject ID:

1) Symptoms of abnormal hepatic function (check the followings if present):

   Decreased appetite □, tired of grease □, indigestion □, nausea □, emesis □, bloating □, abdominal pain □, diarrhea □, constipation □, clay stool □, fatigue □, weakness □, lethargy □, weight loss □, asterixis □, mental state changes □, hemorrhagic tendency □, fever □, others □

2) Signs of abnormal hepatic function (check the followings if present):

   Facial appearance of liver disease □, spider nevus □, liver palm □, ascites □, abdominal wall varicose veins □, jaundice □, yellow body fluid □, hepatomegaly □, splenomegaly □, liver area tenderness □, hepatic encephalopathy □, hepatic dyspnea □, crackles □, pulmonary peripheral edema □, jugular varicose veins □, abnormal heart sounds □, and others □

3) Medical history (check the followings if present):

   Viral hepatitis (HBV-A □; HBV-B □; HBV-C □; HBV-D □; HBV-E □), alcoholic hepatitis □, fatty liver □, hepatic cancer □, hepatic metastasis □, hepatic cirrhosis □, liver transplantation □, blood transfusion □, elevated liver enzymes prior to investigational drug administration □, autoimmune disease □, biliary tract disease □, cardiovascular disease □, hypotension □, diabetes □, surgery □, bone metastasis or bone damage □, HIV infection □, EB virus infection □, drug toxicity □, obesity □, and others □

4) Family history (check the followings if present):

5) Concomitant medication and diet (check the followings if present):

   Chemotherapeutics □, Chinese herbal medicine □, OTC drug □, dietary supplement □, alcohol consumption □, drug abuse □, history of chemical exposure □, anti-infective □, paracetamol □, NSAIDs □, metronidazole □, and others □

6) All the relevant laboratory test results (include those at baseline, and during and after the treatment. If tested, please check and provide the test results, units, and reference ranges):

   Routine blood test □,

   Eosinophil count □,

   AST and ALT levels □, and laboratory test results (including those at baseline and during the treatment) □,

   TBIL □, and direct bilirubin □,

   Total serum protein □, albumin □, and immunoglobulin □,

   Total cholesterol □, cholesterol ester □,

   Coagulation function □, such as:

   Other □, such as:

7) Serological tests (if performed, please check and provide the test results):

   Epstein-Barr virus (EBV) □,

   Cytomegalovirus (CMV) □,

   Herpes simplex virus (HSV) □,

   Toxoplasmosis □,

   Hepatitis (A □, B □, C □, D □, E □),

   HIV □,

   Anti-nuclear antibodies □,

   Anti-smooth muscle antibodies □,

   Other antibodies □, such as:

   Others □, such as:

8) Auxiliary tests or operations (if performed, please check and provide the test results):

Liver ultrasound □,

Abdominal CT □,

Liver biopsy □,

Liver transplantation (planned or completed) □,

Others □, such as:

Appendix 5: List of Pre-Existed Autoimmune Diseases Prior to Enrollment

Ask whether the subject has acquired or congenital immunodeficiency or autoimmune diseases. These subjects are excluded from the study. Unless the subject has a history of allergic reactions and juvenile arthritis, the likelihood of suspected autoimmune disease is very low. In addition, subjects with transient autoimmune manifestations due to acute infections (such as Lyme arthritis) can enroll if have been treated with antibiotics. If an autoimmune disease cannot be confirmed, please contact the sponsor's medical manager.

Autoimmune diseases include but are not limited to:

Acute sporadic encephalomyelitis
IgA nephropathy
Addison's disease
Inflammatory bowel disease
Alopecia
Interstitial cystitis
Ankylosing spondylitis
Myasthenia gravis
Antiphospholipid antibody syndrome
Lupus
Aplastic anemia
Lyme disease (chronic)
Asthma
Meniere's syndrome
Autoimmune hemolytic
Anemia
Corneal ulcer
Autoimmune hepatitis
Localized autoimmune hypophysitis
Multiple sclerosis
Autoimmune hypoparathyroidism
Myasthenia gravis
Autoimmune myocarditis
Neuromuscular ankylosis
Autoimmune ovaritis
Myoclonus syndrome
Autoimmune orchitis
Optic neuritis
Autoimmune thrombocytopenia purpura
Ord's thyroiditis
Bechet disease
Pemphigus
Bullous pemphigoid
Pernicious anemia
Celiac disease
Multiple arteritis
Chronic fatigue syndrome
Polyarthritis
Chronic inflammation demyelinating
Polyneuropathy
Autoimmune syndrome
Churg-Strauss syndrome
Primary biliary cirrhosis
Crohn's disease
Psoriasis dermatomyositis
Rett syndrome
Type I diabetes
Rheumatoid arthritis
Autonomic dysfunction
Sarcoidosis
Eczema
Scleroderma
Sjogren syndrome
Bullous dermolysis
Stiff-person syndrome
Pemphigus during pregnancy
Takayasu arteritis
Giant cell arteritis
Ulcerative colitis
Pulmonary hemorrhage-glomerulonephritis syndrome
Vitiligo
Graves' disease
Vogt-Kovanagi-Harada disease
Guillain-Barre syndrome
Vulvodynia
Hashimoto's disease
Wegener's granulomatosis
Kawasaki disease

Appendix 6: Definition and Main Pathological Types of Interstitial Lung Disease

Interstitial lung disease (ILD) is a generic term of the clinicopathological entities that are composed by an inhomogeneous group of diseases based on the pathological basic changes of diffuse lung parenchyma, alveolar inflammation, and interstitial fibrosis, as well as the clinical manifestations of active dyspnea, diffuse infiltrating shadows on chest X-rays, restrictive ventilation disorder, decreased diffusing capacity for carbon monoxide (DLCO), and hypoxemia.

Based on the pathological changes, ILD can be classified as follows:

① Non-inflammatory non-tumor diseases, such as sarcoidosis and exogenous allergic granulomatous alveolitis.

② Granulomatous interstitial lung diseases, such as chronic interstitial pulmonary edema, alveolar proteinosis, primary pulmonary hemosiderinosis, and uremia.

③ Lung-specific inflammation, such as common interstitial pneumonia, bronchiolitis obliterans combined with organizing pneumonia (BOOP), chronic interstitial pneumonia due to exogenous irritant smog/fluid/other toxic and irritant factors, acute respiratory distress syndrome (ARDS), idiopathic pulmonary fibrosis, and pulmonary vasculitis.

④ Inorganic dust inhalation occupational disease.

⑤ Hyperplasia and neoplastic lesions, such as primary bronchioloalveolar carcinoma-induced pulmonary interstitial lesions and diffuse Hodgkin's lymphoma.

Appendix 7: Child-Pugh Grading and Evaluation System

The Child-Pugh score is used to assess the prognosis of chronic liver disease, which is mainly for cirrhosis. Although the method was initially used to predict mortality during surgery, it is now used to determine the prognosis, necessary treatment intensity, and whether liver transplantation is required.

Scoring

Overall, 5 clinical indicators of liver disease are applied in the scoring. Each indicator will be scored on a scale of 1–3, with 3 points representing the highest severity.

Measurement	1 point	2 point	3 point
TBIL[1] (mg/dL)	<2.0	2.0–3.0	>3.0
Serum albumin (g/dL)	>3.5	2.8–3.5	<2.8
INR[2] or Prothrombin time (PT) prolonged (in seconds)	<1.7 <4.0	1.7–2.3 4.0-6.0	> 2.3 >6.0
Ascites	Absent	Mild (prone to be controlled by medications)	Moderate to severe (poorly controlled)
Hepatic encephalopathy[3]	Absent	Grades I–II (mild to moderate)	Grades III–IV (severe or unconscious)

[1] As for primary sclerosing cholangitis and primary biliary cirrhosis, the reference ranges of bilirubin have been modified to reflect the excessively high levels of combined bilirubin in these diseases. The upper limit for 1-point cases is 68 μmol/L (4 mg/dL), and 170 μmol/L (10 mg/dL) for 2-point cases.

[2] The measures are varied from different textbooks and publications. Some old bibliographies use PT instead of INR.

[3] The classification of hepatic encephalopathy is based on the West Haven criteria for semiquantitative grading of mental state. *Source:Conn H, Lieberthal M. The hepatic coma syndromes and lactulose. Baltimore: Williams & Wilkins; 1979.*

As for primary sclerosing cholangitis and primary biliary cirrhosis, the bilirubin reference values have been changed to reflect the fact that these diseases are characterized by high direct bilirubin levels. The upper limit for 1-point cases is 68 μmol/L (4 mg/dL), and 170 μmol/L (10 mg/dL) for 2-point cases.

Explanation

Using the added score described above, the chronic liver disease is graded from Child-Pugh A to C.

Score	**Grade**	**1-year survival rate**	**2-year survival rate**
5–6	A	100%	85%
7–9	B	81%	57%
10–15	C	45%	35%

Appendix 8: Dose Adjustments and Toxicity Management of IBI308

Table 1. Dose adjustments and toxicity management of potential irAEs

<table>
<tr><th></th><th colspan="2">AE Grade/Dose Adjustments</th><th>Toxicity Management</th></tr>
<tr><td rowspan="5">General principles</td><td colspan="2">AEs are graded according to NCI CTCAE V4.03. Refer to this guideline if the event is an irAE</td><td rowspan="5">It is recommended to manage irAEs according to the guideline in this table
- Subjects should be fully evaluated to rule out any alternative causes (e.g., PD, concomitant medication, and infection)
- The event is an irAE if there are no clear alternative causes and treatment with corticosteroids is required
- Consider symptomatic and local treatment for low grade events (grade 1 or 2, unless otherwise stated)
- Consider systemic glucocorticoid therapy for persistent low grade events (grades 1–2) or severe events (grade ≥ 3)
- If the event re-occurs or worsens during tapering of glucocorticoids, the glucocorticoid dose should be increased until symptoms are stabilized or improved, then tapering with a lower rate
- Once persistent clinical improvement is observed, subjects receiving glucocorticoids IV can start tapering the dose or switch to an equivalent dose of glucocorticoid PO at an earlier time (a lower bioavailability of oral administration should be considered)
- For events unresponsive to glucocorticoid treatment, consider a stronger immunosuppressants, e.g., TNF blockers (e.g., infliximab) or mycophenolate mofetil, after discussing with the physicians
- For grade 3/4 local inflammation of lesions (e.g., local pain, irritation, and rash), IBI308 may be continued as determined by the investigator</td></tr>
<tr><td>Grade 1</td><td>No dose adjustments required</td></tr>
<tr><td>Grade 2</td><td>Interrupt
• If worsens, treat as a grade 3/4 event
• If reduces to grades 0–1 or baseline, continue the treatment at the next scheduled date</td></tr>
<tr><td>Grade 3</td><td>Interrupt or permanently discontinue the treatment</td></tr>
<tr><td>Grade 4</td><td>Permanent discontinuation</td></tr>
</table>

	AE Grade/Dose Adjustments		**Toxicity Management**
Pneumonia	Any grade		– Monitor signs and symptoms of pneumonia or interstitial lung disease (e.g., new shortness of breath, cough, chest pain or exacerbation of existing symptoms and signs), and evaluate subjects by imaging, pulmonary function, and other examinations – Initial examination may include clinical evaluation, arterial oxygen saturation, laboratory tests, and high-resolution CT scans
	Grade 1	No dose adjustments required. However, consider interrupting the treatment based on clinical needs and during diagnostic tests for other causes	For grade 1 events: – Monitor signs and symptoms and arterial oxygen saturation for 2–4 days – Perform other laboratory tests based on clinical indications – Consider consulting a respirologist and infectious diseases specialist
	Grade 2	Interrupt • If worsens, treat as a grade 3/4 event • If reduces to grades 0–1 or baseline, continue the treatment at the next scheduled date	For grade 2 events – Monitor signs and symptoms daily, and consider hospitalization – Discuss with sponsor's medical manager, and consider systemic glucocorticoid treatment – Repeat imaging based on clinical indications – If no improvement is seen within 3–5 days, consider other tests and increasing the glucocorticoid dose – If no improvement is seen within 3–5 days, consider a stronger immunosuppressant (e.g., infliximab) – Once improved, taper glucocorticoids within 4 weeks, and consider prophylactic antibiotics – Consider consulting a respirologist and infectious diseases specialist

	AE Grade/Dose Adjustments		**Toxicity Management**
	Grade 3 or grade 4	Permanent discontinuation	For grade 3–4 events – Discuss with sponsor's medical manager – Consider consulting a respirologist and infectious diseases specialist – Hospitalization – Supportive care (oxygen, etc.) – Begin systemic glucocorticoid treatment based on experience – If no improvement is seen within 3–5 days, consider other tests and stronger immunosuppressants (e.g., infliximab) – Once improved, taper glucocorticoids within ≥ 4 weeks, and consider prophylactic antibiotics
Diarrhea or enterocolitis	Any grade		– Monitor possible signs and symptoms related to diarrhea/enterocolitis (abdominal pain, enterospasm, changes in bowel habits, melena, mucous stool, bloody stool, or muscle guarding) – Subjects should be fully evaluated to rule out any alternative causes (e.g., PD and infection) – If alternative causes cannot be determined, consider glucocorticoid treatment for low grade events to prevent from escalating to high grade – Use analgesics with caution (may mask the symptoms of perforation and peritonitis)
	Grade 1	No dose adjustments required	For grade 1 events – Closely monitor symptom exacerbation – Consider symptomatic treatment, including fluid replacement, electrolyte replacement, diet modifications, and loperamide administration

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

	AE Grade/Dose Adjustments		**Toxicity Management**
	Grade 4	Permanent discontinuation	For grade 4 events – Monitor frequency and volume of bowel movement, and maintain hydration – If applicable, perform emergency GI consultation and lower GI endoscopy and imaging to confirm the presence of intestinal perforation – Begin systemic glucocorticoid treatment based on experience – If no improvement is seen within 3–5 days, consider increasing the glucocorticoid dose – If no improvement is seen within 3–5 days, consider other immunosuppressants (e.g., infliximab, but not in subjects with perforations or sepsis) – Once improved, taper glucocorticoids within ≥ 4 weeks, and consider prophylactic antibiotics
Hepatitis (ALT, AST, or TBIL increased)	Any grade		– Closely monitor hepatitis-related signs and symptoms (e.g., jaundice, tea-colored urine, nausea, emesis, loss of appetite, hepatalgia, and hemorrhagic tendency) – Monitor and evaluate hepatic function – Evaluate alternative causes (e.g., viral hepatitis, PD, and concomitant medication) – The dose adjustments and toxicity management in this table is applicable only to subjects with normal ALT, AST, and TB at baseline; for subjects with ALT, AST, or TB > ULN at baseline, interrupt the drug if ALT, AST, or TB elevation of ≥ 50% for < 7 days and discontinue permanently if ALT, AST, or TB elevation of ≥ 50% for ≥ 7 days. Toxicities should be managed based on the investigator's clinical judgment

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

	AE Grade/Dose Adjustments		**Toxicity Management**
	Grade 3 or grade 4	Permanent discontinuation	For grade 3–4 events – Discuss with sponsor's medical manager – Begin systemic glucocorticoid treatment based on experience – If no improvement is seen within 3–5 days, consider stronger immunosuppressants (e.g., mycophenolate mofetil) – If no further improvement is seen within 3–5 days, consider other immunosuppressants based on local guidelines – If applicable, consult a gastroenterologist and perform abdominal examination and imaging – Once improved, taper glucocorticoids within ≥ 4 weeks, and consider prophylactic antibiotics
Dermatitis	Any grade		– Monitor signs and symptoms or dermatitis, e.g., rash, exudation, hypopigmentation, photaesthesia, and pruritus – If there is formation of bullae, contact the sponsor's medical manager – Consider consulting a dermatologist – Perform skin biopsy when necessary
	Grade 1	No dose adjustments required	For grade 1 events – Consider symptomatic treatment, including oral antipruritic agents (e.g., diphenhydramine or hydroxyzine) and local treatment (e.g., urea cream or topical glucocorticoids)

	AE Grade/Dose Adjustments		**Toxicity Management**
	Grade 2	No dose adjustments required • For a refractory (> 1–2 weeks) grade 2 event, interrupt until reduces to grades 0–1 or baseline, continue the treatment at the next scheduled date	For grade 2 events: – Consider symptomatic treatment including oral antipruritic agents and local treatment – Consider a medium-potent topical glucocorticoid – If no improvement or exacerbation is seen with 3–5 days, discuss with sponsor's medical manager and consider systemic glucocorticoid treatment – Consider consulting a dermatologist – Consider skin biopsy if persists for > 1–2 weeks or relapses – Once improved, taper glucocorticoids within ≥ 4 weeks, and consider prophylactic antibiotics
	Grade 3	Interrupt • If worsens, treat as a grade 4 event • Permanently discontinue if a grade 3 rash does not reduce to grades 0–1 or baseline within 30 days	For grade 3–4 events: – Discuss with sponsor's medical manager – Consider hospitalization – Monitor affected area (rule of nine) – Consult a dermatologist – If clinically feasible, consider skin biopsy (preferably more than once) – Begin systemic glucocorticoid treatment based on experience – If no improvement is seen within 3–5 days, consider other tests and increasing the glucocorticoid dose – Once improved, taper glucocorticoids within ≥ 4 weeks, and consider prophylactic antibiotics
	Grade 4	Permanent discontinuation	

	AE Grade/Dose Adjustments		**Toxicity Management**
Hypopituitarism	All grades		− Monitor signs and symptoms of endocrine disorders, including weakness, fatigue, drowsiness, nausea, emesis, chills, changes in bowel habits, behavioral changes, mental state changes, hypotension, hypoglycemia, dizziness, headache, impaired vision, low libido in males, and irregular menstruation in females − Subjects should be fully evaluated to rule out any alternative causes (e.g., PD, brain metastasis, and infection) − Monitor and evaluate pituitary function: TSH, FT3, FT4, adrenocorticotropic hormone, cortisol, luteinizing hormone, follicle stimulating hormone, growth hormone, prolactin, Na^+, blood glucose, estradiol, testosterone, and other laboratory indexes related to endocrine disorders. Perform functional tests when necessary (including adrenocorticotropic hormone [ACTH] stimulation test and insulin-induced hypoglycemia test) − Consider pituitary MRI − Consider consulting an endocrinologist − Consider submitting a blood sample for appropriate autoantibody testing
	Grade 1	No dose adjustments required	For grade 1 events: − Monitor pituitary function − Subjects should be fully evaluated to rule out any alternative causes − Consider consulting an endocrinologist based on clinical indications

	AE Grade/Dose Adjustments		**Toxicity Management**
	Grade 2	Interrupt • If worsens to grades 3–4, permanently discontinue • If reduces to grades 0–1 or baseline, continue the treatment at the next scheduled date	For grade 2–4 events: – Discuss with sponsor's medical manager – Consult an endocrinologist – Hospitalization when necessary – Evaluate endocrine function, and consider pituitary MRI based on clinical indications – Begin hormone replacement therapy when necessary (cortisone replacement therapy should begin one week prior to levothyroxine treatment) – Begin immunosuppressive therapy based on experience, and consider systemic glucocorticoid treatment – Once improved, taper glucocorticoids within ≥ 4 weeks (the dose of cortisone used for hormone replacement may be adjusted accordingly, but subjects whose endocrine function do not recover require long-term treatment); consider prophylactic antibiotics when tapering to prevent infections
	Grade 3 or grade 4	Permanent discontinuation	

	AE Grade/Dose Adjustments		**Toxicity Management**
Adrenal insufficiency	Any grade		– Monitor signs and symptoms of endocrine disorders, including fatigue, pigmentation, loss of appetite, hypotension, and weakness – Subjects should be fully evaluated to rule out any alternative causes – Monitor and evaluate adrenal function: cortisol, adrenocorticotropic hormone, blood sodium, blood potassium, blood glucose, and other endocrine laboratory indexes suspected to be related to adrenal function. The ACTH stimulation test should be performed when necessary – Immunosuppressive therapy when necessary – Hormone replacement therapy (cortisone) when necessary – Consider consulting an endocrinologist – Consider submitting a blood sample for appropriate autoantibody testing
	Grade 1	No dose adjustments required	For grade 1 events – Appropriately monitor adrenal function tests of the subjects – Consider consulting an endocrinologist based on clinical indications
	Grade 2	Interrupt • If worsens to grades 3–4, permanently discontinue • If reduces to grades 0–1 or baseline, continue the treatment at the next scheduled date	For grade 2 events – Discuss with sponsor's medical manager – Evaluate adrenal function, begin hormone replacement therapy when necessary
	Grade 3 or	Permanent discontinuation	For grade 3–4 events:

	AE Grade/Dose Adjustments		**Toxicity Management**
	Grade 4		- Discuss with sponsor's medical manager - Consult an endocrinologist - Consider systemic corticosteroid treatment - Begin corticosteroids with mineralocorticoid activity immediately for adrenal crisis, severe dehydration, hypotension, or shock - Once improved, taper glucocorticoids within ≥ 4 weeks (the dose of cortisone used for hormone replacement may be adjusted accordingly, but subjects whose endocrine function do not recover require long-term treatment); consider prophylactic antibiotics when tapering to prevent infections
Hyperthyroidism/ hypothyroidism	Any grade		− Monitor signs and symptoms of thyroid dysfunction, e.g., those associated with hyperthyroidism (palpitations, sweating, increased appetite and bowel movement, and weight loss) and hypothyroidism (general weakness, fatigue, cold, memory loss, and constipation) − Subjects should be fully evaluated to rule out any alternative causes − Monitor and evaluate thyroid function − Consider consulting an endocrinologist − Consider submitting a blood sample to test thyroid autoantibodies (antithyroglobulin antibodies, anti-thyroid peroxidase antibodies, and thyroid-stimulating hormone receptor antibodies)
	Grade 1 or grade 2	No dose adjustments required	For grade 1–2 events: − Monitor thyroid function and thyroid autoantibodies regularly − L-thyroxine replacement therapy or anti-thyroid medications when necessary

	AE Grade/Dose Adjustments		**Toxicity Management**
	Grade 3 or grade 4	Hyperthyroidism • Permanent discontinuation Hypothyroidism • No dose adjustments required	For grade 3–4 events: - Discuss with sponsor's medical manager – Monitor thyroid function and thyroid autoantibodies – Consult an endocrinologist *Hyperthyroidism* – Anti-thyroid medications – Consider β-blockers for tachycardia *Hypothyroidism* – L-thyroxine replacement therapy
Type I diabetes	Any grade		– Closely monitor the related signs and symptoms, e.g., polyuria, polydipsia, polyphagia, fatigue, weakness, and weight loss – Subjects should be fully evaluated to rule out any alternative causes – Monitor and assess pancreas islet function: blood glucose, insulin, c-peptide, β-cell autoantibodies, blood ketones, and other endocrine laboratory indexes related to type I diabetes
	Grade 1 or grade 2	No dose adjustments required	For grade 1–2 events - Monitor and assess pancreas islet function - Start insulin therapy when necessary
	Grade 3	Interrupt - Resume treatment after blood glucose is under control	For grade 3–4 events - Consult with sponsor's medical manager - Monitor and assess pancreas islet function

	AE Grade/Dose Adjustments		**Toxicity Management**
	Grade 4	Permanent discontinuation	- Consider consulting an endocrinologist - Control the blood glucose level with insulin, and adjust the dose accordingly - If ketoacidosis occurs, subjects should be hospitalized to receive insulin, fluid replacement, and alkali therapy
Renal insufficiency (blood Cr elevated)	Any grade		- Closely monitor signs and symptoms (e.g., oliguria, dark urine, anemia, fatigue, and weight loss) - Subjects should be fully evaluated to rule out any alternative causes - Monitor and evaluate renal function - Consider consulting a nephrologist - Consider kidney biopsy when necessary to distinguish between inflammatory and non-inflammatory causes
	Grade 1	No dose adjustments required	For grade 1 events – Monitor Cr levels Q1W – If returns to baseline level, resume routine Cr monitoring according to the study protocol

	AE Grade/Dose Adjustments		**Toxicity Management**
	Grade 2 or grade 3	Interrupt • If reduces to grades 0–1, continue the treatment at the next scheduled date • If persists for > 7 days or worsens, treat as a grade 4 event	For grade 2–3 events – Discuss with sponsor's medical manager – Monitor Cr levels every 2–3 days – Begin systemic glucocorticoid treatment based on experience – If reduces to grade 1, taper glucocorticoid for at least 1 month**,** and consider prophylactic antibiotics to prevent opportunistic infections – Consider kidney puncture biopsy – Consult a nephrologist
	Grade 4	Permanent discontinuation	For grade 4 events – Discuss with sponsor's medical manager – Monitor Cr levels once daily – Begin systemic glucocorticoid treatment based on experience – If reduces to grade 1, taper glucocorticoid for at least 1 month**,** and consider prophylactic antibiotics to prevent opportunistic infections – Consult a nephrologist – Consider kidney puncture biopsy
Immune-related neurotoxicities (except for myasthenia gravis and Guillain-Barré syndrome)	Any grade		– Monitor the subject's systemic symptoms (headache, nausea, dizziness, behavioral changes, or weakness) – Subjects should be fully evaluated to rule out any alternative causes (e.g., PD, infection, metabolic syndrome, and medications) – Consider appropriate diagnostic tests (e.g., electromyography and nerve conduction test) – If applicable, begin symptomatic treatment and consult a neurologist

	AE Grade/Dose Adjustments		**Toxicity Management**
	Grade 1	No dose adjustments required	– Closely follow up signs and symptoms
	Grade 2	Interruption • If reduces to grades 0–1, continue the treatment at the next scheduled date • If worsens, treat as a grade 3 event	For grade 2–4 events – Discuss with sponsor's medical manager – Consider consulting a neurologist – Hospitalization when necessary – Manage neuropathy and neuropathic pain with appropriate medications (e.g., gabapentin and duloxetine) – Consider systemic corticosteroid treatment – If no improvement is seen within 3–5 days, consider other tests and immunosuppressants (e.g., intravenous immunoglobulin G, IVIgG) – Once stabilized, taper glucocorticoids within ≥ 4 weeks
	Grade 3	Permanent discontinuation	
	Grade 4		

	AE Grade/Dose Adjustments		**Toxicity Management**
Immune-related peripheral neuropathy, e.g., Guillain-Barré syndrome and myasthenia gravis	Any grade		− Closely monitor signs and symptoms (myasthenia gravis: eye or limb soreness and discomfort, blurred vision, and fatigue, which worsens as the day goes on; and Guillain-Barré syndrome: sudden and severe nerve pain, paralysis of the limbs, and prickling or burning sensation in the limbs) − Timely diagnosis of immune-related peripheral neuropathy is very important, as subjects may suffer from unpredictable acute compensation, which may lead to severe disease or death.Pay special attention to signs and symptoms that may indicate serious consequences, e.g., significant dysphagia, rapidly progressive weakness, respiratory insufficiency, or autonomic dysfunction − Neuroelectrophysiological tests should be performed to rule out any alternative causes (e.g., PD, infection, metabolic syndrome, and medications). It is worth noting that cancer itself and cancer treatment can affect neural function. The diagnosis of immune-related peripheral neuropathies is thus difficult. Neurological consultation should be actively carried out. − Plasmapheresis or IVIgG should be considered for subjects with Guillain-Barré syndrome (glucocorticoids are generally ineffective)
	Grade 1	No dose adjustments required	For grade 1 events − Discuss with a physician − Monitor signs and symptoms − Consider consulting a neurologist

<table>
<tr><th></th><th colspan="2">AE Grade/Dose Adjustments</th><th>Toxicity Management</th></tr>
<tr><td rowspan="2"></td><td>Grade 2</td><td>Interruption
• If reduces to grades 0–1, continue the treatment at the next scheduled date
• If worsens, treat as a grade 3–4 event</td><td rowspan="2">For grade 2–4 events
– Discuss with sponsor's medical manager
– Monitor signs and symptoms
– Consult a neurologist
– Hospitalization when necessary
– Manage neuropathy and neuropathic pain with appropriate medications (e.g., gabapentin and duloxetine)
Myasthenia gravis
– Glucocorticoids may be used to treat myasthenia gravis (should be used under the supervision of a neurologist since corticosteroids, especially high-dose, may result in initial exacerbation of symptoms)
– Subjects intolerant to glucocorticoids may be treated with plasmapheresis or IVIgG
– For myasthenia gravis-like neurotoxicities, consider acetylcholinesterase inhibitors in addition to glucocorticoids
Guillain-Barre Syndrome
– Plasmapheresis or IVIgG should be considered for subjects with Guillain-Barré syndrome (glucocorticoids are generally ineffective)</td></tr>
<tr><td>Grade 3 or grade 4</td><td>Permanent discontinuation</td></tr>
</table>

Table 2.Dose adjustments and toxicity management of other potential irAEs

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

Table 3. Dose adjustments and toxicity management of infusion reactions

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